Experimental Diabetes Research

Impact of Maternal Obesity and Diabetes on Long-Term Health of the Offspring

Guest Editors: Christine Maric-Bilkan, Michael Symonds, Susan Ozanne, and Barbara T. Alexander

Impact of Maternal Obesity and Diabetes on Long-Term Health of the Offspring

Experimental Diabetes Research

Impact of Maternal Obesity and Diabetes on Long-Term Health of the Offspring

Guest Editors: Christine Maric-Bilkan, Michael Symonds, Susan Ozanne, and Barbara T. Alexander

Editorial Board

Contents

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 163438, 2 pages
doi:10.1155/2011/163438

Editorial

Impact of Maternal Obesity and Diabetes on Long-Term Health of the Offspring

Christine Maric-Bilkan,[1,2] Michael Symonds,[3] Susan Ozanne,[4] and Barbara T. Alexander[1,2]

[1] *Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA*
[2] *Women's Health Research Center, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA*
[3] *Division of Child Health, School of Clinical Sciences, Queen's Medical Centre University Hospital, Nottingham NG7 2UH, UK*
[4] *Institute of Metabolic Science, University of Cambridge, Cambridge CB2 3EG, UK*

Correspondence should be addressed to Christine Maric-Bilkan, cmaric@umc.edu

Received 26 October 2011; Accepted 26 October 2011

The initial observations of David Barker, popularly known as the "Barker hypothesis" or "developmental origins of health and disease," show that being born with low birth weight, as a result of intrauterine growth restriction produced by maternal undernutrition, is associated with a number of chronic diseases later in life [1]. Subsequently, studies show that it is not just intrauterine growth restriction, but also exposure to any other adverse factor during fetal and/or early postnatal development that can increase susceptibility to a number of chronic diseases later in life including cardiovascular and renal disease, hypertension, type 2 diabetes, certain forms of cancer, osteoporosis, Parkinson's disease, dementia, and polycystic ovary syndrome [2–4].

Over 346 million people worldwide have diabetes, and according to the estimates of the World Health Organization, the prevalence of type 2 diabetes will double by the year 2030 [5]. Similarly, the prevalence of obesity has reached alarming levels. There are 1.5 billion adults, 20 years of age and older, who are overweight. Of those, 200 million men and nearly 300 million women are obese [6]. As a result of this growing prevalence of type 2 diabetes and obesity, more and more women of child-bearing age are either obese and/or diabetic during pregnancy. Given that maternal health has a significant impact on the long-term health of the offspring, it is clear that both type 2 diabetes and obesity are not only a health concern for the mother, but also a growing concern for the generations to come. Thus, the importance of examining the impact of maternal overnutrition and diabetes on the long-term health of the offspring is paramount.

Several experimental studies report a relationship between maternal overnutrition and health of the offspring in adulthood. Specifically, maternal body weight, overnutrition, or a high fat consumption during pregnancy is linked to the development of elements of the metabolic syndrome, cardiovascular and renal disease, hypertension, and cerebral dysfunction as well as type 2 diabetes and obesity themselves later in the life of the offspring [7–12]. However, the mechanisms by which type 2 diabetes and obesity lead to the development of chronic disease later in life remain unknown. The purpose of this issue is to compile and provide a forum for the discussion of the latest data on the impact of maternal overnutrition and diabetes on the long-term (metabolic) health of the offspring.

The current issue presents 5 clinical research papers as well as 7 review articles. The following is a summary of major points and findings presented in these papers.

(1) In overweight/obese mothers, greater % kcal from sweets early in pregnancy is the strongest, independent predictor of higher weight for gestational age at birth as well as after 6 months and higher odds of fetal macrosomia, suggesting that mothers' eating behaviors during pregnancy may have a lasting effect on child weight.

(2) In nondiabetic women, maternal glucose levels correlate with the extent and distribution of fetal adiposity and birth weight.

(3) In the Jerusalem perinatal study (a cohort of over 92,000 births), offspring of mothers with gestational diabetes have higher body mass index and systolic and diastolic blood pressure at 17 years of age compared with offspring of mothers with no gestational diabetes. These data suggest an association between maternal glycemia and cardiometabolic outcomes in the offspring.

(4) Interestingly, no association between cardiac function in offspring of type 1 diabetic mothers at 7-8 years of age and maternal glycemic control was found. Whether the cardiac phenotype takes longer to develop in this cohort may need to be examined.

(5) At the age of 3 years, offspring of type 1 diabetic mothers were characterized by a delay in cortical evoked responses in both visual and somatosensory systems, suggesting a potential association between maternal glycemia and brain maturation in the offspring.

(6) The 7 review articles all provide a comprehensive summary of some of the mechanisms underlying the developmental programming of metabolic syndrome, cardiovascular disease, and obesity later in the life of the offspring. Interestingly, similar mechanisms seem to contribute to different phenotypic outcomes regardless of what the insult was during early development. Specific emphasis is given to the importance of epigenetic changes induced by the maternal environment in predicting later adversity.

In summary, this special issue highlights the fact that maternal health plays a significant role in determining as well as predicating the health of the offspring later in their life. Future studies are warranted to specifically examine the mechanisms by which the perturbation of the *in utero* environment may translate into a health risk in the offspring.

Christine Maric-Bilkan
Michael Symonds
Susan Ozanne
Barbara T. Alexander

References

[1] D. J. P. Barker, "The origins of the developmental origins theory," *Journal of Internal Medicine*, vol. 261, no. 5, pp. 412–417, 2007.

[2] K. Calkins and S. U. Devaskar, "Fetal origins of adult disease," *Current Problems in Pediatric and Adolescent Health Care*, vol. 41, no. 6, pp. 158–176, 2011.

[3] S. C. Langley-Evans and S. McMullen, "Developmental origins of adult disease," *Medical Principles and Practice*, vol. 19, no. 2, pp. 87–98, 2010.

[4] M. J. Warner and S. E. Ozanne, "Mechanisms involved in the developmental programming of adulthood disease," *Biochemical Journal*, vol. 427, no. 3, pp. 333–347, 2010.

[5] http://www.who.int/mediacentre/factsheets/fs312/en/.

[6] http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

[7] B. T. Alexander, "Fetal programming of hypertension," *American Journal of Physiology*, vol. 290, no. 1, pp. R1–R10, 2006.

[8] T. L. Bale, T. Z. Baram, A. S. Brown et al., "Early life programming and neurodevelopmental disorders," *Biological Psychiatry*, vol. 68, no. 4, pp. 314–319, 2010.

[9] G. J. Howie, D. M. Sloboda, T. Kamal, and M. H. Vickers, "Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet," *Journal of Physiology*, vol. 587, no. 4, pp. 905–915, 2009.

[10] I. Y. Khan, V. Dekou, G. Douglas et al., "A high-fat diet during rat pregnancy or suckling induces cardiovascular dysfunction in adult offspring," *American Journal of Physiology*, vol. 288, no. 1, pp. R127–R133, 2005.

[11] M. Srinivasan, S. D. Katewa, A. Palaniyappan, J. D. Pandya, and M. S. Patel, "Maternal high-fat diet consumption results in fetal malprogramming predisposing to the onset of metabolic syndrome-like phenotype in adulthood," *American Journal of Physiology*, vol. 291, no. 4, pp. E792–E799, 2006.

[12] M. E. Symonds, S. P. Sebert, M. A. Hyatt, and H. Budge, "Nutritional programming of the metabolic syndrome," *Nature Reviews Endocrinology*, vol. 5, no. 11, pp. 604–610, 2009.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 906154, 6 pages
doi:10.1155/2011/906154

Research Article

Obesity and Blood Pressure in 17-Year-Old Offspring of Mothers with Gestational Diabetes: Insights from the Jerusalem Perinatal Study

Meytal Avgil Tsadok,[1] Yechiel Friedlander,[1] Ora Paltiel,[1] Orly Manor,[1] Vardiella Meiner,[2] Hagit Hochner,[1] Yael Sagy,[1] Nir Sharon,[1] Shoshanah Yazdgerdi,[1] David Siscovick,[3] and Uriel Elchalal[4]

[1] *Epidemiology Unit, Hebrew University Braun School of Public Health, P.O. Box 12272, Jerusalem 91120, Israel*
[2] *Department of Human Genetics, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel*
[3] *Department of Medicine and Epidemiology, University of Washington, Seattle, WA 98101, USA*
[4] *Obstetric and Gynecology Department, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel*

Correspondence should be addressed to Meytal Avgil Tsadok, meytala@ekmd.huji.ac.il

Received 8 February 2011; Revised 6 April 2011; Accepted 24 May 2011

Academic Editor: Barbara Alexander

Objective. Gestational diabetes mellitus (GDM) influences fetal development and offspring's metabolic risk. We evaluated this association in 17-year-old offspring adjusting for birth weight (BW) and prepregnancy maternal BMI (mBMI). *Study Design*. The JPS birth cohort contains extensive data on 92,408 births from 1964 to 1976. Offspring's BMI and blood pressure (BP) were obtained from military records. For a subcohort born between 1974 and 1976, prepregnancy mBMI was available. Offspring were classified as born to mothers with GDM ($n = 293$) or born to mothers without recorded GDM ($n = 59,499$). *Results*. GDM offspring had higher mean BMI and systolic and diastolic BP compared to no-recorded-GDM offspring. After adjusting for BW, GDM remained significantly associated with offspring BMI and diastolic BP ($\beta = 1.169$ and 1.520, resp.). In the subcohort, when prepregnancy mBMI was entered to the models, it markedly attenuated the associations with GDM. *Conclusions*. Maternal characteristics have long-term effects on cardiometabolic outcomes of their offspring aged 17 years.

1. Introduction

Fetal development is regulated by maternal and fetal characteristics that influence the intrauterine environment. The adaptation of the fetus to intrauterine conditions results in fetal "programming" which may also determine the metabolic "fate" of the fetus later in life [1].

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with different degrees of severity, first diagnosed during pregnancy [2]. It is the most common metabolic complication during pregnancy and is observed in 3%–5% of all pregnant women.

Intrauterine hyperglycaemic conditions influence fetal metabolism and in turn may influence later life morbidity. The short-term consequences of GDM for the offspring are high birth weight [3] and associated perinatal complications such as shoulder dystocia, hypoglycaemia, hyperbilirubinemia, hypocalcemia, and polycythemia [4]. The intermediate-term consequences include impaired insulin resistance, obesity, and type 2 diabetes during childhood [5–7]. Few studies reported an association between maternal GDM and elevated blood pressure later in offspring life [8, 9], but most of the studies that investigated the long-term consequences of GDM on offspring have not reported analyses of blood pressure measurements.

There is some evidence that neonatal birth weight [10], maternal weight gain during pregnancy [11], and prepregnancy maternal BMI [12, 13] (mBMI) are also important factors predicting long-term morbidity of offspring; however, the impact of these factors on the associations of GDM and the long-term health of the offspring remains unclear.

In a previous report [14] on a subset of the Jerusalem perinatal study (JPS) (offspring born in Jerusalem between 1974 and 1976), there was evidence of an increased risk of adolescent overweight, defined as a body mass index (BMI) >90th percentile, among offspring born to diabetic mothers. However, this report included only univariate correlations and did not analyze the data using multivariate models, taking into account various important factors such as prepregnancy mBMI.

In this study, we aimed to assess the long-term implications of maternal GDM on adolescent BMI and blood pressure, among JPS offspring at age 17, after taking into account different characteristics, such as offspring birth weight and prepregnancy mBMI.

2. Methods

2.1. Population

2.1.1. Whole Cohort. The Jerusalem perinatal study (JPS) is a population-based cohort that includes all births occurred in western Jerusalem and its surroundings between 1964 and 1976. Detailed information on data collection has been previously described [15]. In brief, demographic, socioeconomic, and clinical data (medical conditions of the mother including GDM status during all pregnancies from 1964 to 76), and offspring birth weight were collected. The information was extracted either from birth certificates or maternity ward logbooks at the time of birth.

Data on maternal conditions, obstetric complications, and interventions during labor and delivery, including GDM status, were collected systematically in 92,408 deliveries. The original data collection instruments included rubrics for GDM (i.e., diabetes with onset during pregnancy) and pregestational diabetes (i.e., diabetes, mostly insulin-dependent diabetes, prior to the present pregnancy). In this study, we used only the definition for GDM health condition and did not included the pregestational diabetes cases. In that era, all pregnant women were screened for glycosuria at each antenatal visit, and if found positive, they would be referred for an oral glucose tolerance test.

2.1.2. Subcohort. Postpartum interviews of a subset of mothers (17,003, referred to as the subcohort) who gave birth between November 1974 and the end of 1976 provided further information on medical conditions and lifestyle habits, including prepregnancy mBMI, weight gain during pregnancy, gestational age at delivery, and smoking habits. These interviews were conducted at the bedside on the first or second day postpartum by nurse-midwives and captured 98% of the births.

2.1.3. Military Records. Through the Israeli Population Registry, we verified the identities of 99% of the offspring and 96.2% of the mothers in the JPS cohort using their unique identity (ID) numbers. The ID number and other identifiers enabled us to link the JPS data with military draft records. This linkage provided information regarding the weight, height, and systolic and diastolic blood pressure which were measured in 60,191 JPS singleton offspring (37,308 males and 22,883 females) at age 17.

2.2. Study Variables. The following variables were included in the analysis: parents' ages at birth, birth order, offspring's birth weight (continuous variables), maternal level of education (years of schooling grouped into three categories: 0–8 years, 9–12 years and ≥13 years) and socioeconomic status (SES) using a scale based on husband occupation (grouped into three categories: high, middle, and low). Maternal ethnic origin was classified according to her father's country of birth (categorized as: Israel, West Asia, North Africa and Europe/America).

Maternal medical history included data on diabetes and pre-eclampsia in the current pregnancy or in other pregnancies (between 1964 and 1976, recorded in the JPS database).

Information on maternal smoking during pregnancy, gestational age at delivery (calculated from the date of last menstrual period), prepregnancy mBMI, and weight gain during pregnancy was available only in the subcohort of the mothers who gave birth between 1974 and 1976.

Anthropometric and blood pressure information measured in the offspring at age 17 were obtained from the Israel Defense Forces medical database. Details about these examinations have been described elsewhere [13]. Briefly, blood pressure was measured in the sitting position in the right arm with a Bauman sphygmomanometer with appropriate cuff size. Standing height was measured on barefooted subjects, and body weight was measured with light indoor clothing. BMI was calculated as the ratio of weight (kg) to standing height (m) squared (kg/m^2). The examiners were blinded to the perinatal data.

The current study examined the differences in offspring BMI and blood pressure measured at age 17 among the two groups: offspring whose mothers had GDM in the index pregnancy (GDM) and offspring whose mothers did not have GDM in any of her pregnancies during the period 1964–1976 and recorded in the JPS (no-recorded-GDM). We included only singleton pregnancies in this analysis.

2.3. Statistical Analysis. Baseline characteristics of the study population and variables obtained at age 17 are presented for the two groups of offspring categorized by their mother's GDM status. Descriptive analysis was used to compare the BMI and blood pressure mean values for the offspring groups, and linear regression analysis was used to adjust for other characteristics in multivariate models.

For the 1964–1976 subcohort, two sets of models were examined: (1) model 1 included the maternal GDM status as the main covariate (GDM compared to the no-recorded-GDM group) and (2) model 2 additionally adjusted for offspring birth weight. These models were also adjusted for the following covariates: maternal age at birth, ethnic origin (Israel as a reference group), level of education (0–8 years as a reference group), maternal pre-eclampsia (in one or more pregnancies between 1964 and 1976), birth order, SES (middle class as a reference group), and offspring gender.

For the subcohort of 1974–1976, we further adjusted for prepregnancy mBMI and weight gain during the pregnancy

(model 3). In the 1974–1976 analysis, maternal smoking and gestational age at delivery were also included in the models as covariates.

To account for the correlation between siblings within families, the multivariate analysis for the entire cohort (1964–1976) was repeated using a mixed linear model (SAS PROC MIXED). Both approaches provided similar findings; and therefore, the results from the linear regression models are presented. Analyses were conducted with SPSS version 14.0 (Chicago, Ill, USA) and SAS package version 9.1 (Cary, NC, USA).

3. Results

3.1. Characteristics of the Cohort. Of the 92,408 deliveries recorded in the JPS between 1964 and 1976, military induction examination information was available for 60,191 (65.1%) singleton offspring. Of these, 293 (0.5%) were born to mothers with GDM and 59,499 (98.8%) to mothers with No-recorded-GDM.

An additional 399 (0.7%) offspring were born to mothers who had GDM not in the index pregnancy but in one of her other pregnancies during the period 1964–1976 and recorded in the JPS. These offspring were not included in the analysis.

Of the 16,912 singleton deliveries during the 1974–1976 subcohort, military information was available for 11,412 offspring, of whom 77 offspring were born to GDM mothers, and 11,335 to no-recorded-GDM mothers.

Table 1 describes the parental characteristics of study participants of the two groups of offspring. Both maternal and paternal ages were higher, on average, among infants exposed to GDM in utero. Mean birth weight of the GDM group (3411 ± 616 g) was higher than the no-recorded-GDM group (3301 ± 483 g $P < 0.001$).

Mothers in the GDM group were more educated and from higher SES status compared to mothers from the no-recorded-GDM group. In addition, mothers with GDM were more likely to have pre-eclampsia in one of their pregnancies recorded in the JPS, compared to mothers belonging to the no-recorded-GDM group.

3.2. Anthropometry and Blood Pressure at Age 17. Table 2 presents the gender standardized anthropometric and blood pressure values measured in offspring at age 17, classified by mother's GDM status.

BMI, systolic and diastolic blood pressure mean values were significantly higher in GDM offspring as compared to the mean values obtained in offspring born to no-recorded-GDM mothers ($P < 0.05$ for all outcomes).

3.3. Predictors for BMI and Blood Pressure at Age 17. Table 3 demonstrates the association of GDM with BMI and systolic and diastolic blood pressure of the offspring measured at age 17.

Among offspring who were born between 1964 and 1976, maternal GDM was positively and significantly associated with offspring BMI values (model 1) independent of BW (model 2).

In the analysis of the 1974–1976 subcohort, when models were further adjusted for maternal smoking and gestational age at delivery, GDM was positively and significantly associated with offspring BMI measured at age 17 (model 1); however, when birth weight was included in the model (model 2), it attenuated the association with GDM. When prepregnancy mBMI and weight gain during pregnancy were included in the model (model 3), the association of GDM with the offspring BMI was attenuated markedly.

When we evaluated the association of GDM with systolic blood pressure measured in offspring at age 17, no significant associations were found in the entire cohort and in the subcohort as well (model 1). When prepregnancy mBMI included in the analysis of the subcohort, it was positively associated with systolic blood pressure (model 3).

In distinction to systolic blood pressure, GDM was significantly associated with diastolic blood pressure in the entire cohort, even after introducing birth weight to the model (model 2). In the subcohort models, there was no evidence of an association between GDM and offspring diastolic blood pressure, and prepregnancy mBMI was positively associated with diastolic blood pressure at age 17.

4. Comments

Our study implies that maternal characteristics pre- and during pregnancy and the intrauterine environment are important factors for future cardiometabolic conditions of their offspring.

In the entire JPS cohort of 1964–1976, we found that the contribution of maternal GDM to offspring BMI in young adulthood is independent of neonatal birth weight. These findings are consistent with previous studies [16–18]. However, the analysis of the smaller and more detailed subcohort indicates that when prepregnancy maternal BMI is included in the model, the association of maternal GDM with offspring BMI at age 17 is considerbly reduced (Table 3).

Our study suggested a positive association between maternal GDM and diastolic blood pressure measured in the 17-years-old offspring, in the whole cohort. Other studies, focusing on childhood blood pressure, have demonstrated higher blood pressure values in offspring of mothers with GDM [8, 9], while others have not [6].

Even though the association between GDM and diastolic blood pressure did not reach statistical significance in the smaller subcohort (1974–1976), the coefficient of GDM was attenuated when prepregnancy mBMI was included in the model. This implies that the association between maternal GDM and offspring diastolic blood pressure in young adulthood might as well be accounted for prepregnancy mBMI.

There is growing evidence in the literature, that prepregnancy mBMI is a strong predictor of offspring health status later in life [6, 19–21]. Regarding GDM, other studies concluded that maternal obesity and diabetes are independent

Table 1: Characteristics of the study population.

JPS entire cohort, 1964–1976	GDM ($n = 293$)	No-recorded-GDM ($n = 59499$)
Maternal age at delivery (years, mean ± SD)	31.2 ± 5.9	27.6 ± 5.5
Paternal age at delivery (years, mean ± SD)	35.0 ± 7.1	31.5 ± 6.6
Birth order (mean ± SD)	1.93 ± 1.1	1.87 ± 1.1
Birth Weight (grams, mean ± SD)	3411 ± 616	3301 ± 483
Male	3495 ± 633	3347 ± 490
Female	3284 ± 569	3226 ± 462
Birth place of mother's father (%):		
Israel	10.6	12.9
West Asia	28.0	31.7
North Africa	21.2	24.4
Europe/America	40.3	31.0
Maternal education (%):		
Unknown	0.7	5.6
0–8 years	29.4	31.7
9–12 years	31.7	35.8
13+ years	38.2	26.8
Socio economic status (%)		
High	36.9	33.1
Middle	45.4	41.3
Low	17.7	25.6
Maternal health condition (%)		
Pre-eclampsia	14.4	3.4
JPS subcohort 1974–1976	($n = 77$)	($n = 11335$)
Prepregnancy maternal BMI (mean ± SD)	25.3 ± 4.4	21.9 ± 3.0
Weight gain during pregnancy (mean ± SD)	12.3 ± 6.1	11.5 ± 4.4

Table 2: Gender standardized anthropometry and blood pressure measured in offspring at age 17 by maternal health characteristic ($n = 60191$).

	GDM	No-recorded-GDM
Weight (kg)	69.13 ± 13.26[a]	64.05 ± 10.70
BMI (kg/m^2)	22.47 ± 3.86[a]	21.18 ± 3.11
Systolic BP (mm HG)	121.56 ± 12.30[a]	119.84 ± 12.06
Diastolic BP (mm HG)	75.12 ± 7.44[a]	73.47 ± 8.30

[a] Significantly different, $P < 0.05$.

risk factors for adverse short-term perinatal outcomes [22–24]. Our study suggests that the effect of maternal GDM on cardiometabolic outcomes in their 17-year-old offspring is not independent of prepregnancy mBMI.

This study has potential limitations that should be considered. During the JPS data collection period (1964–1976), screening for GDM was not routine in Israel and the prevalence of GDM in the cohort was lower (0.5%) than the current reported prevalence of 3%–5%, possibly due to differences both in the diagnosis of GDM, and in the study population, as 85% of the mothers had a pre pregnancy BMI less than 25 at that time. In addition, we do not have information regarding GDM severity or mode of treatments of the mothers. We assume that the more severe cases of GDM were ascertained and diagnosed at that time; therefore, our results may represent the associations for the offspring of a group of mothers with a more severe form of GDM rather than the GDM detected today by screening during pregnancy. Another limitation is that military induction examination information was available for only 65.1% of the offspring included in the JPS cohort. In the Israeli Defense Force, military service is compulsory for all Jewish males and females, but female subjects are less commonly recruited to army service due to religious belief and practice, so the proportion of females with available information is lower than that of males (38% versus 62%). In addition, citizens may be exempted if they are religiously observant or have physical or mental disabilities. Therefore, the ultra-orthodox

Table 3: Predictors of offspring's BMI and systolic and diastolic BP at age 17: estimated coefficients from multiple linear regression models.

BMI at age 17	Model 1		Model 2		Model 3	
	β	95%CI	β	95%CI	β	95%CI
1964–76[b]						
GDM	1.220[a]	0.863, 1.576	1.169[a]	0.814, 1.523		
Birth weight			0.586[a]	0.534, 0.638		
1974–1976[c] subcohort						
GDM	0.950[a]	0.172, 1.728	0.719	−0.058, 1.496	0.013	−0.740 0.766
Birth weight			0.651[a]	0.502, 0.799	0.265[a]	0.116, 0.414
Prepregnancy mBMI					0.303[a]	0.281, 0.325
Weight gain in pregnancy					0.052[a]	0.038, 0.067
Systolic BP at age 17	β	95%CI	β	95%CI	β	95%CI
1964–76[b]						
GDM	1.229	−0.156, 2.613	1.206	−0.179, 2.590		
Birth weight			0.266[a]	0.063, 0.469		
1974–1976[c] subcohort						
GDM	0.822	−1.918, 3.562	0.668	−2.058, 3.434	0.020	−2.726, 2.766
Birth weight			0.375	−0.148, 0.899	0.039	−0.503, 0.582
Prepregnancy mBMI					0.288[a]	0.207, 0.368
Weight gain in pregnancy					0.036	−0.019, 0.090
Diastolic BP at age 17	β	95%CI	β	95%CI	β	95%CI
1964–76[b]						
GDM	1.549[a]	0.587, 2.510	1.520[a]	0.559, 2.481		
Birth weight			0.333[a]	0.193, 0.474		
1974–1976[c] subcohort						
GDM	1.582	−0.314, 3.478	1.538	−0.363, 3.439	1.167	−0.735, 3.070
Birth weight			0.123	−0.240, 0.485	−0.084	−0.459, 0.292
Prepregnancy mBMI					0.159[a]	0.103, 0.215
Weight gain in pregnancy					0.029	−0.008, 0.067

(Birth weight and weight gain in pregnancy are presented in kg).
[a]$P < 0.05$.
[b]Model was also adjusted for: maternal age at birth, birth order, maternal ethnic origin, education, SES, maternal pre-eclampsia, and offspring gender.
[c]Model was also adjusted for: maternal age at birth, birth order, maternal ethnic origin, education, SES, maternal pre-eclampsia, offspring gender, gestational age at delivery and maternal smoking.

and disabled population may be underrepresented in this study. We believe that this underrepresentation has potential effect on the point estimates, but due to the composition of our study population, it does not alter the inspected associations.

The findings from the JPS cohort add to the knowledge regarding the long term effects of maternal prepregnancy characteristics on cardiometabolic outcomes in offspring aged 17 years, and point to populations at risk. Given the fact that in the US, 13.9% to 25.1% of births are to obese mothers [25] and the prevalence of GDM is 3%–5%, the findings of this study are important because they indicate that in the long term, these maternal characteristics have potential health consequences not only to the mother themselves but to the next generation as well. Therefore, we encourage continuous public health interventions to prevent not only GDM but also high prepregnancy mBMI, since prepregnancy maternal obesity might be the major component account for the association of GDM with the long-term health consequences of the offspring.

Abbreviations

GDM: Gestational diabetes mellitus
JPS: Jerusalem Perinatal Study
mBMI: Maternal BMI
BP: Blood pressure.

Condensation

This study implies that maternal characteristics have long term effects on cardiometabolic outcomes of their offspring aged 17 years.

Acknowledgment

The study was conducted in Jerusalem, Israel, in the Epidemiology unit, Hebrew University-Hadassah Braun School of Public Health. This study was presented in the SMFM 29th annual meeting, as an oral presentation, San Diego, Calif,

USA, Jan 31 2009. The authors declare that there is no duality of interest associated with this paper.

References

[1] P. Bateson, D. Barker, T. Clutton-Brock et al., "Developmental plasticity and human health," *Nature*, vol. 430, no. 6998, pp. 419–421, 2004.

[2] B. E. Metzger, T. A. Buchanan, D. R. Coustan et al., "Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus," *Diabetes Care*, vol. 30, supplement 2, pp. S251–S260, 2007.

[3] O. Langer, Y. Yogev, O. Most, and E. M. J. Xenakis, "Gestational diabetes: the consequences of not treating," *American Journal of Obstetrics and Gynecology*, vol. 192, no. 4, pp. 989–997, 2005.

[4] N. Weintrob, M. Karp, and H. Moshe, "Short- and long-range complications in offspring of diabetic mothers," *Journal of Diabetes and Its Complications*, vol. 10, no. 5, pp. 294–301, 1996.

[5] A. Plagemann, T. Harder, R. Kohlhoff, W. Rohde, and G. Dörner, "Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes," *International Journal of Obesity*, vol. 21, no. 6, pp. 451–456, 1997.

[6] C. M. Boney, A. Verma, R. Tucker, and B. R. Vohr, "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus," *Pediatrics*, vol. 115, no. 3, pp. e290–e296, 2005.

[7] D. Dabelea, R. L. Hanson, P. H. Bennett, J. Roumain, W. C. Knowler, and D. J. Pettitt, "Increasing prevalence of type II diabetes in American Indian children," *Diabetologia*, vol. 41, no. 8, pp. 904–910, 1998.

[8] N. H. Cho, B. L. Silverman, T. A. Rizzo, and B. E. Metzger, "Correlations between the intrauterine metabolic environment and blood pressure in adolescent offspring of diabetic mothers," *Journal of Pediatrics*, vol. 136, no. 5, pp. 587–592, 2000.

[9] J. C. Bunt, P. Antonio Tataranni, and A. D. Salbe, "Intrauterine exposure to diabetes is a determinant of hemoglobin A1c and systolic blood pressure in pima indian children," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 6, pp. 3225–3229, 2005.

[10] E. C. Cottrell and S. E. Ozanne, "Early life programming of obesity and metabolic disease," *Physiology and Behavior*, vol. 94, no. 1, pp. 17–28, 2008.

[11] J. J. M. Geelhoed, L. Van Osch-Gevers, B. O. Verburg et al., "Maternal anthropometrics in pregnancy are associated with left ventricular mass in infancy. The generation R study," *Pediatric Research*, vol. 63, no. 1, pp. 62–66, 2008.

[12] B. R. Vohr, S. T. McGarvey, and R. Tucker, "Effects of maternal gestational diabetes on offspring adiposity at 4–7 years of age," *Diabetes Care*, vol. 22, no. 8, pp. 1284–1291, 1999.

[13] A. Laor, D. K. Stevenson, J. Shemer, R. Gale, and D. S. Seidman, "Size at birth, maternal nutritional status in pregnancy, and blood pressure at age 17: population based analysis," *British Medical Journal*, vol. 315, no. 7106, pp. 449–453, 1997.

[14] D. S. Seidman, A. Laor, D. K. Stevenson, E. Sivan, R. Gale, and J. Shemer, "Macrosomia does not predict overweight in late adolescence in infants of diabetic mothers," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 77, no. 1, pp. 58–62, 1998.

[15] S. Harlap, A. M. Davies, N. B. Grover, and R. Prywes, "The Jerusalem perinatal study: the first decade 1964–73," *Israel Journal of Medical Sciences*, vol. 13, no. 11, pp. 1073–1091, 1977.

[16] D. J. Pettitt, W. C. Knowler, and P. H. Bennett, "Obesity in offspring of diabetic Pima Indian women despite normal birth weight," *Diabetes Care*, vol. 10, no. 1, pp. 76–80, 1987.

[17] T. A. Hillier, K. L. Pedula, M. M. Schmidt, J. A. Mullen, M. A. Charles, and D. J. Pettitt, "Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia," *Diabetes Care*, vol. 30, no. 9, pp. 2287–2292, 2007.

[18] M. W. Gillman, S. Rifas-Shiman, C. S. Berkey, A. E. Field, and G. A. Colditz, "Maternal gestational diabetes, birth weight, and adolescent obesity," *Pediatrics*, vol. 111, no. 3, pp. e221–e226, 2003.

[19] I. Koupil and P. Toivanen, "Social and early-life determinants of overweight and obesity in 18-year-old Swedish men," *International Journal of Obesity*, vol. 32, no. 1, pp. 73–81, 2008.

[20] P. Gordon-Larsen, L. S. Adair, and C. M. Suchindran, "Maternal obesity is associated with younger age at obesity onset in U.S. adolescent offspring followed into adulthood," *Obesity*, vol. 15, no. 11, pp. 2790–2796, 2007.

[21] T. J. Parsons, C. Power, and O. Manor, "Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal," *British Medical Journal*, vol. 323, no. 7325, pp. 1331–1335, 2001.

[22] J. G. Ray, M. J. Vermeulen, J. L. Shapiro, and A. B. Kenshole, "Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study," *QJM*, vol. 94, no. 7, pp. 347–356, 2001.

[23] W. Ricart, J. López, J. Mozas et al., "Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia," *Diabetologia*, vol. 48, no. 9, pp. 1736–1742, 2005.

[24] H. M. Ehrenberg, C. P. Durnwald, P. Catalano, and B. M. Mercer, "The influence of obesity and diabetes on the risk of cesarean delivery," *American Journal of Obstetrics and Gynecology*, vol. 191, no. 3, pp. 969–974, 2004.

[25] S. Y. Chu, S. Y. Kim, and C. L. Bish, "Prepregnancy obesity prevalence in the United States, 2004-2005," *Maternal and Child Health Journal*, vol. 13, no. 5, pp. 614–620, 2009.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 640535, 5 pages
doi:10.1155/2011/640535

Research Article

Cortical Evoked Potentials in Children of Diabetic Mothers

Mario Brinciotti,[1] Angela Napoli,[2] Antonio Mittica,[1] Olimpia Bitterman,[2] and Maria Matricardi[1]

[1] *Department of Pediatrics and Child Neuropsychiatry, Faculty of Medicine and Dentistry, Sapienza University of Rome, 00185 Rome, Italy*
[2] *Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, 00189 Rome, Italy*

Correspondence should be addressed to Mario Brinciotti, mario.brinciotti@uniroma1.it

Received 14 April 2011; Revised 29 July 2011; Accepted 8 August 2011

Academic Editor: Susan Ozanne

Type 1 diabetic mothers' infants show a delay of visual evoked potential (VEP) significantly related to some parameters of poor metabolic control during pregnancy. In the present paper we analyzed the characteristics of VEPs and somatosensory evoked potentials (SEPs) recorded in 16 three-year-old type 1 diabetic mothers' children (DMC). Compared with controls (23 nondiabetic mothers' healthy matched children), DMC showed significantly delayed mean latency of VEP (P2) and SEP (P22). In 3 cases (19%), we found pathological responses (+3 SD from the mean value of controls) of VEPs and SEPs. At the age of 3 years, the offspring of type 1 diabetic mothers showed delay of cortical evoked responses in both visual and somatosensory systems.

1. Introduction

Evoked potentials are commonly used in clinical practice to study brain maturation and clinical disorders [1–3]. Diabetic patients frequently show abnormal evoked potentials, usually related to neuropathy, retinopathy, and poor metabolic control [4, 5]. Subclinical CNS dysfunctions have been reliably detected by evoked potentials in adult patients with uncomplicated diabetes and normal brain CT scan [6]. Moreover, evoked potentials are sensitive to drug administration effects and prenatal substance exposure [7, 8]. In previous studies [9, 10] on diabetic mothers' infants, we found a delayed mean latency of the fourth (P2) component of VEPs compared to matched healthy infants. These results were significantly related to some parameters of poor metabolic control during pregnancy in type 1 diabetic mothers' infants; on the contrary, in infants born from mothers with gestational diabetes VEPs did not show any significant relation with metabolic parameters during pregnancy, but latencies correlated with Apgar scores of perinatal distress. These features suggest that in the offspring of type 1 diabetic mothers VEP changes may be related to adverse effects due to exposure of the fetus to metabolic imbalance during intrauterine life.

These observations raise two main points: (i) whether the VEP abnormalities recorded at the age of 2 months are transient and (ii) whether the abnormalities of evoked responses are restricted to the visual system or extended to other cortical structures. To investigate both these aspects, in the present study we analyzed the characteristics of VEPs and somatosensory evoked potentials (SEPs) recorded in 3-year-old type 1 diabetic mothers' children (DMC).

2. Materials and Methods

2.1. Sample. We studied VEPs and SEPs of 16 three-year-old children (11 females, 5 males, mean age 2.6 ± 0.9 years), whose mothers suffered of type 1 diabetes. VEPs had already been recorded at the age of two months (24 infants, 8 missing cases; 33% attrition rate between 2 months and 3 years). VEPs and SEPs were obtained according to the American Electroencephalographic Society guidelines [11] with electrodes placement based on the International 10–20 System. Recordings were performed without knowledge of

mothers' antepartum metabolic status and infants' perinatal history. Informed consent was obtained from each child's parents after explaining to them the procedures' nature and purpose. A matched sample of 23 nondiabetic mothers' healthy children was used as control.

2.2. VEP Recording. VEPs were recorded in a partially darkened room (mean background light 0.15 ft-Lamberts; dark adaptation for 20 minutes) in awake condition (without sedation). The state of alertness was carefully checked during the entire recording session. VEPs were elicited by binocular stimulation with a stroboscopic unpatterned flash (white light; intensity 0.3 Joule; frequency 1 Hz) placed about 25 cm from the eyes. Responses were recorded from silver-silver chloride electrodes applied to the occipital region, using a four-channel montage (O1-Fz, Oz-Fz, O2-Fz, Fz-M1; M2 as ground). At least two trials of 100 artifact-free responses (automatic artifact rejection; amplitude threshold <20% of rejected traces) were recorded within 512 ms after stimulus.

2.3. SEP Recording. SEPs were obtained in conscious subjects (without sedation) checking the alertness during the entire recording session. Responses were elicited by electrical stimulation applied on the left median nerve at the wrist using a constant current square wave pulse (0.1 ms width, cathode proximal) at a repetition rate of 4 Hz. The stimulus intensity was regulated to produce a small thumb twitch. Cortical responses were recorded by surface silver-silver chloride electrodes placed on the contralateral parietal and frontal areas with two channel montage with an active electrode on C4′ (2 cm posterior to C4 in the International 10–20 System) referenced to Fz, and an active electrode on F4 referenced to C3′. At least two trials of 250 artifact-free samples (automatic artifact rejection; amplitude threshold <20% of rejected traces) were recorded with an analysis time of 100 ms.

All reproducible peaks of VEPs and SEPs were identified and labelled according to the American Electroencephalographic Society guidelines [11]. Peak latencies and peak-to-peak amplitudes of all components were measured but only the most stable components were used for statistical comparisons (III, IV, and V for VEPs; N20 and P22 for SEPs). Pathological responses were considered when latency value was more than 3 SD from the mean value of controls.

2.4. Statistical Analysis. Means and limits were calculated adopting tolerance limit of 99% with a confidence of 95%. To obtain normative data for VEPs and SEPs, the distribution of observed values was previously examined by the Shapiro-Will's goodness of fit for skewness and/or kurtosis. Statistical analysis was performed by software (STATISTICA 9.1-StatSoft, Inc., OK, USA), using ANOVA with post hoc comparison (Bonferroni test for multiple comparisons), nonparametric tests, and χ^2 with Yates correction when appropriate. Statistical significance was defined as $P < 0.05$.

3. Results

DMC showed mean latency of all VEP components significantly increased compared with controls at the age of two months and the forth (P2) component was still delayed at the age of three years (Table 1). No differences were found for VEP amplitudes.

The P22 component of SEP was significantly delayed compared with controls (Table 2) whereas no differences were found for N20 latency and for amplitudes of both waves. Pathological responses of VEPs and SEPs were found in 3 cases (19%).

4. Discussion

At the age of two months, type 1 diabetic mothers' offspring showed that all VEP latencies were increased than controls, and this finding is still evident at the age of three years for the fourth VEP component (P2). The cortical origin of this wave is well documented by multichannel scalp recordings and clinical studies [12, 13]. According to the hypothesis of subcortical-cortical development, during the first postnatal weeks, the visual system is under the prevailing control of subcortical centres, afterwards the primary geniculocalcarine cortical system assumes the major control, due to synaptogenesis and myelination [14]. Visual processes continue to mature during childhood and these changes may be well documented by VEP recording, as a decrease in latency, an increase in amplitude, and a development of the waveform [15, 16]. Data of VEPs in our sample suggest the occurrence of adverse effects of maternal diabetes on visual system especially at cortical level; these effects are not limited to the neonatal period but appear to be persistent, at least in the first 3 years of age.

Regarding SEPs, we found a delay in the P22 but not in the N20 component. These waves represent the initial response of the primary somatosensory cortex to stimulation of the upper extremity. Clinical and experimental data suggest differential generators for N20 and P22 (N20 generator in the postcentral gyrus-S1, Brodmann area 3b; P22 generator assigned either to the area 4 in the precentral gyrus either to area 1 in the postcentral gyrus) [17, 18]. Our data are consistent with these observations, and they support the possibility of separate functional testing of Brodmann areas, as recently reported [19]. Moreover, the delay of the P22 component in the offspring of diabetic mothers suggests that effects of metabolic imbalance during the intrauterine life are not confined to the visual system but act more diffusely.

All these data confirm previous studies on the adverse effects of maternal diabetes on offspring's brain development [20–23]. Cortical dysfunctions could be related to poor metabolic control, as suggested by clinical and experimental studies, with subtle negative effects on the offspring's CNS [24–26].

Finally, in the present study we found pathological responses of both VEPs and SEPs in 3 children, currently asymptomatic. Central nervous system degeneration is a well-known long-term complication in diabetic patients,

Table 1: Comparison between DMC and controls for VEP latencies.

Age	VEP components	DMC Latency (ms)			Controls Latency (ms)			P^*
		Mean ± SD	Confidence interval −99%	Confidence interval +99%	Mean ± SD	Confidence interval −99%	Confidence interval +99%	
2 months	Right (O2)							
	III	136.2 ± 29.9	114.2	158.2	109.0 ± 31.1	89.8	129.3	<0.01
	IV	190.9 ± 33.4	166.3	215.5	156.6 ± 30.8	137.4	175.7	<0.01
	V	275.8 ± 50.1	238.9	312.8	223.6 ± 47.1	194.4	252.9	<0.01
	Left (O1)							
	III	132.3 ± 29.6	110.5	154.1	108.4 ± 31.6	88.7	128.0	<0.05
	IV	187.8 ± 37.1	160.4	215.1	156.7 ± 31.7	137.0	176.4	<0.01
	V	267.2 ± 47.3	232.3	302.1	220.1 ± 50.0	189.0	251.1	<0.01
3 years	Right (O2)							
	III	71.53 ± 15.2	62.3	78.4	67.63 ± 9.0	61.5	74.0	NS
	IV	105.53 ± 13.1	98.7	114.5	99.96 ± 8.8	93.8	106.1	<0.05
	V	149.03 ± 36.2	133.2	174.2	149.05 ± 22.5	133.5	165.5	NS
	Left (O1)							
	III	74.47 ± 13.4	65.8	81.3	68.02 ± 9.7	62.0	74.0	NS
	IV	106.13 ± 14.0	98.4	116.0	98.69 ± 10.2	91.8	105.6	<0.05
	V	151.12 ± 43.3	135.9	180.1	150.0 ± 22.4	132.8	167.3	NS

* ANOVA (post hoc comparison with correction for multiple comparisons—Bonferroni test).

Table 2: Comparison between DMC and controls for SEP latencies.

SEP components	DMC Latency (ms)			Controls Latency (ms)			P^*
	Mean ± SD	Confidence interval −99%	Confidence interval +99%	Mean ± SD	Confidence interval −99%	Confidence interval +99%	
N20	18.11 ± 1.98	14.20	22.02	17.55 ± 1.42	13.87	21.23	NS
P22	24.86 ± 2.38	15.22	34.50	21.71 ± 1.57	14.12	29.30	<0.001

* ANOVA (post hoc comparison with correction for multiple comparisons—Bonferroni test).

and it is possible to reveal this involvement in an early asymptomatic stage by using evoked potentials [27, 28]. Neuropsychological deficits have been noted in children with type 1 diabetes [29], suggesting the occurrence of subtle negative effects related to diabetes on cognitive development in school-age children. Recurrent episodes of hypoglycaemia as well extended periods of hyperglycemia have been reported as possible causes of brain dysfunction in poorly controlled diabetic patients [30, 31]. Moreover, the recent concept of developmental programming postulates long-term detrimental effects on adult health due to nutritional imprinting during critical developmental periods; according to this finding, alterations and/or modifications in nutrients supply during fetal and neonatal life may be associated with abnormal growth patterns, resulting in the development of future diseases [32–36]. To clarify the clinical significance of the abnormal evoked responses found in our sample, we are carrying out a clinical and neurophysiologic followup of these children.

5. Conclusions

Type 1 diabetes mothers' offspring showed a significant delay of cortical evoked responses to both visual and somatosensory stimulation compared with controls. These results do not seem to be transient, since the delay of VEP found in the neonatal period is still present at the age of three years. The recording of evoked potentials may be proposed as a useful tool of investigation since it is particularly sensitive to highlight functional abnormalities of the CNS.

References

[1] R. J. Ellingson, "Development of visual evoked potentials and photic driving responses in normal full term, low risk premature, and trisomy-21 infants during the first year of life," *Electroencephalography and Clinical Neurophysiology*, vol. 63, no. 4, pp. 309–316, 1986.

[2] S. Tsuneishi and P. Casaer, "Stepwise decrease in VEP latencies and the process of myelination in the human visual pathway," *Brain and Development*, vol. 19, no. 8, pp. 547–551, 1997.

[3] A. M. Halliday and J. Musshin, "The visual evoked potential in neuroophtalmology," *International Ophthalmology Clinics*, vol. 20, pp. 155–183, 1980.

[4] M. K. G. L. Lovestam Adrian, G. Andersson, and S. Andreasson, "Patients with diabetic retinopathy and neuropathy showed lower amplitudes on the multifocal VEP than diabetic patients with the same level of retinopathy but no neuropathy," *Investigative Ophthalmology & Visual Science*, vol. 48, pp. 5010–5158, 2007.

[5] O. Ziegler, B. Guerci, M. Algan, P. Lonchamp, M. Weber, and P. Drouin, "Improved visual evoked potential latencies in poorly controlled diabetic patients after short-term strict metabolic control," *Diabetes Care*, vol. 17, no. 10, pp. 1141–1147, 1994.

[6] T. Das, S. Kundu, A. K. Mazumdar, and S. C. Mukhopadhyay, "Studies on central nervous system function in diabetes mellitus," *Journal of the Indian Medical Association*, vol. 99, no. 2, pp. 84–89, 2001.

[7] M. Brinciotti, "Effects of chronic high serum levels of phenobarbital on evoked potentials in epileptic children," *Electroencephalography and Clinical Neurophysiology*, vol. 92, pp. 11–16, 1994.

[8] C. Till, J. F. Rovet, G. Koren, and C. A. Westall, "Assessment of visual functions following prenatal exposure to organic solvents," *NeuroToxicology*, vol. 24, no. 4-5, pp. 725–731, 2003.

[9] M. Brinciotti, M. Matricardi, A. Colatrella, F. Torcia, F. Fallucca, and A. Napoli, "Effects of maternal diabetes on visual evoked potentials and early psychomotor development of the offspring," *Diabetes Care*, vol. 30, no. 12, p. e128, 2007.

[10] M. Brinciotti, M. Matricardi, C. Colatrella, F. Torcia, F. Fallucca, and A. Napoli, "Visual evoked potentials in infants of diabetic mothers: relations to clinical and metabolic status during pregnancy and delivery," *Clinical Neurophysiology*, vol. 120, no. 3, pp. 563–568, 2009.

[11] "American Electroencephalographic Society guidelines in electroencephalography, evoked potentials, and polysomnography," *Journal of Clinical Neurophysiology*, vol. 11, pp. 1–147, 1994.

[12] F. Di Russo, A. Martínez, M. I. Sereno, S. Pitzalis, and S. A. Hillyard, "Cortical sources of the early components of the visual evoked potential," *Human Brain Mapping*, vol. 15, no. 2, pp. 95–111, 2002.

[13] S. Tobimatsu and G. G. Celesia, "Studies of human visual pathophysiology with visual evoked potentials," *Clinical Neurophysiology*, vol. 117, no. 7, pp. 1414–1433, 2006.

[14] T. L. Hickey, "Postnatal development of the human lateral geniculate nucleus: relationship to a critical period for the visual syste," *Science*, vol. 198, no. 4319, pp. 836–838, 1977.

[15] M. J. Taylor and D. L. McCulloch, "Visual evoked potentials in infants and children," *Journal of Clinical Neurophysiology*, vol. 9, no. 3, pp. 357–372, 1992.

[16] J. Brecelj, "From immature to mature pattern ERG and VEP," *Documenta Ophthalmologica*, vol. 107, no. 3, pp. 215–224, 2003.

[17] J. E. Desmedt, T. H. Nguyen, and M. Bourguet, "Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses," *Electroencephalography and Clinical Neurophysiology*, vol. 68, no. 1, pp. 1–19, 1987.

[18] T. Allison, G. McCarthy, C. C. Wood, and S. J. Jones, "Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve: a review of scalp and intracranial recordings," *Brain*, vol. 114, no. 6, pp. 2465–2503, 1991.

[19] U. Baumgärtner, H. Vogel, S. Ohara, R. D. Treede, and F. A. Lenz, "Dipole source analyses of early median nerve SEP components obtained from subdural grid recordings," *Journal of Neurophysiology*, vol. 104, no. 6, pp. 3029–3041, 2010.

[20] T. Rizzo, B. E. Metzger, W. J. Burns, and K. Burns, "Correlations between antepartum maternal metabolism and intelligence of offspring," *The New England Journal of Medicine*, vol. 325, no. 13, pp. 911–916, 1991.

[21] C. J. Sells, N. M. Robinson, Z. Brown, and R. H. Knopp, "Long-term development follow-up of infants of diabetic mothers," *Journal of Pediatrics*, vol. 125, no. 1, pp. S9–S17, 1994.

[22] B. L. Silverman, T. A. Rizzo, N. H. Cho, and B. E. Metzger, "Long-term effects of the intrauterine environment: the northwestern university diabetes in pregnancy center," *Diabetes Care*, vol. 21, supplement 2, pp. B142–B149, 1998.

[23] T. Rizzo, E. Ogata, S. Dooley, B. Metzger, and N. Cho, "Perinatal complications and cognitive development in 2- to 5-year-old children of diabetic mothers," *American Journal of Obstetrics and Gynecology*, vol. 171, pp. 706–713, 1994.

[24] A. J. Emerick, M. P. Richards, G. L. Kartje, E. J. Neafsey, and E. B. Stubbs, "Experimental diabetes attenuates cerebral cortical-evoked forelimb motor responses," *Diabetes*, vol. 54, no. 9, pp. 2764–2771, 2005.

[25] M. Kowalczyk, G. IRcha, M. Zawodniak-Szalapska, K. Cypryk, and J. Wilczynski, "Psychomotor development in the children of mothers with type 1 diabetes mellitus or gestational diabetes mellitus," *Journal of Pediatric Endocrinology & Metabolism*, vol. 15, pp. 277–281, 2002.

[26] C. A. Nelson, S. S. Wewerka, A. J. Borscheid, R. A. DeRegnier, and M. K. Georgieff, "Electrophysiologic evidence of impaired cross-modal recognition memory in 8-month-old infants of diabetic mothers," *Journal of Pediatrics*, vol. 142, no. 5, pp. 575–582, 2003.

[27] R. A. DeRegnier, J. D. Long, M. K. Georgieff, and C. A. Nelson, "Using event-related potentials to study perinatal nutrition and brain development in infants of diabetic mothers," *Developmental Neuropsychology*, vol. 31, no. 3, pp. 379–396, 2007.

[28] N. Uzun, D. Uluduz, S. Mikla, and A. Aydin, "Evaluation of asymptomatic central neuropathy in type I diabetes mellitus," *Electromyography and Clinical Neurophysiology*, vol. 46, no. 3, pp. 131–137, 2006.

[29] A. M. McCarthy, S. Lindgren, M. A. Mengeling, E. Tsalikian, and J. Engvall, "Factors associated with academic achievement in children with type 1 diabetes," *Diabetes Care*, vol. 26, no. 1, pp. 112–117, 2003.

[30] E. J. Austin and I. J. Deary, "Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data," *Diabetes Care*, vol. 22, no. 8, pp. 1273–1277, 1999.

[31] Y. D. Reijmer, E. van den Berg, C. Ruis, L. J. Kappelle, and G. J. Biessels, "Cognitive dysfunction in patients with type 2 diabetes," *Diabetes/Metabolism Research and Reviews*, vol. 26, no. 7, pp. 507–519, 2010.

[32] M. E. Symonds, S. P. Sebert, M. A. Hyatt, and H. Budge, "Nutritional programming of the metabolic syndrome," *Nature Reviews Endocrinology*, vol. 5, no. 11, pp. 604–610, 2009.

[33] C. Lau, J. M. Rogers, M. Desai, and M. G. Ross, "Fetal programming of adult disease: implications for prenatal care," *Obstetrics & Gynecology*, vol. 117, no. 4, pp. 978–985, 2011.

[34] M. J. Warner and S. E. Ozanne, "Mechanisms involved in the developmental programming of adulthood disease," *Biochemical Journal*, vol. 427, no. 3, pp. 333–347, 2010.

[35] C. Maric, "Mechanisms of fetal programming of adult hypertension: role of sex hormones," *Hypertension*, vol. 50, no. 4, pp. 605–606, 2007.

[36] N. B. Ojeda, D. Grigore, and B. T. Alexander, "Developmental programming of hypertension: insight from animal models of nutritional manipulation," *Hypertension*, vol. 52, no. 1, pp. 44–50, 2008.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 218598, 12 pages
doi:10.1155/2011/218598

Review Article

Maternal Diabetes in Pregnancy: Early and Long-Term Outcomes on the Offspring and the Concept of "Metabolic Memory"

Akadiri Yessoufou[1, 2] and Kabirou Moutairou[2]

[1] *Centre for Integrative Genomics, University of Lausanne, Genopode Building, 5è Etage, 1015 Lausanne, Switzerland*
[2] *Laboratory of Cell Biology and Physiology, Department of Biochemistry and Cellular Biology, Faculty of Sciences and Techniques and Institute of Biomedical and Applied Sciences (ISBA), University of Abomey-Calavi, 01 BP 918 Cotonou, Benin*

Correspondence should be addressed to Akadiri Yessoufou, yeskad2001@yahoo.fr

Received 12 May 2011; Revised 18 August 2011; Accepted 7 September 2011

Academic Editor: Susan Ozanne

The adverse outcomes on the offspring from maternal diabetes in pregnancy are substantially documented. In this paper, we report main knowledge on impacts of maternal diabetes on early and long-term health of the offspring, with specific comments on maternal obesity. The main adverse outcome on progenies from pregnancy complicated with maternal diabetes appears to be macrosomia, as it is commonly known that intrauterine exposure to hyperglycemia increases the risk and programs the offspring to develop diabetes and/or obesity at adulthood. This "fetal programming", due to intrauterine diabetic milieu, is termed as "*metabolic memory*". In gestational diabetes as well as in macrosomia, the complications include metabolic abnormalities, degraded antioxidant status, disrupted immune system and potential metabolic syndrome in adult offspring. Furthermore, there is evidence that maternal obesity may also increase the risk of obesity and diabetes in offspring. However, women with GDM possibly exhibit greater macrosomia than obese women. Obesity and diabetes in pregnancy have independent and additive effects on obstetric complications, and both require proper management. Management of gestational diabetes mellitus and maternal obesity is essential for maternal and offspring's good health. Increasing physical activity, preventing gestational weight gain, and having some qualitative nutritional habits may be beneficial during both the pregnancy and offspring's future life.

1. Introduction

Compelling evidence exists suggesting that exposure to an adverse fetal and/or early postnatal environment may enhance susceptibility to a number of chronic diseases in the future life of offspring. Gestational diabetes mellitus (GDM) and obesity are both complications which occur during pregnancy and substantially influence the development of offspring during fetal life and postnatally. Indeed, fetuses from mothers with gestational diabetes are at high risk of developing fetal macrosomia [1, 2]. Although most of the women with GDM return to normal glucose tolerance after delivery, they have an increased risk of developing diabetes, mainly type 2 diabetes mellitus [3]. Offspring of women with gestational diabetes are prone to adverse side effects such as macrosomia, which is strongly associated with fetal death, prematurity, birth trauma, and respiratory distress syndrome [4]. These offspring have a high risk of developing obesity, impaired glucose tolerance, and type 2 diabetes in adulthood [4]. The concern of most researchers, during the last decade, is to explore the physiopathology of the relationship between the health conditions of offspring born from pregnancy complicated with diabetes. Our team has evidence in many experimental studies, in which we have observed a high incidence of macrosomia in the litters of diabetic animals [1]. The macrosomic (large-sized) offspring of diabetic animals exhibit many physiological disorders associated with metabolic syndrome. However, the mechanisms by which excess maternal weight and/or diabetes during pregnancy may lead to disease in the offspring at childhood and adulthood are not fully understood. The aim of this paper is to summarize new knowledge on the various physiological and pathophysiological aspects of early and long-term offspring outcomes of maternal diabetes during pregnancy. Specific

comments on impacts of maternal obesity on offspring health are also evoked, since the impact of obesity and GDM on fetus and mother often becomes circular, as the majority of mothers with GDM are obese and a significant proportion of those who are obese have GDM [5].

2. Gestational Diabetes: Meaning and Diagnosis

Depending on the diagnostic and screening criteria, it has been observed that prevalence of GDM ranged from 1.3% to 19.9% [6]. In obesity context, a meta-analysis [7] showed that the risk of developing GDM was 2.14-fold higher in overweight pregnant women, 3.56-fold higher in obese pregnant women, and 8.56-fold higher in severely obese pregnant women compared to pregnant women with normal weight. This analysis prompted the International Association of Diabetes and Pregnancy Study Groups (IADPSG) to propose new criteria for the diagnosis of GDM, based on the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study [8]. The criteria use a 75-g oral glucose tolerance test (OGTT) without prior glucose challenge and diagnose GDM when the fasting glucose is $\geq$5.1 mmol/L and/or when the 1-h postload glucose is $\geq$10.0 mmol/L and/or when the 2-h postload glucose is $\geq$8.5 mmol/L.

With the greater number of pregnancies complicated with diabetes, it will be interesting to monitor the long-term impacts of maternal diabetes in pregnancy on the health condition of offspring.

3. Macrosomia: The Main Adverse Outcome of Diabetes in Pregnancy

3.1. Studies in Humans. Maternal diabetes is characterized by an increased placental transport of glucose and other nutrients from the mother to the fetus, resulting in macrosomia [9]. Convincing studies have shown that either preexisting diabetes (type 1 and type 2 diabetes) or GDM (diabetes only during pregnancy) are associated with macrosomia [10–17]. Indeed, epidemiological and clinical studies have shown that maternal type 1 diabetes during pregnancy is an important risk factor for fetal overnutrition and macrosomia and for the development of obesity and diabetes in offspring [10, 11]. Type 2 diabetes and GDM are also associated with macrosomia and diabetes in the progenies [12, 13]. The risk of diabetes in offspring of type 2 diabetes genitors is significantly higher when the mother rather than the father is diabetic [12]. Moreover, the risk of insulin resistance is higher in children of mothers with GDM (diabetes only during pregnancy) than in children from mothers developing diabetes after pregnancy [14]. Macrosomia, the most commonly reported effect of maternal diabetes in newborns [15], is usually defined in humans as birth weight above either 4 kg or birth weight above the 95th percentile of the gestational age. In human studies, 43% of GDM patients had a macrosomia history [16, 17]. In total, 75% of the diabetic mothers had an episiotomy during delivery. Babies from GDM patients whose birth weight was 2.0 SD greater than the mean birth weight of control infants were considered as macrosomic babies.

3.2. Animal Models. In animal studies, the model reported here concerns streptozotocin-induced type 1 diabetic pregnancy which also leads to macrosomia in offspring [18, 19]. Several modes exist for inducing diabetes with streptozotocin. The group of Van Assche has exhaustively investigated the consequences of experimental maternal diabetes induced by streptozotocin on fetus and adult progeny [9, 20].

The streptozotocin, when administered at a high single dose, induces diabetes by the direct toxic effects on pancreatic β-islet cells [9]. The fetus is confronted with severe intrauterine hyperglycemia which induces fetal islet hypertrophy and β-cell hyperactivity and may result in early hyperinsulinemia [20]. This overstimulation of fetal β cells limits their adaptation, and they become depleted of insulin granules [20], and incapable to secrete insulin [9]. β-cell exhaustion results in fetal hypoinsulinemia. Hypoinsulinemia and a reduced number of insulin receptors on target cells lead to a reduction in fetal glucose uptake [9]. The growth of fetal protein mass is suppressed, and fetal protein synthesis is consistently low, leading to fetal microsomia [9]. Postnatal development is retarded, and these offspring remain small at adulthood; however, they develop insulin resistance [9, 21].

However, streptozotocin, administered at low doses during 5 consecutive days, induces mild type 1 diabetes, following a T-lymphocyte-dependent process, an autoimmune destruction of pancreatic β cells, mediated by both $CD4^+$ and $CD8^+$ T cells [22, 23]. The administration of low doses of streptozotocin to rodents represents a good model of diabetes development for several reasons [22, 24, 25]. The intrauterine mild hyperglycemia also induces fetal hyperinsulinemia with hypertrophy of the endocrine pancreas and hyperplasia of the β cells [20]. Animals with perinatal hyperinsulinemia display an impaired glucose tolerance at adulthood only under high glucose [9].

A model of diabetic pregnancy and macrosomia through administration to pregnant *Wistar* rats of five low doses of streptozotocin starting on day 5 of gestation is also well established [1, 26, 27]. Pups from diabetic pregnant rats whose birth weights were 1.7 SD greater than the mean birth weight of the control pups were considered as macrosomic offspring [1, 26, 27]. As far as the model is concerned, it is important to note that maternal streptozotocin administration before pregnancy affects fertility and impairs embryo development during preimplantation period [28]. However, the induction of diabetes by streptozotocin injection on day 5 of gestation [1] has no effect on embryo development [19]. We observed that 62% to 75% of pups born to diabetic pregnant rats were macrosomic at birth [1, 27, 29]. These macrosomic (large-sized) offspring of diabetic dams were hyperglycemic at birth and maintained an accelerated weight gain until the monitoring time of 12 weeks [26, 30], compared to offspring of control rats.

Furthermore, maternal hyperlipidemia during diabetic pregnancy [1] has been shown to be one of the predisposing factors of macrosomia in offspring. In fact, high levels of

triglyceride in maternal circulation of diabetic rats may create a steep concentration gradient across placenta, which accelerates their transport and deposition in fetal tissues [31]. In macrosomic offspring, this hypertriglyceridemia persists with age and is linked to the development of insulin resistance and hyperlipogenesis [32]. Besides, maternal hyperglycemia also leads to fetal hyperglycemia, which stimulates pancreatic islet cells and induces fetal hyperinsulinemia [26, 27, 32]. The intrauterine hyperinsulinemic state results in an increase of fat synthesis and body size [33]. The increase in body weight is a consequence of an increase in adipose tissue weight and lipid content at all ages.

Thus, macrosomia appears as the main outcome of maternal diabetes, and both pathologies are associated with several metabolic disorders, implicating lipid metabolism and antioxidant status.

4. Main Metabolic Consequences during Maternal Diabetes and Macrosomia

4.1. Lipid Metabolism Is Altered during Maternal Diabetes and Macrosomia

4.1.1. Animal Models. As far as lipid metabolism is concerned, experimental diabetes has been shown to impair maternal and fetal lipid metabolism [31, 34]. In experimental models, type 1 diabetic pregnancy in rats is associated with a significant increase in serum and hepatic triglyceride (TG) and total cholesterol (TC) [1, 27, 29]. Macrosomic and obese offspring of diabetic rats exhibit high adipose tissue weight, together with high adipose tissue lipid contents [27], and they show high serum and liver lipid levels [1, 26, 29, 30]. The hypertriglyceridemia and hypercholesterolemia, common features of experimental obesity, are the direct consequences of hyperinsulinemia and hepatic hyperlipogenesis [35, 36]. The major findings on fatty acid composition in adult macrosomic offspring were parallel with those of their diabetic mothers. Diabetic pregnancy causes a profound decline in plasma arachidonic acid (AA, $C_{20}:4$n-6) and an increase in linoleic acid (LA, $C_{18}:2$n-6) concentrations in rats and in their macrosomic and obese offspring [1, 29], and this may be due to an impaired activity of Δ5- and Δ6-desaturases enzyme [37]. Diabetes-induced low concentration of plasma AA may have a critical role in maintaining the appropriate mass and function of islet β cells by influencing rates of cell proliferation and insulin secretion [38, 39].

4.1.2. Studies in Humans. Human studies revealed in GDM patients that diabetes appeared at second or third trimester of pregnancy [16, 17] as determined by oral glucose tolerance test according to the World Health Organization criteria. GDM patients were hyperglycemic and hyperinsulinemic at the diagnosis of the disease [16, 17], reflecting a decrease in insulin sensitivity in diabetic pregnant women [40]. Several studies including ours have shown that, when compared with normal values, GDM mothers as well as control mothers exhibited hypertriglyceridemia and hypercholesterolemia, throughout pregnancy, and no significant difference exists between healthy and diabetic women [16, 17, 40–42]. However, macrosomic babies showed high levels of serum triglyceride and total and free cholesterol compared with control infants [16, 17].

Thus, maternal diabetes and macrosomia induce an alteration in lipid metabolism.

4.2. Antioxidant Status Is Affected during Maternal Diabetes and Macrosomia. One of the earliest abnormalities observed in diabetic subjects is the involvement of oxidative stress [43]. Moreover, fetuses from mothers with gestational diabetes are at increased risk of developing platelet hyperaggregability and oxidative stress [2]. High blood glucose levels in these newborns induce oxidative stress [2], which, in turn, induces the production of highly reactive oxygen radicals, being toxic to cells, particularly to the plasma membranes where these radicals interact with the lipid bilayer. Endogenous antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase, and reductase) and vitamins are responsible for the detoxification of deleterious oxygen radicals [44]. In diabetes as well as in macrosomia, protein glycation and glucose auto-oxidation may generate free radicals, which, in turn, catalyze lipid peroxidation [45]. Moreover, disturbances in the antioxidant defense system in diabetes and macrosomia have been reported as follows: alteration in antioxidant enzymes activities [46], impaired glutathione metabolism [47], and decreased ascorbic acid levels [48].

4.2.1. Studies in Humans. In human studies [17], we assess the serum antioxidant status through antiradical resistance (KRL; Kirial International SA, Couternon, France) and levels of vitamin A, C, and E and activity of superoxide dismutase (SOD). GDM as well as macrosomia induce an altered total serum antioxidant defense status [17]. Indeed, gestational diabetic women exhibit decreased levels of vitamin E and enhanced concentrations of vitamin C without any changes in vitamin A. Macrosomia also induces decreased levels of vitamin E. GDM and macrosomia are also associated with impaired SOD activities and enhanced levels of serum thiobarbituric acid-reactive substances (TBARSs), suggesting an increased oxidative stress [17].

4.2.2. Animal Models. In experimental model [1], type 1 diabetic pregnancy and macrosomia lead to a significant decrease in the plasma total antioxidant status as measured by diminished plasma oxygen radical absorbance capacity (ORAC) in diabetic pregnant rats and their macrosomic pups [1]. We have also observed increased plasma TBARS, decreased erythrocyte superoxide dismutase and glutathione peroxidase activities in diabetic rats and their macrosomic offspring, and diminished vitamin A levels in diabetic dams and vitamin C concentrations in macrosomic pups. Several authors have also shown diminished antioxidant enzyme activities and vitamin levels in streptozotocin-induced diabetic rats [46–48].

To sum up, in animals as well as in humans, maternal diabetes and macrosomia are associated with altered antioxidant status [1, 17].

5. Is Neonatal Obesity Programmed during *In Utero* Life? New Concept of a "*Metabolic Memory*"

The hypothesis on fetal origin suggests that the fetal malnutrition, which, during pregnancy, induces disruption in fetal growth and thinness at birth, programs latter type 2 diabetes and metabolic syndrome [49]. At critical and delicate period of fetal development, the process by which a stimulus induces long-term impacts on fetus, previously described and established as "*fetal programming*" by Hales and Barker [49], is termed as new concept of "*metabolic memory*." In the same line, all the observed metabolic abnormalities among gestational diabetic women create an *in-utero* environment around the fetus which programs him to diseases during his adulthood [49, 50]. This *in utero programming* seems to create a kind of "*metabolic memory*," since physiological anomalies of gestational period are responsible for the onset of diseases in offspring at adulthood, such as type 2 diabetes and obesity associated with metabolic syndrome. It is noteworthy that several alterations in carbohydrate and lipid metabolism, observed in infants of diabetic mothers at birth, also persist postnatally. As an example of this phenomenon of metabolic memory, we can mention a study of Palinski and Napoli [51] who demonstrated that maternal hypercholesterolemia during pregnancy is associated with greatly increased fatty streak formation in human fetal arteries and accelerated progression of atherosclerosis during childhood [51]. A good correlation exists between maternal and fetal plasma cholesterol levels in 5-6-month-old human fetuses [52, 53]. Moreover, maternal hyperglycemia has been shown to lead to fetal hyperglycemia which stimulates fetal pancreatic islet cells to produce fetal hyperinsulinemia [54]. The ability of fetal hyperinsulinemia to increase the availability of farnesylated p21-Ras may represent one of mechanisms of the growth-promoting action of insulin during fetal development [55].

Another example of *metabolic memory* is revealed by Franke et al. [56] who have shown that diabetic pregnancy in rats alters the differentiation of hypothalamic neurons of newborns (Figure 1). The alterations of hypothalamic neurons may be avoided by normalizing the glycemia among diabetic pregnant rats [56]. The increased levels of neuropeptide-Y (Figure 1) in offspring of hyperglycemic rats may be explained by a defected *programming* of the hypothalamic neurons, due to intrauterine environment of gestational diabetic milieu [56]. These alterations may increase the risk of trend in high food taking, overweight, obesity, and diabetogenic status in offspring at adulthood (Figure 1). All these observations prove an *in utero programming* of metabolic syndrome in offspring born to maternal diabetes.

6. Modulation of Insulin Resistance and Inflammation during Maternal Diabetes and Macrosomia

Gestational diabetes and obesity are two pathologies associated with insulin resistance and inflammation which are profoundly modulated by adipokines and cytokines [16]. Obesity is associated with high adiposity and hyperlipidemia [57]. Moreover, low-grade inflammation has been reported to be a link between insulin resistance, obesity, and type 2 diabetes [57]. Thus, it appears that inflammation may modulate insulin resistance in GDM.

6.1. Studies in Humans. There is evidence that hypoadiponectinemia is associated with pathogenesis of GDM and macrosomia [58]. Adipokines and cytokines, through their ability to interfere with insulin signaling, have been implicated in insulin resistance [59]. Adiponectin, a physiologically active polypeptide hormone derived from adipose tissue, exhibits insulin-sensitizing, antiatherogenic, and anti-inflammatory properties [60].

In human studies, we and other investigators have shown that women with GDM, compared with non-diabetic women, exhibited a decreased concentration of adiponectin (anti-inflammatory agent) [16, 61], concomitant with an increased concentration of TNF-α and IL-6 (pro-inflammatory cytokines) [16]. Is there any physiological crosstalk between the high levels of TNF-α and the low adiponectin concentrations in women with GDM? It has been shown that adiponectin and TNF-α produce opposite effects on insulin signaling, with inhibiting action of TNF-α [62] and increasing action of adiponectin [63] on tyrosine phosphorylation of the insulin receptor. Besides, it is also possible that TNF-α may be responsible for lowered synthesis of adiponectin in GDM subjects, as suggested by Lihn et al. [64] that TNF-α and IL-6 downregulate adiponectin expression (Figure 1). Regarding the long-term effect on the offspring of gestational diabetic women, it is important to mention the study of Tsai et al. [65], who have demonstrated that decreased maternal adiponectin concentration and insulin sensitivity may increase the risk of fetal overgrowth in women suffering from GDM. However, our study revealed that concentrations of TNF-α, IL-6, adiponectin, and leptin are decreased in macrosomic babies compared to control infants [16]. Furthermore, IL-6 has been shown to be one of the mediators of hyperinsulinemic state [66], 10%−35% of the body's basal circulating IL-6 is derived from adipose tissue, and a positive correlation has been found between insulin resistance and circulating IL-6 [57].

Leptin is not only produced by the placenta but principally by the adipocytes, secreted into the bloodstream [67], and involved in weight gain regulation and lipid metabolism. Leptin is an appetite-suppressant agent, and it exerts its effects by interacting with neuropeptide-Y in the hypothalamus (Figure 1) [68]. Contradictory results have been reported about leptin secretion during GDM and macrosomia. GDM is either associated with high levels of leptin [69], no change [70], or reduced level of leptin

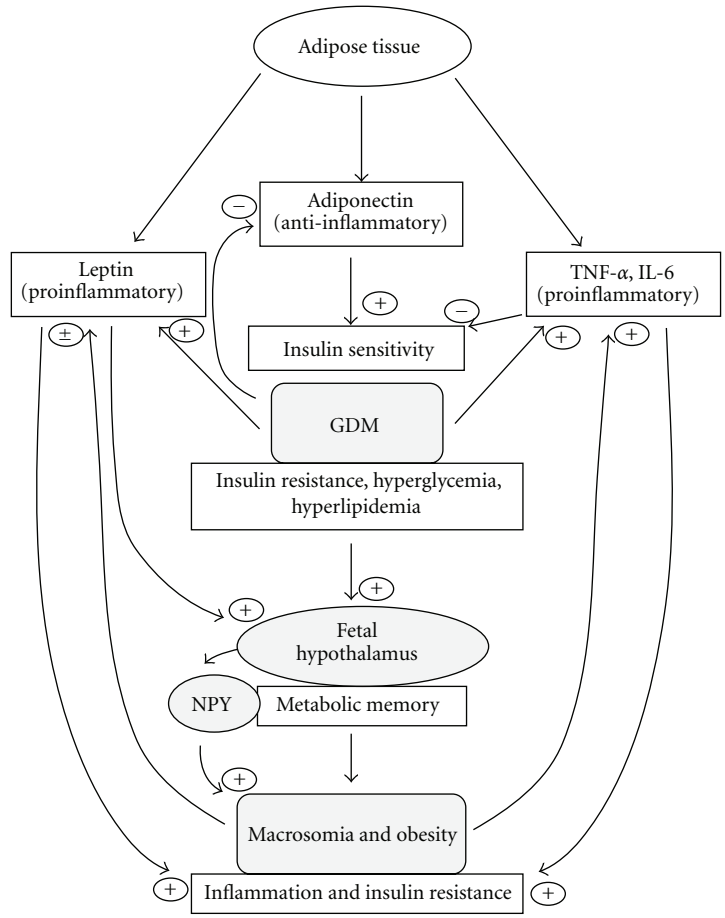


Figure 1: In GDM, adipose tissue secretes low adiponectin (anti-inflammatory and positive stimulator of insulin sensitizing) and high TNF-α and IL-6 which contribute to inflammatory state and insulin resistance in diabetic pregnancy as well as in macrosomia. Leptin, being pro-inflammatory, is highly produced by adipose tissue during diabetic pregnancy and insulin resistance (experimental study [75]) and implicated in the pathogenesis of weight gain in macrosomic babies. Leptin may exert its effects by interacting with neuropeptide-Y in the hypothalamus. The intrauterine hyperglycemia may act on the fetal hypothalamus and create a kind of "*metabolic memory*" which programs obesity and metabolic syndrome in the offspring during adulthood. (+) positive regulation (−) negative regulation. NPY, neuropeptide-Y.

[71]. Our previous reports have shown high leptin level in mothers with GDM and reduced level of leptin in their macrosomic infants [16]. This discrepancy could be a result of the difference in the time of maternal blood collection (i.e., gestational age). However, elevated leptin concentrations during diabetic pregnancy may be due to its secretion by adipocytes in presence of elevated estrogen [72] and by placenta [73]. In fact, leptin, acting as a signal for sufficient energy supply, is persistently increased in women with GDM after delivery and associated with hyperglycemia and insulin resistance [69]. Hence, leptin, as a pro-inflammatory factor, may contribute to the inflammatory state during gestational diabetes. In contrast, low leptin level in macrosomic babies may contribute to the weight gain, since leptin-deficient rodents [68] and human [74] have been shown to develop obesity.

6.2. Animal Models. In order to investigate the relationship between insulin resistance and inflammation along with the obesity-related parameters such as adiponectin and leptin and pro-inflammatory markers, we have very recently undertaken a study in insulin-resistant offspring born to streptozotocin-induced diabetic pregnant mice [75]. Adiponectin and leptin expression is positively correlated with the epididymal adipose tissue mass which decreases in insulin-resistant offspring of diabetic mice [75]. Hence, reduced adiponectin contributes to insulin resistance as this adipokine, an anti-inflammatory agent, has been shown to enhance insulin sensitivity [63, 76]. Insulin resistance induces high expression of IL-6 and TNF-α mRNA in epididymal adipose tissue [75]. Adipose tissue secrete IL-6 and TNF-α during insulin resistance [77], and high levels of TNF-α and IL-6 may downregulate the expression of adiponectin [64] (Figure 1). During insulin resistance, increased IL-6 might not only diminish insulin sensitivity by suppressing insulin signal transduction but also interfere with anti-inflammatory effect of insulin, and might favour inflammation during insulin resistance [57].

All these clinical and experimental observations suggest that TNF-α and IL-6 may be involved in the pathogenesis

of insulin resistance, and there is a positive correlation between insulin resistance and inflammation in GDM and macrosomia.

7. Immune System Modulation during Maternal Diabetes and Macrosomia

There is a growing body of evidence that suggests the implication of a pathological role of immune system and inflammation in type 1 diabetes, type 2 diabetes, and GDM. Indeed, T-cell-derived cytokines are involved in the autoimmune destruction of pancreatic islet cells leading to type 1 diabetes [22] whereas type 2 diabetes is associated with a generalized activation of innate immune system, in which there is a chronic, cytokine-mediated state of low-grade inflammation [78–80]. Moreover, evidence from human and experimental models suggests that a shift between Th1 and Th2 cells may modulate the severity of type 1 diabetes [22, 41], in which Th1 cytokines are highly produced during the islet inflammatory response and may partially explain the ability of $CD4^+$ T cells to cause β-cell destruction [23]. In the nonobese diabetic (NOD) mouse, the most common animal model of human type 1 diabetes, it is observed an autoimmune destruction of pancreatic β cells, mediated by both $CD4^+$ and $CD8^+$ T cells [23].

Besides, in normal pregnancy, Th1 cytokines are downregulated, whereas Th2 cytokines are upregulated [81, 82], in animals as well as in humans. Even though the induction of type 1 diabetes is closely associated with high expression of Th1 cytokines, IFN-γ in particular [81], experimental and clinical studies reveal that, in pregnancy complicated with type 1 diabetes, Th1 cytokines are downregulated in diabetic pregnant rats and in women with GDM [16, 29]. Type 1 diabetic pregnancy in rats and GDM in women also induce increased level of IL-10, a Th2 cytokine [16, 29]. The level of IL-4 (another Th2 cytokine) is either decreased in diabetic animals [16, 83] or unchanged in GDM patients [16], due to the presence of diabetes [25]. Diminished Th1 cytokines and increased IL-10 (a Th2 cytokine) may be implicated in maintaining the pregnancy in diabetic rats and GDM patients (Figure 2). In fact, the shift of Th1/Th2 ratio to a protective Th2 phenotype during pregnancy (in animal and humans) has been shown to encourage vigorous production of antibodies which not only combat infections during pregnancy but also offer passive immunity to fetus [84]. On the other hand, the downregulated Th1 profile in diabetic pregnant animals and GDM patients (associated with successful pregnancy) may be contributed by elevated levels of reproductive hormones like hCG (human chorionic gonadotrophin) whose administration is known to diminish the production of Th1 cytokines [85].

As far as macrosomia is concerned, evidence in animals and humans reveals that macrosomia and obesity are associated with the shift of Th1/Th2 ratio to the Th1 phenotype [16, 29].

To sum up, it is interesting to note that diabetes during pregnancy in animals and human shifts the balance of Th1/Th2 cells to a protective Th2 phenotype, whereas, in macrosomic and obese offspring of diabetic dams, the Th1/Th2 balance is shifted to a pro-inflammatory Th1 phenotype (Figure 2). This upregulated Th1 profile in obese offspring may confer to these animals a potential pro-inflammatory and "diabetogenic status," as revealed by the hyperglycemia and hyperinsulinemia observed in these animals in adulthood [27]. All these observations presume the long-term effects of maternal diabetes on the health of the offspring during their adulthood.

8. Problems Associated with Obesity and Diabetes during Pregnancy

The prevalence of obesity is increasing across the world [86]. Using the WHO criteria, obesity can now be defined by three grades of severity: grade I obesity with $30 \leq \text{BMI} \leq 34.9\,\text{kg/m}^2$, grade II or severe obesity with $35 \leq \text{BMI} \leq 39.9\,\text{kg/m}^2$, and grade III or massive obesity with $\text{BMI} \geq 40\,\text{kg/m}^2$. Overweight is defined as $25 \leq \text{BMI} \leq 29.9\,\text{kg/m}^2$. People whose BMI is comprised between 18.5 and $24.9\,\text{kg/m}^2$ are considered as being normal weight (subjects with a BMI below $18.5\,\text{kg/m}^2$ are considered as being underweight).

Obesity pandemic is affecting all groups of age, including children, adolescents, young adults, and adults [87, 88]. Consequently, there are a growing number of obese women who are becoming pregnant.

To an extent, obesity epidemic is explained by the increase in availability and consumption of energy-dense foods and a reduction in physical activity. However, there are additional putative factors which may explain the entire explosion in obesity prevalence [89]. These putative contributors operate through genetic factors, reproductive behaviors, and/or the intrauterine milieu, matters of importance for those involved with obesity and diabetes in pregnancy [89].

Naturally in normal pregnancy, there is a physiological trend of insulin resistance from the second trimester. But in context of obesity, hyperinsulinemia associated with insulin resistance leads to the occurrence of GDM [90]. Moreover, it is known that obesity is linked to high adiposity and hyperlipidemia [57]; however, central fat, rather than peripheral adiposity, is more associated with insulin resistance, a predisposing factor to GDM [91, 92].

On the other hand, some investigators have recently found that maternal weight gain during pregnancy increases the offspring birth weight and the offspring's risk of obesity later in life, independently of genetic factors [93]. Similarly, Roman et al. [94] have found that maternal obesity was significantly associated with complications on the mother as well as on her baby: maternal obesity leads to the need for oral hypoglycemic agents or insulin, development of pregnancy-related hypertension, interventional delivery, and cesarean delivery. Adverse neonatal outcomes were also significantly increased including stillbirth, macrosomia, shoulder dystocia, hypoglycemia, and jaundice [94]. However, recent investigations report that macrosomia appears to be the predominant adverse outcome in cases of GDM

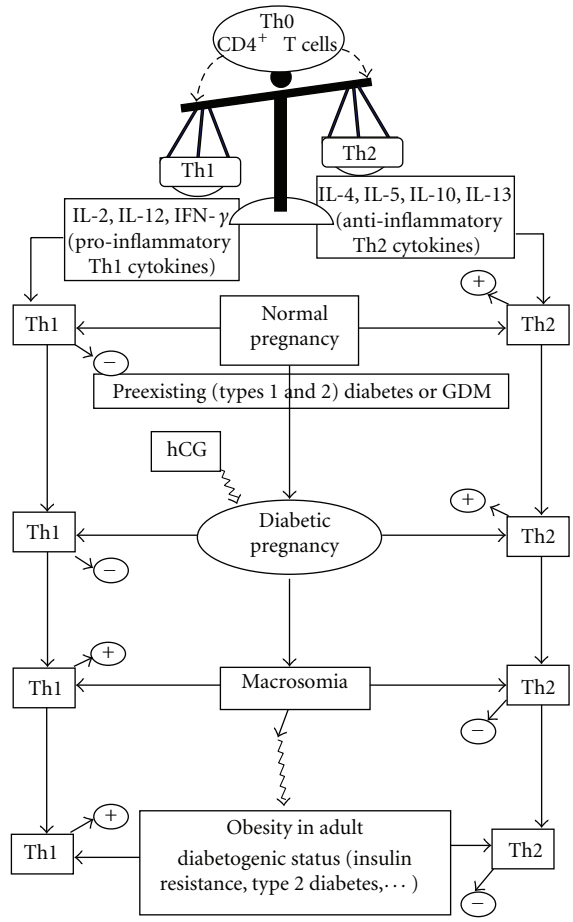


Figure 2: Naïve CD4+ T-helper (Th0) cells can be differentiated into either Th1 cells, producing pro-inflammatory cytokines (IL-2, IL-12, IFN-γ) or Th2 cells, secreting anti-inflammatory cytokines (IL-4, IL-10, IL-5, IL-13). In normal pregnancy as well as in diabetic pregnancy, the Th1/Th2 balance shifts towards a protective Th2 phenotype, whereas it shifts towards a pro-inflammatory Th1 phenotype in macrosomia as well as in obesity. Moreover, reproductive hormone like hCG may contribute to the low Th1 phenotype in diabetic pregnancy associated with the successful pregnancy. Th, T helper cells; hCG, human chorionic gonadotrophin; GDM, gestational diabetes mellitus; (+) upregulation; (−) downregulation.

[15]. Maternal obesity is an additional risk factor for complications, regardless of diabetes status [15].

To sum up, there are differences between women with GDM and obese women in pregnancy, as women with GDM possibly have greater macrosomia (even after treatment). There is clearly far greater neonatal hypoglycemia and jaundice among the offspring of women with GDM than those from obese women, but this observation and other data have to be interpreted with caution as some women may have had undiagnosed preexisting diabetes [5].

9. Management of Long-Term Impact of Maternal Obesity and Diabetes on the Offspring

Only few studies are available on pregnancy intervention for maternal diabetes and obesity during pregnancy. Weight loss may not be recommended during pregnancy [95]. However, evidence suggests that obesity's surgery-associated weight loss may be linked to less obesity in the offspring [96]. The outcomes of pregnancy complicated with maternal obesity or preexisting diabetes (mainly type 1 and type 2 diabetes, including undiagnosed type 2 diabetes) and GDM depend upon the intensity of treatment. Some studies show that treatment of GDM appears to reduce the risk of postpartum depression symptoms in the mothers [97]. Untreated GDM may be associated with a 2-fold risk of increased weight in offspring at 5–7 years [98]. Some observations show that more intensive treatment with insulin in GDM might be associated with less adiposity in offspring by 2 years 8 months [99]. However, randomized clinical studies of the management of GDM showed that treatment of GDM reduced macrosomia at birth, but did not show a reduction in BMI at the age 4-5 years [15, 100].

Nutritional strategies have also been proposed, since experimental and clinical evidence prove the beneficial effects of omega-3 fatty acid consumption during diabetes [101, 102]. Epidemiological studies have shown low incidence of inflammatory diseases in Greenland Eskimos

and Japanese people [103], and this is attributed to large consumption of cold water marine fish that contain omega-3 fatty acids [104, 105]. In experimental studies, omega-3 fatty-acid enriched diet improves the hyperlipidemia induced by diabetic pregnancy and macrosomia [1, 27, 34]. Diabetic pregnancy and macrosomia are associated with increased oxidative stress (see above), and omega-3 fatty acid consumption also restores the decreased antioxidant status of diabetic pregnant animals and their macrosomic and obese offspring [1]. Moreover, omega-3 fatty acid enriched-diet exerts beneficial effects on immune system by promoting a protective Th2 phenotype during diabetic pregnancy and macrosomia [29]. Consumption of omega-3 fatty acid also prevents long-term metabolic abnormalities associated with macrosomia [27, 34].

Furthermore, many studies have reported that dietary supplements by vitamins and minerals prevent or, at least, attenuate organic deterioration caused by an excessive oxidative stress in diabetic subjects [106, 107]. As regards recent observations that many obese women are serologically vitamin D deficient, it is now recommended in the UK that Vitamin D supplementation may be provided for all women with a prepregnancy BMI of 30 kg/m^2 [108].

10. Conclusion

Maternal diabetes or obesity during pregnancy appears to be an important risk factor for fetal obesity or macrosomia. Alterations in macrosomic infants persist postnatally and conduct to several abnormalities including the development of insulin resistance, obesity, diabetes, and metabolic syndrome at adulthood. Management of GDM and maternal obesity, including nutritional strategies, may have real improvement on maternal health and offspring in the future life.

Abbreviations

GDM: Gestational diabetes mellitus
BMI: Body mass index
CD: Cluster of differentiation
HAPO: Hyperglycemia and adverse pregnancy outcomes
hCG: human chorionic gonadotrophin
IL: Interleukin
IFN: Interferon
AA: Arachidonic acid
LA: Linoleic acid
NOD: Nonobese diabetic
OGTT: Oral glucose tolerance test
ORAC: Oxygen radical absorbance capacity
TNF: Tumor necrosis factor
Th cells: T helper cells
TBARS: Thiobarbituric acid-reactive substances
TG: Triglyceride
TC: Total cholesterol
SOD: Superoxide dismutase.

Conflict of Interests

All of the authors have nothing to declare as far as the conflict of interest is concerned.

Acknowledgments

The work performed in the authors' laboratory was supported by the French Foreign Office and the Ministry of Higher Education and Research (France) which sanctioned the contingent grants for the work. The authors also express our sincere thanks to the Islamic Development Bank (IDB) and the Office of Scholarship Programme that granted a postdoctoral fellowship to A. Yessoufou at the Centre for Integrative Genomics (University of Lausanne, Switzerland). Their thanks also go to Dr. Rousseau F. Djouaka (The International Institute for Tropical Agriculture, Ibadan, Nigeria, and Collaborator of the Liverpool School of Tropical Medicine, UK) for checking the English style and for his valuable linguistic advice.

References

[1] A. Yessoufou, N. Soulaimann, S. Merzouk et al., "N-3 fatty acids modulate antioxidant status in diabetic rats and their macrosomic offspring," *International Journal of Obesity*, vol. 30, no. 5, pp. 739–750, 2006.

[2] U. Kamath, G. Rao, C. Raghothama, L. Rai, and P. Rao, "Erythrocyte indicators of oxidative stress in gestational diabetes," *Acta Paediatrica*, vol. 87, no. 6, pp. 676–679, 1998.

[3] C. Kim, K. M. Newton, and R. H. Knopp, "Gestational diabetes and the incidence of type 2 diabetes," *Diabetes Care*, vol. 25, no. 10, pp. 1862–1868, 2002.

[4] N. J. Cox, "Maternal component in NIDDM transmission: how large an effect?" *Diabetes*, vol. 43, no. 1, pp. 166–168, 1994.

[5] D. Simmons, "Diabetes and obesity in pregnancy," *Best Practice and Research & Clinical Obstetrics and Gynaecology*, vol. 25, no. 1, pp. 25–36, 2011.

[6] D. Simmons, "Epidemiology of diabetes in pregnancy," in *Practical Management of Diabetes in Pregnancy*, D. McCance and M. Maresh, Eds., Blackwell Publishing, London, UK, 2010.

[7] S. Y. Chu, W. M. Callaghan, S. Y. Kim et al., "Maternal obesity and risk of gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 8, pp. 2070–2076, 2007.

[8] IADPSG Consensus Panel, "International association of diabetes and pregnancy study groups (IADPSG) recommendations on the diagnosis and classification of hyperglycemia in pregnancy," *Diabetes Care*, vol. 33, no. 7, pp. 676–682, 2010.

[9] F. A. Van Assche, K. Holemans, and L. Aerts, "Long-term consequences for offspring of diabetes during pregnancy," *British Medical Bulletin*, vol. 60, pp. 173–182, 2001.

[10] I. M. Evers, H. W. de Valk, and G. H. Visser, "Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands," *British Medical Journal*, vol. 328, pp. 915–920, 2004.

[11] C. Giordano, "Immunobiology of normal and diabetic pregnancy," *Immunology Today*, vol. 11, no. 9, pp. 301–303, 1990.

[12] W. Knowler, D. J. Pettitt, C. L. Kunzelman, and J. Everhart, "Genetic and environment determinants of non-insulin dependent diabetes mellitus," *Diabetes Research and Clinical Practice*, vol. 1, p. S309, 1985.

[13] G. Dörner, A. Plagemann, and H. Reinagel, "Familial diabetes aggregation in type I diabetics: gestational diabetes an apparent risk factor for increased diabetes susceptibility in the offspring," *Experimental and Clinical Endocrinology & Diabetes*, vol. 89, no. 1, pp. 84–90, 1987.

[14] D. J. Pettitt, K. A. Aleck, H. R. Baird, M. J. Carraher, P. H. Bennett, and W. C. Knowler, "Congenital susceptibility to NIDDM. Role of intrauterine environment," *Diabetes*, vol. 37, no. 5, pp. 622–628, 1988.

[15] D. Mitanchez, "Fetal and neonatal complications of gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal outcomes," *Journal de Gynecologie Obstetrique et Biologie de la Reproduction*, vol. 36, no. 6, part 2, pp. S617–S627, 2010.

[16] J. M. Ategbo, O. Grissa, A. Yessoufou et al., "Modulation of adipokines and cytokines in gestational diabetes and macrosomia," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 10, pp. 4137–4143, 2006.

[17] O. Grissa, J. M. Atègbo, A. Yessoufou et al., "Antioxidant status and circulating lipids are altered in human gestational diabetes and macrosomia," *Translational Research*, vol. 150, no. 3, pp. 164–171, 2007.

[18] R. H. Knopp, M. R. Warth, D. Charles et al., "Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes," *Biology of the Neonate*, vol. 50, no. 6, pp. 297–317, 1986.

[19] I. Lopez-Soldado and E. Herrera, "Different diabetogenic response to moderate doses of streptozotocin in pregnant rats, and its long-term consequences in the offspring," *Experimental Diabesity Research*, vol. 4, no. 2, pp. 107–118, 2003.

[20] L. Aerts, K. Holemans, and F. A. Van Assche, "Impaired insulin response and action in offspring of severely diabetes rats," in *Frontiers in Diabetes Research. Lessons from Animal Diabetes III*, E. Shafrir, Ed., pp. 561–566, Smith-Gordon, Cambridgeshire, UK, 1990.

[21] K. Holemans, L. Aerts, and F. A. van Assche, "Evidence for an insulin resistance in the adult offspring of pregnant streptozotocin-diabetic rats," *Diabetologia*, vol. 34, no. 2, pp. 81–85, 1991.

[22] K. C. Herold, V. Vezys, Q. Sun et al., "Regulation of cytokine production during development of autoimmune diabetes induced with multiple low doses of streptozotocin," *Journal of Immunology*, vol. 156, no. 9, pp. 3521–3527, 2002.

[23] A. Rabinovitch, "Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM: therapeutic intervention by immunostimulation?" *Diabetes*, vol. 43, no. 5, pp. 613–621, 1994.

[24] A. A. Rossini, R. M. Williams, M. C. Appel, and A. A. Like, "Complete protection from low-dose streptozotocin-induced diabetes in mice," *Nature*, vol. 276, no. 5684, pp. 182–184, 1978.

[25] A. Muller, P. Schott-Ohly, C. Dohle, and H. Gleichmann, "Differential regulation of Th1-type and Th2-type cytokine profiles in pancreatic islets of C57BL/6 and BALB/c mice by multiple low doses of streptozotocin," *Immunobiology*, vol. 205, no. 1, pp. 35–50, 2002.

[26] H. Merzouk, S. Madani, A. Hichami, J. Prost, J. Belleville, and N. A. Khan, "Age-related changes in fatty acids in obese offspring of streptozotocin-induced diabetic rats," *Obesity Research*, vol. 10, no. 7, pp. 703–714, 2002.

[27] N. A. Soulimane-Mokhtari, B. Guermouche, A. Yessoufou et al., "Modulation of lipid metabolism by n-3 polyunsaturated fatty acids in gestational diabetic rats and their macrosomic offspring," *Clinical Science*, vol. 109, no. 3, pp. 287–295, 2005.

[28] M. Vercheval, R. De Hertogh, S. Pampfer et al., "Experimental diabetes impairs rat embryo development during the preimplantation period," *Diabetologia*, vol. 33, no. 4, pp. 187–191, 1990.

[29] N. A. Khan, A. Yessoufou, M. Kim, and A. Hichami, "N-3 fatty acids modulate Th1 and Th2 dichotomy in diabetic pregnancy and macrosomia," *Journal of Autoimmunity*, vol. 26, no. 4, pp. 268–277, 2006.

[30] H. Merzouk, S. Madani, A. Boualga, J. Prost, M. Bouchenak, and J. Belleville, "Age-related changes in cholesterol metabolism in macrosomic offspring of rats with streptozotocin-induced diabetes," *Journal of Lipid Research*, vol. 42, no. 7, pp. 1152–1159, 2001.

[31] E. Shafrir and S. Khassis, "Maternal-fetal fat transport versus new fat synthesis in the pregnant diabetic rat," *Diabetologia*, vol. 22, no. 2, pp. 111–117, 1982.

[32] H. Merzouk, M. Bouchenak, B. Loukidi, S. Madani, J. Prost, and J. Belleville, "Fetal macrosomia related to maternal poorly controlled type 1 diabetes strongly impairs serum lipoprotein concentrations and composition," *Journal of Clinical Pathology*, vol. 53, no. 12, pp. 917–923, 2000.

[33] A. L. Fowden, "The role of insulin in prenatal growth," *Journal of Developmental Physiology*, vol. 12, no. 4, pp. 173–182, 1989.

[34] H. Merzouk and N. A. Khan, "Implication of lipids in macrosomia of diabetic pregnancy: can n-3 polyunsaturated fatty acids exert beneficial effects?" *Clinical Science*, vol. 105, no. 5, pp. 519–529, 2003.

[35] A. Boulange, E. Planche, and P. Gasquet, "Onset and development of hypertriglyceridemia in the Zucker rat (fa/fa)," *Metabolism: Clinical and Experimental*, vol. 30, no. 11, pp. 1045–1052, 1981.

[36] K. E. Suckling and B. Jackson, "Animal models of human lipid metabolism," *Progress in Lipid Research*, vol. 32, no. 1, pp. 1–24, 1993.

[37] K. Ghebremeskel, D. Bitsanis, E. Koukkou, C. Lowy, L. Poston, and M. A. Crawford, "Liver triacylglycerols and free fatty acids in streptozotocin-induced diabetic rats have atypical n-6 and n-3 pattern," *Comparative Biochemistry and Physiology*, vol. 132, no. 3, pp. 349–354, 2002.

[38] G. Dixon, J. Nolan, N. H. McClenaghan, P. R. Flatt, and P. Newsholme, "Arachidonic acid, palmitic acid and glucose are important for the modulation of clonal pancreatic β-cell insulin secretion, growth and functional integrity," *Clinical Science*, vol. 106, no. 2, pp. 191–199, 2004.

[39] N. L. Gelardi, C. J. M. Cha, and W. Oh, "Evaluation of insulin sensitivity in obese offspring of diabetic rats by hyperinsulinemic-euglycemic clamp technique," *Pediatric Research*, vol. 30, no. 1, pp. 40–44, 1991.

[40] P. M. Catalano, J. P. Kirwan, S. Haugel-de Mouzon, and J. King, "Gestational diabetes and insulin resistance: role in short—and long-term implications for mother and fetus," *Journal of Nutrition*, vol. 133, no. 5, pp. 1674–1683, 2003.

[41] V. Toescu, S. L. Nuttall, U. Martin et al., "Changes in plasma lipids and markers of oxidative stress in normal pregnancy and pregnancies complicated by diabetes," *Clinical Science*, vol. 106, no. 1, pp. 93–98, 2004.

[42] G. Di Cianni, R. Miccoli, L. Volpe et al., "Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance," *Diabetic Medicine*, vol. 22, no. 1, pp. 21–25, 2005.

[43] J. W. Baynes and S. R. Thorpe, "Role of oxidative stress in diabetic complications: a new perspective on an old paradigm," *Diabetes*, vol. 48, no. 1, pp. 581–589, 1999.

[44] H. K. Biesalski, "The role of antioxidants in nutritional support," *Nutrition*, vol. 16, no. 7-8, pp. 578–581, 2000.

[45] J. V. Hunt, C. C. T. Smith, and S. P. Wolff, "Autoxidative glycosylation and possible involvement of peroxides and free radicals in LDL modification by glucose," *Diabetes*, vol. 39, no. 11, pp. 1420–1424, 1990.

[46] Y. Dincer, Z. Alademir, H. Ilkova, and T. Akcay, "Susceptibility of glutatione and glutathione-related antioxidant activity to hydrogen peroxide in patients with type 2 diabetes: effect of glycemic control," *Clinical Biochemistry*, vol. 35, no. 4, pp. 297–301, 2002.

[47] S. V. McLennan, S. Heffernan, L. Wright et al., "Changes in hepatic glutathione metabolism in diabetes," *Diabetes*, vol. 40, no. 3, pp. 344–348, 1991.

[48] I. S. Young, J. J. Torney, and E. R. Trimble, "The effects of ascorbate supplementation on oxidative stress in the streptozotocin diabetic rat," *Free Radical Biology and Medicine*, vol. 13, no. 1, pp. 41–46, 1992.

[49] C. N. Hales and D. J. P. Barker, "The thrifty phenotype hypothesis," *British Medical Bulletin*, vol. 60, pp. 5–20, 2001.

[50] G. Dörner and A. Plagemann, "Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life," *Hormone and Metabolic Research*, vol. 26, no. 5, pp. 213–221, 1994.

[51] W. Palinski and C. Napoli, "The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis," *The Journal of Federation of American Societies for Experimental Biology*, vol. 16, no. 11, pp. 1348–1360, 2002.

[52] C. Napoli, F. P. D'Armiento, F. P. Mancini et al., "Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia," *Journal of Clinical Investigation*, vol. 100, no. 11, pp. 2680–2690, 1997.

[53] R. A. Vogel, M. C. Corretti, and G. D. Plotnick, "Effect of a single high-fat meal on endothelial function in healthy subjects," *American Journal of Cardiology*, vol. 79, no. 3, pp. 350–354, 1997.

[54] R. Schwartz and K. A. Teramo, "Effects of diabetic pregnancy on the fetus and newborn," *Seminars in Perinatology*, vol. 24, no. 2, pp. 120–135, 2000.

[55] P. Thureen, M. Reece, D. Rodden et al., "Increased farnesylation of p21-Ras and neonatal macrosomia in women with gestational diabetes," *Journal of Pediatrics*, vol. 149, no. 6, pp. 871–873, 2006.

[56] K. Franke, T. Harder, L. Aerts et al., ""Programming" of orexigenic and anorexigenic hypothalamic neurons in offspring of treated and untreated diabetic mother rats," *Brain Research*, vol. 1031, no. 2, pp. 276–283, 2005.

[57] P. Dandona, A. Aljada, and A. Bandyopadhyay, "Inflammation: the link between insulin resistance, obesity and diabetes," *Trends in Immunology*, vol. 25, no. 1, pp. 4–7, 2004.

[58] S. W. Coppack, "Pro-inflammatory cytokines and adipose tissue," *Proceedings of the Nutrition Society*, vol. 60, no. 3, pp. 349–356, 2001.

[59] A. S. Greenberg and M. L. McDaniel, "Identifying the links between obesity, insulin resistance and β-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes," *European Journal of Clinical Investigation*, vol. 32, no. 3, pp. 24–34, 2002.

[60] J. J. Diez and P. Iglesias, "The role of the novel adipocyte-derived hormone adiponectin in human and possible biological roles," *European Journal of Endocrinology*, vol. 148, no. 3, pp. 293–300, 2003.

[61] M. Meller, C. Qiu, S. Vadachkoria, D. F. Abetew, D. A. Luthy, and M. A. Williams, "Changes in placental adipocytokine gene expression associated with gestational diabetes mellitus," *Physiological Research*, vol. 55, no. 5, pp. 501–512, 2006.

[62] G. S. Hotamisligil, D. L. Murray, L. N. Choy, and B. M. Spiegelman, "Tumor necrosis factor-α inhibits signaling from the insulin receptor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 11, pp. 4854–4858, 1994.

[63] N. Stefan, B. Vozarova, T. Funahashi et al., "Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans," *Diabetes*, vol. 51, no. 6, pp. 1884–1888, 2002.

[64] A. S. Lihn, B. Richelsen, S. B. Pedersen et al., "Increased expression of TNF-α, IL-6, and IL-8 in HALS: implications for reduced adiponectin expression and plasma levels," *American Journal of Physiology*, vol. 285, no. 585, pp. E1072–E1080, 2003.

[65] P. J. Tsai, C. H. Yu, S. P. Hsu et al., "Maternal plasma adiponectin concentrations at 24 to 31 weeks of gestation: negative association with gestational diabetes mellitus," *Nutrition*, vol. 21, no. 11-12, pp. 1095–1099, 2005.

[66] A. Cartier, I. Lemieux, N. Alméras, A. Tremblay, J. Bergeron, and J. P. Després, "Visceral obesity and plasma glucose-insulin homeostasis: contributions of interleukin-6 and tumor necrosis factor-α in men," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 5, pp. 1931–1938, 2008.

[67] Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, and J. M. Friedman, "Positional cloning of the mouse obese gene and its human homologue," *Nature*, vol. 372, no. 6505, pp. 425–432, 1994.

[68] J. L. Halaas, K. S. Gajiwala, M. Maffei et al., "Weight-reducing effects of the plasma protein encoded by the obese gene," *Science*, vol. 269, no. 5223, pp. 543–546, 1995.

[69] A. Kautzky-Willer, G. Pacini, A. Tura et al., "Increased plasma leptin in gestational diabetes," *Diabetologia*, vol. 44, no. 2, pp. 164–172, 2001.

[70] D. Simmons and B. H. Breier, "Fetal overnutrition in polynesian pregnancies and in gestational diabetes may lead to dysregulation of the adipoinsular axis in offspring," *Diabetes Care*, vol. 25, no. 9, pp. 1539–1544, 2002.

[71] A. Festa, N. Shnawa, W. Krugluger, P. Hopmeier, G. Schernthaner, and S. M. Haffner, "Relative hypoleptinaemia in women with mild gestational diabetes mellitus," *Diabetic Medicine*, vol. 16, no. 8, pp. 656–662, 1999.

[72] E. Sivan, P. G. Whittaker, D. Sinha et al., "Leptin in human pregnancy: the relationship with gestational hormones," *American Journal of Obstetrics and Gynecology*, vol. 179, no. 5, pp. 1128–1132, 1998.

[73] H. Masuzaki, Y. Ogawa, N. Sagawa et al., "Nonadipose tissue production of leptin: leptin as a novel placenta- derived

hormone in humans," *Nature Medicine*, vol. 3, no. 9, pp. 1029–1033, 1997.

[74] C. T. Montague, J. B. Prins, L. Sanders et al., "Depot-related gene expression in human subcutaneous and omental adipocytes," *Diabetes*, vol. 47, no. 9, pp. 1384–1391, 1998.

[75] A. Yessoufou, K. Moutairou, and N. A. Khan, "A model of insulin resistance in mice, born to diabetic pregnancy, is associated with alterations of transcription-related genes in pancreas and epididymal adipose tissue," *Journal of Obesity*, vol. 2011, Article ID 654967, 11 pages, 2011.

[76] Y. Arita, S. Kihara, N. Ouchi et al., "Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity," *Biochemical and Biophysical Research Communications*, vol. 257, no. 1, pp. 79–83, 1999.

[77] H. Wu, S. Ghosh, X. D. Perrard et al., "T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity," *Circulation*, vol. 115, no. 8, pp. 1029–1038, 2007.

[78] T. Sathyapalan and S. L. Atkin, "Is there a role for immune and anti-inflammatory therapy in type 2 diabetes?" *Minerva Endocrinologica*, vol. 36, no. 2, pp. 147–156, 2011.

[79] Z. Z. Li, J. B. Liu, L. Li, L. Jiao, and L. Chen, "Intensive therapy for diabetes through influence on innate immune system," *Medical Hypotheses*, vol. 72, no. 6, pp. 675–676, 2009.

[80] J. A. Ehses, G. Lacraz, M. H. Giroix et al., "IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 33, pp. 13998–14003, 2009.

[81] R. Raghupathy, "Pregnancy: success and failure within the Th1/Th2/Th3 paradigm," *Seminars in Immunology*, vol. 13, no. 4, pp. 219–227, 2001.

[82] M. Makhseed, R. Raghupathy, F. Azizieh, A. Omu, E. Al-Shamali, and L. Ashkanani, "Th1 and Th2 cytokine profiles in recurrent aborters with successful pregnancy and with subsequent abortions," *Human Reproduction*, vol. 16, no. 10, pp. 2219–2226, 2001.

[83] A. Yessoufou, A. Hichami, P. Besnard, K. Moutairou, and N. A. Khan, "PPARα deficiency increases the risk of maternal abortion and neonatal mortality in murine pregnancy with or without diabetes mellitus: modulation of T cell differentiation," *Endocrinology*, vol. 147, no. 9, pp. 4410–4418, 2006.

[84] G. Reinhard, A. Noll, H. Schlebusch, P. Mallmann, and A. V. Ruecker, "Shifts in the TH1/TH2 balance during human pregnancy correlate with apoptotic changes," *Biochemical and Biophysical Research Communications*, vol. 245, no. 3, pp. 933–938, 1998.

[85] N. A. Khan, A. Khan, H. F. Savelkoul, and R. Benner, "Inhibition of diabetes in NOD mice by human pregnancy factor," *Human Immunology*, vol. 62, no. 12, pp. 1315–1323, 2001.

[86] B. Caballero, "The global epidemic of obesity: an overview," *Epidemiologic Reviews*, vol. 29, no. 1, pp. 1–5, 2007.

[87] I. Guelinckx, R. Devlieger, K. Beckers, and G. Vansant, "Maternal obesity: pregnancy complications, gestational weight gain and nutrition," *Obesity Reviews*, vol. 9, no. 2, pp. 140–150, 2008.

[88] B. Caballero, "A nutrition paradox—underweight and obesity in developing countries," *The New England Journal of Medicine*, vol. 352, no. 15, pp. 1514–1516, 2005.

[89] E. J. McAllister, N. V. Dhurandhar, S. W. Keith et al., "Ten putative contributors to the obesity epidemic," *Critical Reviews in Food Science and Nutrition*, vol. 49, no. 10, pp. 868–913, 2009.

[90] N. J. Sebire, M. Jolly, J. P. Harris et al., "Maternal obesity and pregnancy outcome: a study of 287, 213 pregnancies in London," *International Journal of Obesity*, vol. 25, no. 8, pp. 1175–1182, 2001.

[91] V. J. Carey, E. E. Walters, G. A. Colditz et al., "Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the nurses' health study," *American Journal of Epidemiology*, vol. 145, no. 7, pp. 614–619, 1997.

[92] R. H. Knopp, M. S. Magee, C. E. Walden, B. Bonet, and T. J. Benedetti, "Prediction of infant birth weight by GDM screening tests: importance of plasma triglyceride," *Diabetes Care*, vol. 15, no. 11, pp. 1605–1613, 1992.

[93] D. S. Ludwig and J. Currie, "The association between pregnancy weight gain and birthweight: a within-family comparison," *The Lancet*, vol. 376, no. 9745, pp. 984–990, 2010.

[94] A. S. Roman, A. Rebarber, N. S. Fox et al., "The effect of maternal obesity on pregnancy outcomes in women with gestational diabetes," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 24, no. 5, pp. 723–727, 2011.

[95] K. M. Rasmussen, P. M. Catalano, and A. L. Yaktine, "New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know," *Current Opinion in Obstetrics & Gynecology*, vol. 21, no. 6, pp. 521–526, 2009.

[96] J. G. Kral, S. Biron, S. Simard et al., "Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years," *Pediatrics*, vol. 118, no. 6, pp. e1644–e1649, 2006.

[97] G. Beucher, B. Viaris de Lesegno, and M. Dreyfus, "Maternal outcome of gestational diabetes mellitus," *Journal de Gynecologie Obstetrique et Biologie de la Reproduction*, vol. 36, no. 6, part 2, pp. 522–537, 2010.

[98] T. A. Hillier, K. L. Pedula, M. M. Schmidt, J. A. Mullen, M. A. Charles, and D. J. Pettitt, "Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia," *Diabetes Care*, vol. 30, no. 9, pp. 2287–2292, 2007.

[99] D. Simmons and S. Robertson, "Influence of maternal insulin treatment on the infants of women with gestational diabetes," *Diabetic Medicine*, vol. 14, no. 9, pp. 762–765, 1997.

[100] M. W. Gillman, H. Oakey, P. A. Baghurst, R. E. Volkmer, J. S. Robinson, and C. A. Crowther, "Effect of treatment of gestational diabetes mellitus on obesity in the next generation," *Diabetes Care*, vol. 33, no. 5, pp. 964–968, 2010.

[101] T. A. Mori, D. W. Dunstan, V. Burke et al., "Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients," *Metabolism*, vol. 48, no. 11, pp. 1402–1408, 1999.

[102] O. Yilmaz, Y. Ozkan, M. Yildirim, A. I. Ozturk, and Y. Ersan, "Effects of alpha lipoic acid, ascorbic acid-6-palmitate, and fish oil on glutathione, malonaldehyde and fatty acid levels in erythrocytes of streptozotocine induced diabetic male rats," *Journal of Cellular Biochemistry*, vol. 86, no. 3, pp. 530–539, 2002.

[103] A. P. Simopoulos, "Omega-3 fatty acids in health and disease and in growth and development," *American Journal of Clinical Nutrition*, vol. 54, no. 3, pp. 438–463, 1991.

[104] T. L. Roberst, H. Kato, T. Gordon et al., "Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: coronary heart disease risk factors in Japan and Hawaii," *American Journal of Cardiology*, vol. 39, no. 2, pp. 224–250, 1998.

[105] A. Wesley, "Immunonutrition: the role of n-3 fatty acids," *Nutrition*, vol. 14, no. 7-8, pp. 627–633, 1998.

[106] K. Ylonen, G. Alfthan, L. Groop, C. Saloranta, A. Aro, and S. M. Virtanen, "Dietary intakes and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of type 2 diabetes: the botnia dietary study," *American Journal of Clinical Nutrition*, vol. 77, no. 6, pp. 1434–1441, 2003.

[107] J. I. Elejalde Guerra, "Oxidative stress, diseases and antioxidant treatment," *Anales de Medicina Interna*, vol. 18, no. 6, pp. 326–335, 2001.

[108] K. J. Fitzsimons and J. Modder, "Centre for maternal and child enquires. Setting maternity care standards for women with obesity in pregnancy," *Seminars in Fetal and Neonatal Medicine*, vol. 15, no. 2, pp. 100–107, 2010.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 951203, 6 pages
doi:10.1155/2011/951203

Research Article

Influence of Maternal Glycemia on Intrauterine Fetal Adiposity Distribution after a Normal Oral Glucose Tolerance Test at 28 Weeks Gestation

Nadine Farah, Jennifer Hogan, Vicky O'Dwyer, Bernard Stuart, Mairead Kennelly, and Michael J. Turner

UCD Centre for Human Reproduction, Coombe Women and Infants University Hospital, Dublin 8, Ireland

Correspondence should be addressed to Nadine Farah, drnfarah@gmail.com

Received 15 May 2011; Revised 28 July 2011; Accepted 2 September 2011

Academic Editor: Barbara Alexander

Objective. To examine the relationship between maternal glucose levels and intrauterine fetal adiposity distribution in women with a normal oral glucose tolerance test (OGTT) at 28 weeks gestation. *Study Design*. We recruited 231 women with a singleton pregnancy. At 28 and 37 weeks gestation, sonographic measurements of fetal body composition were performed. Multiple regression analysis was used to study the influence of different maternal variables on fetal adiposity distribution. *Results*. Maternal glucose levels correlated with the fetal abdominal subcutaneous tissue measurements ($r = 0.2$; $P = 0.014$) and with birth weight ($r = 0.1$; $P = 0.04$). Maternal glucose levels did not correlate with the fetal mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements. *Conclusion*. We found that in nondiabetic women maternal glucose levels not only influence fetal adiposity and birth weight, but also influence the distribution of fetal adiposity. This supports previous evidence that maternal glycemia is a key determinant of intrauterine fetal programming.

1. Introduction

Gestational diabetes mellitus (GDM) has been associated with increased birth weight and fetal macrosomia [1]. Increased birth weight is associated with increases in the rates of instrumental vaginal delivery, cesarean section, perineal trauma, and postpartum haemorrhage [2, 3]. Fetal macrosomia increases the risk of shoulder dystocia, brachial plexus injury, intrapartum death, admissions to the neonatal unit, and newborn metabolic problems, including hypoglycemia [4]. Large babies are also predisposed to childhood obesity and to increased morbidity in later life such as hypertension, insulin resistance, and diabetes mellitus [5, 6].

Recently, the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study found that in 25,505 women with a normal oral glucose tolerance test (OGTT) at 24–32 weeks gestation, maternal glycemia is associated with a birth weight >90th centile and with neonatal adiposity measured using skinfold callipers postnatally [7, 8]. These findings provided further support for the importance of the intrauterine environment in programming lifelong health and raise the possibility that optimizing maternal glycemia may improve pregnancy outcomes [5].

Over the past 20 years, several investigators have examined the role of fetal soft-tissue measurements in the evaluation of fetal growth abnormalities [9]. Fetal adiposity approximately increases tenfold between 19 and 40 weeks gestation [10]. As a result of accelerated rate of growth in late gestation, measurements of the fetal adiposity, as well as estimates of fetal weight, may potentially be useful in the evaluation of fetal growth abnormalities [9]. The purpose of this study was to examine the relationship between maternal glucose levels at 28 weeks gestation and intrauterine fetal adiposity distribution in women with a normal OGTT.

2. Materials and Methods

We conducted a longitudinal prospective observational study in a large university teaching hospital. To minimize

confounding variables, the study was confined to white European women with a singleton pregnancy. Women with chronic medical problems that predispose to abnormal intrauterine growth were excluded as well as cases of known congenital fetal malformations.

Women were enrolled at their convenience between July 2008 and December 2009 when they presented for an OGTT. It is hospital practice to selectively screen for GDM at 28 weeks gestation, based on risk factors [11]. A normal glucose response in pregnancy was defined as a fasting value of <5.3 mmol/L, a 1-hour postprandial value of <10.0 mmol/L, a 2-hour postprandial value of <8.6 mmol/L and a 3-hour postprandial value of <7.8 mmol/L after a 3-hour 100 g OGTT [12].

All the women enrolled had an early pregnancy ultrasound scan previously to confirm gestational age. In early pregnancy weight and height had been measured digitally in a standardized way, and the body mass index (BMI) calculated [13]. At recruitment, maternal weight was again measured and sonographic evaluation of fetal body composition was carried out by one operator (NF) using a transabdominal curved array transducer on an ALOKA prosound α7. The fetal head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) were measured.

The fetal abdominal subcutaneous tissue was measured on the anterior abdominal wall in millimetres anterior to the margins of the ribs, using magnification at the level of the AC [14]. The fetal mid-thigh muscle thickness was measured at the level of the femur diaphysis as the distance from the outer border of the femur to the inner edge of the subcutaneous layer. The fetal mid-thigh subcutaneous tissue was calculated by subtracting the distance from the outer border of the femur to the outer border of the subcutaneous layer from the thigh muscle. At 37 weeks gestation, maternal weight and fetal body composition were measured again by same operator (NF). Birth weight was measured at delivery. The clinical outcomes of the pregnancy were obtained from the obstetric records.

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc. Chicago, Ill, USA). Relevant descriptive statistics (mean, standard deviation and percentages) were obtained for the study population. All the variables were checked for normality using the Kolmogorov-Smirnov test. The relationship of fetal body composition measurements and birth weight to a range of possible explanatory variables was investigated, in the first instance, by use of Pearson correlation coefficients. Explanatory variables identified as significant in this bivariate analysis were subsequently entered into a multiple regression model. Trajectories were tested using repeated measures ANOVA with the predictors identified in the regression analysis.

To determine whether there is a sex difference in the fetal parameters measured the independent Student's t-test was used. The 5% level of significance was used throughout. Written informed consent was obtained and the study was approved by the Hospital Research and Ethics Committee.

In a sample of 25 women, two measurements of the fetal abdominal subcutaneous tissue, mid-thigh muscle thickness and mid-thigh subcutaneous tissue were carried out 5 minutes apart. The test-retest reliability, based on Bland-Altman analysis, for the fetal abdominal subcutaneous tissue, mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements yielded limits of agreement of (−0.64, 0.74), (−1.03, 1.08), and (−0.77, 0.65), respectively, with coefficients of repeatability of 10.0%, 7.5%, and 11.5% respectively [15].

3. Results

In total, 320 women were initially enrolled into the study of which 61 women did not attend for a second visit assessment at 37 weeks gestation. Of those women that did not to attend, 20 women delivered before their second assessment visit at 37 weeks gestation. In the group of women that attended for their second assessment, 28 women were excluded from the study because of an abnormal OGTT.

The mean age of the final study population ($n = 231$) was 30.6 ± 4.8 years with 41.1% ($n = 95$) primigravidas. The mean gestation at the first antenatal visit was 12.3 ± 1.6 weeks and the mean early pregnancy BMI was 28.2 ± 6.0 kg/m^2. Of the women studied, 36.4% ($n = 84$) had a normal BMI, 28.6% ($n = 66$) were overweight, and 34.7% ($n = 81$) were obese according to the WHO classification. The mean birth weight was 3.7 (±0.5) kg and 3.9% of the babies had a birth weight ≥4.5 kg. The characteristics and outcomes of the study population are shown in Table 1.

At the normal OGTT, the maternal fasting and one-hour postprandial glucose levels correlated positively with maternal early pregnancy BMI ($r = 0.2$; $P < 0.001$). The fasting and one-hour postprandial glucose levels did not correlate with maternal age, parity, height, and gestational weight gain (GWG) between booking and 28 weeks gestation.

The two-hour postprandial glucose level correlated with maternal age and early pregnancy BMI ($r = 0.2$ and 0.1; $P = 0.016$ and 0.04, resp.). The three-hour postprandial glucose level correlated with maternal height and GWG between the booking visit and 28 weeks gestation ($r = 0.2$ and 0.1; $P = 0.016$ and 0.046, resp.).

There were no differences in the mean maternal age, height, early pregnancy weight, and BMI between women with a male fetus and women with a female fetus. There were also no differences in maternal gestational weight gain between booking and recruitment and between recruitment and 37 weeks gestation between the two groups. We also found no differences in the maternal blood sugars between the two groups. There was, however, a difference in the parity between the two groups ($P = 0.001$). In the fetal parameters measured there were no sex differences in the abdominal subcutaneous tissue, mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements at 28 and 37 weeks gestation (Table 2). We also found no sex differences in the birth weight (Table 2).

The mean fetal abdominal subcutaneous tissue, mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements at 28 weeks gestation were 3.4 ± 0.8, 7.7 ± 1.7 and 2.9 ± 0.9 mm, respectively. Table 3 shows the correlation

Table 1: Characteristics of the study participants, their newborn, and frequency of outcomes ($n = 231$).

Maternal characteristics	Frequency (%)	Mean ± SD	Range
Age (years)		30.6 ± 4.8	19.0–41.0
Parity		0.9 ± 1.0	0–4
Early pregnancy BMI (kg/m^2)		28.2 ± 6.0	19.1–45.8
Prenatal smoking	14.7		
Newborn characteristics			
Gestational age at delivery (weeks)		40.2 ± 1.1	36.6–42.0
Birth weight (kg)		3.7 ± 0.5	2.1–5.0
Birth weight >4.5 kg	3.9		
Male sex	49.8		
Obstetric outcomes			
Hypertension			
Gestational hypertension	10.0		
Preeclampsia	3.9		
Induction rate	32.4		
Caesarean delivery	26.5		

BMI: body mass index.

Table 2: Mean values for fetal parameters analysed by fetal sex.

	Male fetuses ($n = 124$)	Female fetuses ($n = 122$)	P value
At recruitment (*28 weeks*)			
Abdominal Circumference (mm)	243.5 (14.5)	243.3 (13.8)	NS
Abdominal subcutaneous tissue (mm)	3.4 (0.7)	3.4 (0.8)	NS
Mid-thigh muscle thickness (mm)	7.7 (1.9)	7.5 (1.6)	NS
Mid-thigh subcutaneous tissue (mm)	2.9 (0.9)	2.9 (0.8)	NS
At second assessment (*37 weeks*)			
Abdominal circumference (mm)	331.6 (19.4)	333.0 (16.6)	NS
Abdominal subcutaneous tissue (mm)	6.4 (1.5)	6.6 (1.3)	NS
Mid-thigh muscle thickness (mm)	10.4 (2.8)	10.4 (2.5)	NS
Mid-thigh subcutaneous tissue (mm)	5.2 (1.4)	5.0 (1.4)	NS
At birth			
Gestation (weeks)	40.2 (1.2)	40.2 (1.0)	NS
Birth weight (kg)	3.7 (0.5)	3.6 (0.4)	NS

between maternal parameters, including blood sugars, and fetal body composition at 28 weeks gestation.

At 28 weeks gestation, maternal age and the maternal one-hour postprandial glucose level both influenced the fetal abdominal subcutaneous tissue measurement independently ($r^2 = 0.095$; $P < 0.001$). Maternal age and gestational weight gain both influenced the fetal mid-thigh subcutaneous tissue measurement independently ($r^2 = 0.065$; $P = 0.002$). Early pregnancy maternal BMI and fasting glucose levels did not correlate with any of the fetal body composition parameters.

The mean fetal abdominal subcutaneous tissue measurement, mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements at 37 weeks gestation were 6.5 ± 1.5, 10.4 ± 2.7, and 5.0 ± 1.6 mm respectively. Table 4 shows the correlation between maternal parameters, including blood sugars, and fetal body composition at 37 weeks gestation.

At 37 weeks gestation, the fetal AC measurement correlated with maternal weight and height in early pregnancy and with maternal fasting and one-hour postprandial glucose levels at the time of the normal OGTT (Table 4). To determine which of the variables continued to correlate with the fetal AC measurement, regression analysis was performed incorporating maternal weight, height, and fasting and one-hour postprandial glucose levels. In the resulting regression equation maternal height and fasting and one-hour postprandial glucose levels continued to be predictive ($r^2 = 0.099$; $P < 0.001$). The fetal abdominal subcutaneous tissue measurement correlated with all four maternal glucose levels. None of the maternal glucose parameters correlated

Table 3: Correlation between maternal parameters and fetal body composition at 28 weeks gestation (r and P values).

Maternal parameter	Fetal AC	Fetal abdominal subcutaneous tissue	Fetal mid-thigh muscle thickness	Fetal mid-thigh subcutaneous tissue
Age (years)	0.1 (NS)	0.3 (<0.001)	−0.1 (NS)	0.2 (0.005)
Parity	0.0 (NS)	0.1 (NS)	0.0 (NS)	0.0 (NS)
Early pregnancy				
Weight (kg)	0.0 (NS)	−0.4 (NS)	0.1 (NS)	0.0 (NS)
Height (cm)	0.0 (NS)	0.0 (NS)	0.1 (NS)	0.1 (NS)
BMI (kg/m^2)	0.0 (NS)	0.0 (NS)	0.1 (NS)	0.0 (NS)
GWG (1) (kg)	0.1 (NS)	0.0 (NS)	0.1 (NS)	0.2 (0.019)
OGTT glucose levels				
fasting	0.0 (NS)	0.1 (NS)	0.0 (NS)	0.0 (NS)
1-hour postprandial	0.1 (NS)	0.2 (0.006)	0.1 (NS)	0.1 (NS)
2-hour postprandial	0.1 (0.026)	0.1 (NS)	0.1 (NS)	0.0 (NS)
3-hour postprandial	0.0 (NS)	0.1 (NS)	0.1 (NS)	0.0 (NS)

AC: abdominal circumference. BMI: body mass index. GWG (1): gestational weight gain per week between the booking visit and 28 weeks gestation. OGTT: oral glucose tolerance test.

Table 4: Correlation between maternal parameters and fetal body composition at 37 weeks gestation (r and P values).

Maternal parameter	Fetal AC	Fetal abdominal subcutaneous tissue	Fetal mid-thigh muscle thickness	Fetal mid-thigh subcutaneous tissue
Age (years)	0.1 (NS)	0.1 (NS)	−0.1 (NS)	0.0 (NS)
Parity	0.1 (NS)	0.0 (NS)	0.0 (NS)	0.0 (NS)
Early pregnancy				
Weight (kg)	0.2 (0.006)	0.0 (NS)	0.1 (NS)	0.1 (NS)
Height (cm)	0.2 (0.007)	−0.1 (NS)	0.1 (NS)	0.1 (NS)
BMI (kg/m^2)	0.1 (NS)	0.1 (NS)	0.1 (NS)	0.1 (NS)
GWG (1) (kg)	0.1 (NS)	0.0 (NS)	0.1 (NS)	0.1 (NS)
GWG (2) (kg)	0.1 (NS)	0.1 (NS)	0.0 (NS)	0.2 (0.003)
OGTT glucose levels				
fasting	0.2 (0.002)	0.2 (0.006)	0.0 (NS)	0.0 (NS)
1-hour postprandial	0.2 (0.003)	0.2 (0.002)	0.0 (NS)	0.1 (NS)
2-hour postprandial	0.1 (NS)	0.2 (0.014)	0.0 (NS)	0.1 (NS)
3-hour postprandial	0.1 (NS)	0.2 (0.001)	0.0 (NS)	0.0 (NS)

AC: abdominal circumference. BMI: body mass index. GWG (1): gestational weight gain per week between the booking visit and 28 weeks gestation. GWG (2): gestational weight gain per week between 28 and 37 weeks gestation. OGTT: oral glucose tolerance test.

with the fetal mid-thigh muscle thickness and mid-thigh subcutaneous tissue measurements.

The fetal AC trajectories from 28 to 37 weeks gestation were influenced by the maternal fasting glucose levels (F (1,220) = 4.177, P = 0.042). The fetal AC trajectories were not influenced by maternal age, early pregnancy BMI, gestational weight gain and the one-, two- and three-hour postprandial glucose levels. The fetal abdominal subcutaneous tissue trajectories from 28 and 37 weeks gestation were influenced by the maternal three-hour postprandial glucose levels (F (1,218) = 4.732, P = 0.033). The fetal abdominal subcutaneous tissue trajectories were not influenced by maternal age, early pregnancy BMI, gestational weight gain and the fasting, one and two-hour postprandial glucose levels. The fetal mid-thigh subcutaneous tissue trajectories were not influenced by maternal glucose parameters.

Birth weight correlated with maternal age, height, and parity (r = 0.2, 0.2 and 0.2; P = 0.024, <0.001 and 0.001 resp.). Birth weight correlated with GWG between the first antenatal visit and 28 weeks gestation (r = 0.2; P = 0.004) and with GWG between 28 and 37 weeks (r = 0.2; P = 0.015). The maternal fasting (r = 0.1; P = 0.04), one-hour postprandial (r = 0.2; P = 0.008) and 2-hour postprandial (r = 0.2; P = 0.003) glucose levels all correlated with birth weight.

To determine which of the above variables continued to correlate with birth weight, regression analysis was performed. The regression equation incorporated maternal age, parity, smoking habit, height, fasting, and one-hour postprandial glucose levels, GWG between booking and 28 weeks, GWG between booking and 28 weeks, and gestational age at delivery. In the resulting regression equation, maternal

parity, smoking habit, height, one-hour postprandial glucose level, GWG between booking and 28 weeks, and gestational age at delivery all continued to be predictive of birth weight ($r^2 = 0.306$; $P < 0.001$).

4. Discussion

In women where GDM was excluded at the start of the third trimester, we found that maternal glycemia correlated with subsequent birth weight. We also found using ultrasound measurement of fetal soft tissues that maternal glycemia influences not only fetal adiposity, but also the distribution of adipose tissue.

We had a high proportion of obese women in our study because one of the indications for an OGTT was a maternal weight >90 kg. Although the women were not representative of our pregnant population, it did, however, allow us to include obese women who did not have GDM.

In an American study of 220 multiethnic pregnant women with a normal OGTT, women with a BMI $\geq$25.0 kg/m^2 had heavier babies (>4.0 kg) than women with a BMI <25.0 kg/m^2 [16]. Postnatal measurements of neonatal skinfold thickness and total body electrical conductivity estimates of body composition within 72 hours of delivery found that fetal adiposity increased in women who were in the overweight/obese BMI categories. However, it was not possible to comment on the distribution of neonatal adiposity.

In another study of 33 neonates delivered by women with a normal BMI and 39 neonates delivered by overweight/obese women with singleton pregnancies and a normal OGTT, birth weight, and neonatal body composition were compared [17]. Although there was no difference in birth weight between the groups, neonates born to women with a normal pregravid BMI had less fat mass and greater fat-free mass than neonates born to women who were overweight/obese.

Maternal obesity has been shown to effect glucose metabolism with a loss of the reduction in fasting glucose in early pregnancy and enhancement of peripheral and hepatic insulin resistance [18]. We found that maternal glucose levels, at the time of the normal OGTT, were influenced by early pregnancy BMI. However, we also found that the influence of maternal glucose on fetal body composition was independent of maternal BMI.

An Italian group assessed fetal adiposity at 31 and 37 weeks gestation in fifteen well-controlled insulin-dependent pregnant women and 16 controls with normal glucose [19]. The fasting and postprandial glucose concentrations were higher in the well-controlled diabetic pregnancies compared with the controls. They found no difference in the birth weight and ponderal index between the two groups. However, they found that in the diabetic group fetal abdominal adiposity was increased despite the tight maternal glycemic control.

Another Italian group compared fetal soft-tissue measurements in 228 mothers with normal and abnormal oral glucose challenge tests [20]. The mothers were not obese and did not have GDM. They found that in the women with an abnormal oral glucose challenge test fetal adiposity was increased. This study again suggests that any degree of maternal glycemia represents an altered intrauterine environment for fetal growth even if less than that required for the diagnosis of GDM.

While the numbers in our study are not representative of all pregnant women, it does have strengths. The early pregnancy calculation of BMI and subsequent weight gain was based on accurate measurement throughout pregnancy and was not based on self-reporting [13]. In the HAPO study, BMI was only recorded at the time of the OGTT, which varied between 24 and 32 weeks gestation [8]. We were also able to standardize GWG based on measurements of maternal weight at 28 and 37 weeks gestation allowing us to study the influence of GWG as well as BMI on fetal adiposity [21]. Confining our study to white European women with a singleton pregnancy avoided potential confounding variables such as ethnicity and multiple pregnancies [22]. All women in our study had an early pregnancy ultrasound to confirm gestational age which is a key determinant of estimated fetal weight in utero and of birth weight. The value of measuring fetal adiposity at both 28 and 37 weeks gestation rather than postnatally allowed us to study the relationship between maternal glycemia and intrauterine growth avoiding possible confounding variables such as growth restriction after 37 weeks gestation, neonatal age at measurement and type of infant feeding.

In adults, excess fat deposited abdominally carries higher risk of cardiovascular disease than excess fat deposited in the limbs [23]. Our finding that maternal glycemia independently of GDM influences birth weight, fetal adiposity, and the distribution of fetal adiposity strengthens the possibility that maternal glycemia is a key determinant of intrauterine fetal programming. What implications the increased abdominal adiposity has in later life for the baby's visceral fat levels and risk of metabolic syndrome, however, remains uncertain. Further studies are required to assess whether interventions, such as dietary manipulation, drugs, or exercise, optimize fetal adiposity and birth weight by reducing maternal glycemia even in women who do not have a diagnosis of GDM.

Conflict of Interests

The authors have no potential conflict of interests to disclose.

Acknowledgment

The authors thank Dr. Tim Grant, Consultant Statistician, for his advice.

References

[1] E. A. Reece, "The fetal and maternal consequences of gestational diabetes mellitus," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 23, no. 3, pp. 199–203, 2010.

[2] M. J. Turner, M. J. Rasmussen, J. E. Turner, P. C. Boylan, D. MacDonald, and J. M. Stronge, "The influence of birth weight

on labour in nulliparas," *Obstetrics and Gynecology*, vol. 76, pp. 159–163, 1990.

[3] X. Zhang, A. Decker, R. W. Platt, and M. S. Kramer, "How big is too big? The perinatal consequences of fetal macrosomia," *American Journal of Obstetrics and Gynecology*, vol. 198, no. 5, pp. 517.e1–517.e6, 2008.

[4] S. L. Boulet, H. M. Salihu, and G. R. Alexander, "Mode of delivery and birth outcomes of macrosomic infants," *Journal of Obstetrics and Gynaecology*, vol. 93, pp. 332–346, 2005.

[5] D. J. P. Barker, P. D. Gluckman, K. M. Godfrey, J. E. Harding, J. A. Owens, and J. S. Robinson, "Fetal nutrition and cardiovascular disease in adult life," *Lancet*, vol. 341, no. 8850, pp. 938–941, 1993.

[6] A. Plagemann, T. Harder, R. Kohlhoff, W. Rohde, and G. Dörner, "Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes," *International Journal of Obesity*, vol. 21, no. 6, pp. 451–456, 1997.

[7] BE. Metzger, "The HAPO Study Cooperative Research Group. Hyperglycaemia and adverse pregnancy outcomes," *The New England Journal of Medicine*, vol. 358, pp. 1991–2002, 2008.

[8] HAPO Study Group, "Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations with neonatal anthropometrics," *Diabetes*, vol. 58, no. 2, pp. 453–459, 2009.

[9] N. Farah, B. Stuart, V. Donnelly, G. Rafferty, and M. Turner, "What is the value of ultrasound soft tissue measurements in the prediction of abnormal fetal growth?" *Journal of Obstetrics and Gynaecology*, vol. 29, no. 6, pp. 457–463, 2009.

[10] I. M. Bernstein, M. I. Goran, S. B. Amini, and P. M. Catalano, "Differential growth of fetal tissues during the second half of pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 176, no. 1 I, pp. 28–32, 1997.

[11] N. Farah, B. Stuart, E. Harrold, C. Fattah, M. Kennelly, and M. J. Turner, "Are there sex differences in Fetal Abdominal Subcutaneous Tissue (FAST) measurements?" *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 148, no. 2, pp. 118–120, 2010.

[12] American Diabetes Association, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 27, pp. 5–10, 2004.

[13] C. Fattah, N. Farah, F. O'Toole, S. Barry, B. Stuart, and M. J. Turner, "Body Mass Index (BMI) in women booking for antenatal care: comparison between selfreported and digital measurements," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 144, no. 1, pp. 32–34, 2009.

[14] F. Gardeil, R. Greene, B. Stuart, and M. J. Turner, "Subcutaneous fat in the fetal abdomen as a predictor of growth restriction," *Obstetrics and Gynecology*, vol. 94, no. 2, pp. 209–212, 1999.

[15] J. M. Bland and D. G. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement," *Lancet*, vol. 1, no. 8476, pp. 307–310, 1986.

[16] M. F. Sewell, L. Huston-Presley, D. M. Super, and P. Catalano, "Increased neonatal fat mass, not lean body mass, is associated with maternal obesity," *American Journal of Obstetrics and Gynecology*, vol. 195, no. 4, pp. 1100–1103, 2006.

[17] H. R. Hull, M. K. Dinger, A. W. Knehans, D. M. Thompson, and D. A. Fields, "Impact of maternal body mass index on neonate birthweight and body composition," *American Journal of Obstetrics and Gynecology*, vol. 198, no. 4, pp. 416.e1–416.e6, 2008.

[18] M. M. Avram, A. S. Avram, and W. D. James, "Subcutaneous fat in normal and diseased states. 3. Adipogenesis: from stem cell to fat cell," *Journal of the American Academy of Dermatology*, vol. 56, no. 3, pp. 472–492, 2007.

[19] P. Greco, A. Vimercati, J. Hyett et al., "The ultrasound assessment of adipose tissue deposition in fetuses of 'well controlled' insulin-dependent diabetic pregnancies," *Diabetic Medicine*, vol. 20, no. 10, pp. 858–862, 2003.

[20] E. Parretti, L. Carignani, R. Cioni et al., "Sonographic evaluation of fetal growth and body composition in women with different degrees of normal glucose metabolism," *Diabetes Care*, vol. 26, no. 10, pp. 2741–2748, 2003.

[21] M. J. Turner and N. Farah, "Gestational weight gain and birth weight," *Irish Medical Journal*, vol. 103, pp. 293–294, 2010.

[22] N. Farah, M. Murphy, N. O'Connor, M. Ramphul, M. Kennelly, and M. J. Turner, "Differences in maternal body composition between women from the Indian Subcontinent and Irish women," *Journal of Obstetrics and Gynaecology*, vol. 31, pp. 483–485, 2011.

[23] L. Lapidus, C. Bengtsson, and B. Larsson, "Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden," *British Medical Journal*, vol. 289, no. 6454, pp. 1257–1261, 1984.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 564316, 7 pages
doi:10.1155/2011/564316

Clinical Study

Cardiac Function in 7-8-Year-Old Offspring of Women with Type 1 Diabetes

Maarten Rijpert,[1] Johannes M. P. J. Breur,[2] Inge M. Evers,[3] Harold W. de Valk,[4] Cobi J. Heijnen,[1] Folkert J. Meijboom,[2] and Gerard H. A. Visser[1]

[1] *Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, P.O. Box 85090, 3508 AB Utrecht, The Netherlands*
[2] *Department of Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, P.O. Box 85090, 3508 AB Utrecht, The Netherlands*
[3] *Department of Obstetrics and Gynecology, Meander Medical Center, P.O. Box 1502, 3800 BM Amersfoort, The Netherlands*
[4] *Department of Internal Medicine, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands*

Correspondence should be addressed to Maarten Rijpert, m.rijpert@umcutrecht.nl

Received 21 May 2011; Revised 17 August 2011; Accepted 29 August 2011

Academic Editor: Barbara Alexander

Offspring of type 1 diabetic mothers (ODMs) are at risk of short-term and long-term complications, such as neonatal macrosomia (birth weight >90th percentile), hypertrophic cardiomyopathy, and cardiovascular morbidity in later life. However, no studies have been performed regarding cardiac outcome. In this study, we investigated cardiac dimensions and function in 30 ODMs at 7-8 years of age in relation to neonatal macrosomia and maternal glycemic control during pregnancy and compared these with those in a control group of 30 children of nondiabetic women. We found that cardiac dimensions and systolic and diastolic function parameters in ODMs were comparable with those in controls. Neonatal macrosomia and poorer maternal glycemic control during pregnancy were not related to worse cardiac outcome in ODM. We conclude that cardiac function at 7-8 years of age in offspring of women with type 1 diabetes is reassuring and comparable with that in controls.

1. Introduction

Despite good prepregnancy care and adequate maternal glycemic control during type 1 diabetic pregnancies, the risk of perinatal complications in the offspring, such as preterm birth and neonatal macrosomia (birth weight >90th percentile), is still high compared with the general population [1]. Furthermore, there is increasing evidence that children born after a diabetic pregnancy are at increased risk of cardiovascular and metabolic morbidity at later age [2], especially when macrosomic at birth [3, 4].

Intrauterine hyperglycemia during type 1 diabetic pregnancy may lead to congenital heart defects, as has been shown in animal studies [5, 6]. In human studies, structural cardiac defects occur in 2–15% of newborn infants of type 1 diabetic women [1, 7–9]. Hypertrophic cardiomyopathy (HCM, mainly interventricular septal hypertrophy) can be demonstrated in 25–45% of offspring of type 1 diabetic women [9–13]. Interventricular septal hypertrophy may be associated with functional cardiac changes during pregnancy as well as in the neonatal period [13–18] and seems to normalize within the first six months after birth [12, 13]. Despite the fact that possible mechanisms regulating the development and resolution of neonatal HCM have been investigated in diabetic rats, they are still unknown [19, 20]. It is therefore not clear whether neonatal HCM may be important in terms of residual cardiac pathology at later age. However, to the best of our knowledge no follow-up studies regarding cardiac structure or function have been performed in offspring of women with type 1 diabetes at later age.

Because of the high prevalence of HCM in the neonatal period and the risk of later cardiovascular diseases in offspring of type 1 diabetic women, we hypothesized that cardiac dimensions and/or function may be altered at later age. The objectives of this study were to evaluate cardiac dimensions and function at school age in children who were born

Table 1: Maternal and child characteristics in ODM and controls.

	Controls	ODM	P
n	30	30	
Maternal characteristics			
Age at delivery (years)	33.8 ± 3.0	31.4 ± 3.9	0.01
Parity (nulliparity)	10 (33.3)	21 (70.0)	<0.01
Race: Caucasian	30 (100)	29 (96.7)	1.0
Pregnancy characteristics			
Maternal smoking	1 (3.3)	2 (6.7)	1.0
Preeclampsia	2 (6.7)	4 (13.3)	0.7
Mean HbA1c 1st trim. (%)	—	6.51 ± 0.74	—
Mean HbA1c 2nd trim. (%)	—	6.04 ± 0.85	—
Mean HbA1c 3rd trim. (%)	—	6.32 ± 0.93	—
Child characteristics			
Gestational age (days)	277 [270–284]	260 [246–268]	<0.01
Birth weight (grams)	3793 ± 631	3400 ± 646	0.02
Birth weight percentile	87 [20–95]	84 [50–98]	0.2
Neonatal macrosomia	15 (50.0)	14 (46.7)	0.8
Sex (male)	16 (53.3)	14 (46.7)	0.6
Congenital malformation	0 (0)	1 (3.3)[a]	1.0
HCM at birth	0 (0)	3 (10.0)	0.2
Height at age 7 (cm)	131.0 ± 5.7	129.7 ± 5.9	0.4
BMI at age 7 (kg/m^2)	15.3 [14.9–16.9]	16.3 [15.5–17.6]	0.1
SBP at age 7 (mmHg)	95.5 [91–100]	97 [94–105]	0.09
DBP at age 7 (mmHg)	58.0 ± 4.0	58.1 ± 5.0	0.9

Data represent mean ± standard deviation, median with interquartile range, or number with percentage. [a]Single umbilical artery. Trim.: trimester; HCM: hypertrophic cardiomyopathy; SBP: systolic blood pressure; DBP: diastolic blood pressure.

after a type 1 diabetic pregnancy in relation to neonatal macrosomia and maternal glycemic control during pregnancy and to compare these measurements to those in a control group of children of nondiabetic women.

2. Materials and Methods

2.1. Study Population. The study group consisted of offspring of type 1 diabetic mothers (ODMs) who participated in a previous nationwide study on type 1 diabetes and pregnancy outcome in The Netherlands [1]. We performed a follow-up study in 213 of these children at school age, which consisted of a home visit (for anthropometric measurements, blood pressure recordings, and neurocognitive tests) and a fasting blood sample on a separate occasion. More details of this cohort and results from anthropometric and cardiovascular measurements have been described elsewhere [21, 22]. ODM who participated in the follow-up study and lived within 50 kilometers of our hospital ($n = 43$) were invited for an additional echocardiogram, and 30 of them participated. Mean age of the ODM at time of the echocardiogram was 7.6 years (range 7.3–8.1). Information regarding maternal characteristics and pregnancy outcome was obtained from the previous study on pregnancy outcome [1], which had been provided by the attending gynecologist/internist. Information on neonatal outcome (including clinical diagnosis of HCM) had been provided by the attending pediatrician. Neonatal macrosomia was defined as birth weight >90th percentile for gestational age, sex, and parity according to the Netherlands Perinatal Registry data [23].

The control group of the original follow-up study consisted of randomly selected offspring of nondiabetic women without severe maternal disease during pregnancy, who were born in the same period as the ODM at the University Obstetric Center, Utrecht, The Netherlands ($N = 79$). In this center both low- and high-risk women from the province of Utrecht (from cities as well as from the countryside) deliver. From this control group we invited children based on order of inclusion to participate in an additional echocardiography study until we included 15 macrosomic and 15 nonmacrosomic controls.

Mean age of the controls at time of the echocardiogram was 7.4 years (range 6.9–8.1). Information regarding maternal characteristics and pregnancy outcome was obtained from hospital records and additional questionnaires.

This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands. All parents gave written informed consent.

2.2. Measurements. During a home visit (previous to the echocardiography) blood pressure was recorded three times on the right arm in sitting position after five minutes of rest

Table 2: Echocardiographic measurements in ODM and controls at 7-8 years of age.

	Controls	ODM	P
n	30	30	
Dimensions			
IVSd (Z-score)	0.74 [0.30–1.12]	0.70 [0.28–1.15]	0.9
LVPWd (Z-score)	0.78 [0.29–1.38]	0.84 [0.36–1.18]	0.8
LVEDd (Z-score)	0.05 [−0.53–0.27]	−0.36 [−0.80–0.22]	0.2
Systolic LV function			
SF (%)	34.6 ± 4.9	35.3 ± 4.4	0.6
CO (mL/min/kg)	116 [102–134]	117 [99–131]	0.8
IVS ′S (cm/s)	7.4 [7.0–8.0]	7.4 [7.0–8.1]	0.5
LVPW ′S (cm/s)	10.6 [9.6–11.6]	10.0 [8.5–11.4]	0.3
Systolic RV function			
TAPSE (cm)	1.99 [1.85–2.21]	1.98 [1.86–2.17]	0.9
TR max PG (mmHg)	15.0 [14.1–17.0]	15.8 [13.1–17.3]	0.7
Diastolic LV function			
E/A ratio	2.2 [2.0–2.37]	2.14 [1.74–2.75]	0.9
S/D ratio	0.83 ± 0.27	0.83 ± 0.25	1.0
E/E′ ratio	6.1 [5.4–6.8]	6.3 [5.7–7.3]	0.4
MV DecT (ms)	175.5 ± 30.6	173.1 ± 33.7	0.8
IVS ′De (cm/s)	13.2 [12.7–14.4]	13.3 [12.0–14.9]	0.7
IVS ′Da (cm/s)	5.5 [5.0–6.5]	6.0 [5.4–6.1]	0.5
LVPW ′De (cm/s)	17.9 [15.6–19.7]	18.2 [16.5–19.0]	0.7
LVPW ′Da (cm/s)	6.2 [5.1–7.0]	6.7 [5.7–7.5]	0.2

Data represent means ± standard deviation or median with interquartile range. IVSd: interventricular septal end diastolic dimension; LVPWd: left ventricular posterior wall end diastolic dimension; LVEDd: left ventricular end diastolic dimension; SF: shortening fraction; CO: cardiac output; TAPSE: tricuspid annular plane systolic excursion; TR max PG: maximum tricuspid regurgitation pressure gradient; E/A: ratio of early and late left ventricular filling speed; S/D: ratio of systolic and diastolic pulmonary vein filling speed; E/E′ ratio: ratio of early diastolic peak E to E′ velocity; MV DecT: mitral valve deceleration time; ′S, ′De, ′Da: peak wall motion velocity during systole, early diastole or late diastole.

with a two-minute interval period, using an automated oscillometric device (DINAMAP, Critikon, Tampa, Fla). The average of the last two measurements of systolic (SBP) and diastolic (DBP) blood pressure was used for analysis. The children's height and weight were measured on the day of the echocardiography, and BMI was calculated.

All participants underwent a full echocardiographic evaluation including a structural echo for cardiac defects and evaluation of systolic and diastolic left ventricular function. Diastolic dimensions of the left ventricle (LVEDd), interventricular septum (IVSd), and left ventricular posterior wall (LVPWd) were measured and Z-scores (corrected for height and weight) calculated [24]. Systolic left ventricular function was evaluated using shortening fraction (SF) and tissue Doppler imaging of the IVS and LVPW with measurement of IVS ′S and LVPW ′S (systolic peak wall motion velocity) [25–27]. Finally cardiac output (CO) was calculated per kilogram body weight as $CO = (SV \cdot HR)$ (with SV being stroke volume and HR being heart rate). SV was calculated as $SV = LVOT_{area} \cdot VTI(LVOT)$, with $LVOT_{area}$ being left ventricular outflow tract area ($\pi \cdot (\text{diameter}/2)^2$) and VTI(LVOT) being velocity time integral of LVOT which was established through averaging three pulsed wave Doppler tracings in the LVOT. Systolic right ventricular function was evaluated based on measurement of the tricuspid annular plane systolic excursion (TAPSE). Maximal tricuspid regurgitation pressure gradient (TR max PG) was measured if present to estimate RV pressure. Diastolic left ventricular function was evaluated with pulsed wave Doppler signal of the mitral valve inflow pattern and pulmonary vein pattern [28]. E/A and S/D ratios were calculated (ratio of early/late left ventricular filling speed and ratio of systolic/diastolic pulmonary vein filling speed, resp.). Tissue Doppler imaging of the IVS and LVPW was performed with measurement of ′De (early diastolic peak wall motion velocity) and ′Da (late diastolic peak wall motion velocity) values. Finally, E/E′ ratios were calculated to estimate LV filling pressures [29].

All examinations were performed using a GE Vivid 7 Ultrasound Machine (GE Healthcare, UK). The echo technician was blinded for the origin of the participants (ODM or controls).

2.3. Statistical Methods. General characteristics and differences in measurements between ODM and controls and between subgroups of ODM were compared using independent t-test for normally distributed variables, Mann-Whitney U test for not normally distributed variables, and χ^2-test (or Fisher's exact test if appropriate) for categorical variables. The relation between maternal HbA1c level during pregnancy and measurements in the offspring was evaluated

Table 3: Echocardiographic measurements in macrosomic ODM, appropriate-for-dates ODM, and macrosomic controls at 7-8 years of age.

	ODM BW > p90	ODM BW ≤ p90	P^a	Controls BW > p90	P^b
n	14	16		15	
Age at echo (years)	7.6 [7.4–7.8]	7.6 [7.4–7.8]	0.7	7.6 [7.2–7.8]	0.7
BMI (kg/m^2)	16.6 [16.0–17.7]	16.0 [15.2–17.0]	0.2	15.3 [15.1–16.9]	0.1
Dimensions					
IVSd (Z-score)	0.85 [0.31–1.29]	0.52 [0.25–1.11]	0.4	0.65 [0.07–1.10]	0.4
LVPWd (Z-score)	0.68 [0.21–1.21]	0.88 [0.48–1.14]	0.6	0.73 [0.03–1.03]	1.0
LVEDd (Z-score)	−0.37 [−0.60–0.25]	−0.35 [−1.22–0.25]	0.5	0.16 [−0.31–0.58]	0.2
Systolic LV function					
SF (%)	34.4 [31.4–37.7]	35.3 [33.5–38.7]	0.5	36.2 [33.9–41.8]	0.3
CO (mL/min/kg)	117 [113–126]	105 [102–136]	0.1	114 [100–133]	0.8
IVS ′S (cm/s)	7.2 [7.0–8.0]	8.0 [7.0–8.2]	0.6	8.0 [7.4–8.0]	0.4
LVPW ′S (cm/s)	9.8 [8.1–11.2]	10.0 [9.0–11.4]	0.6	10.7 [9.7–12.0]	0.4
Systolic RV function					
TAPSE (cm)	2.0 [1.8–2.3]	2.0 [1.9–2.1]	0.9	2.0 [1.9–2.1]	1.0
TR max PG (mmHg)	15.7 [13.1–17.3]	15.8 [13.3–17.4]	0.8	15.8 [14.5–18.2]	1.0
Diastolic LV function					
E/A ratio	2.1 [1.6–2.7]	2.1 [1.8–2.9]	0.4	2.1 [2.0–2.5]	1.0
S/D ratio	0.8 [0.7–1.0]	0.8 [0.6–0.9]	0.7	0.8 [0.7–1.0]	0.9
E/E′ ratio	6.1 [5.1–7.1]	6.5 [5.8–7.4]	0.7	5.9 [5.3–6.5]	0.6
MV DecT (ms)	175 [149–205]	176 [162–189]	0.8	176 [158–210]	0.6
IVS ′De (cm/s)	13.3 [12.0–15.0]	13.3 [11.8–14.5]	0.7	14.0 [13.0–15.0]	0.4
IVS ′Da (cm/s)	6.0 [5.5–6.0]	6.0 [5.4–6.3]	0.9	6.0 [5.0–7.0]	1.0
LVPW ′De (cm/s)	19.0 [18.2–20.7]	17.8 [16.3–18.8]	0.1	18.4 [17.0–20.0]	0.6
LVPW ′Da (cm/s)	6.2 [5.7–7.1]	7.0 [5.8–7.5]	0.6	6.3 [5.5–7.9]	1.0

Data represent median with interquartile range. [a]Macrosomic ODM versus appropriate-for-date ODM. [b]Macrosomic ODM versus macrosomic controls. BW: birth weight.

using Pearson's (or Spearman's, if appropriate) correlation coefficients. Data were analyzed using SPSS 15.0 for Windows (SPSS, Chicago, Ill). A P value <0.05 was considered to be statistically significant.

3. Results and Discussion

3.1. General Characteristics. Participating mothers in the ODM group ($n = 30$) only differed significantly from the nonparticipating mothers (i.e., women who had participated in the previous nationwide study on pregnancy outcome but had not participated in this study, $n = 283$) regarding parity (70.0% versus 49.8% nulliparous women, $P = 0.04$). All other maternal and neonatal characteristics did not significantly differ between the participating and nonparticipating ODM group.

In the participating ODM group, maternal mean age at delivery was significantly lower compared with that in the control group, and the percentage of nulliparous women was significantly higher (Table 1). Mean gestational age at delivery and mean birth weight were lower in ODM compared with controls. The macrosomic and appropriate-for-date ODM subgroups did not significantly differ regarding maternal or child characteristics, except for a higher mean birth weight in macrosomic ODM (3835 (3459–4210) grams versus 3132 (2748–3495) grams, $P < 0.01$). Neonatal HCM was diagnosed in three children from the ODM group (two boys and one girl) [1]. Maternal and child characteristics of these three children did not significantly differ from the rest of the ODM group. Mean systolic blood pressure in ODM was slightly higher compared with controls, but the difference did not reach significance (Table 1).

3.2. Echocardiography. There were no significant differences in cardiac dimensions or systolic and diastolic cardiac function parameters between ODM and controls at 7 years of age (Table 2). All cardiac dimensions and function parameters in the three children with neonatal HCM were within the normal range (Figure 1(a)) and did not significantly differ from the other ODM or from controls. Subgroup analyses showed no significant differences in cardiac function or dimensions between macrosomic and appropriate-for-date ODM or between macrosomic ODM and macrosomic controls (Table 3).

Echocardiographic measurements in ODM did not significantly correlate with maternal glycemic control during

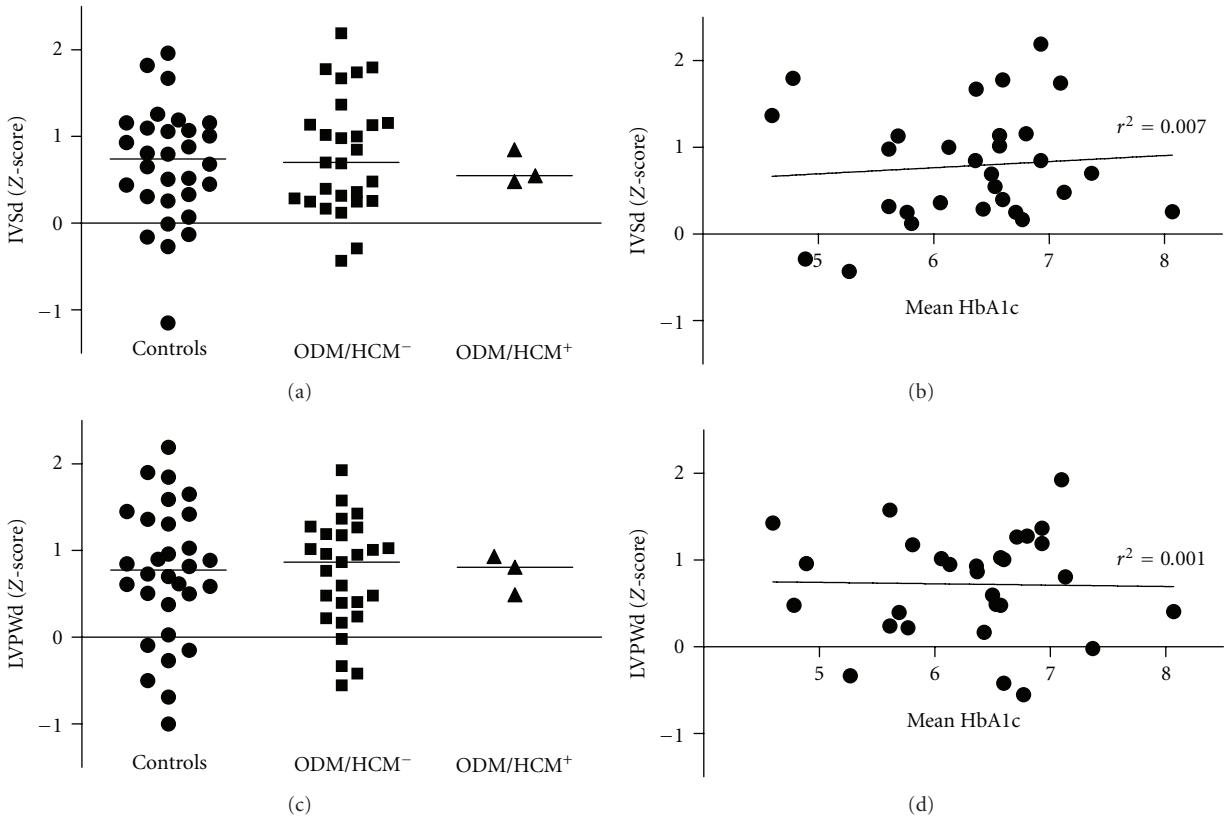


Figure 1: Cardiac dimensions in ODM regarding (a) neonatal hypertrophic cardiomyopathy and (b) maternal glycemic control during pregnancy (mean HbA1c level). ODM/HCM+ and ODM/HCM−: offspring of type 1 diabetic mothers with (+) or without (−) neonatal hypertrophic cardiomyopathy.

pregnancy (assessed by mean HbA1c level during first, second, and third trimester and mean HbA1c level during pregnancy; see also Figure 1(b)).

4. Discussion

Since (subclinical) HCM can be demonstrated in up to 45% of ODM and long-term cardiovascular sequelae in offspring born after a type 1 diabetic pregnancy may already present in childhood [2], we hypothesized that subtle changes in cardiac dimensions or function might also be present in ODM at school age. In this study, we are the first to show that systolic and diastolic function as well as cardiac dimensions in ODM at 7-8 years of age are completely normal and comparable with those in a control group of nondiabetic women.

In our cohort of ODM only three children (out of 30) were diagnosed with HCM after birth. However, in newborn ODM from our cohort echocardiography was only performed when HCM was clinically suspected, in contrast to the studies reporting higher prevalences of neonatal HCM [9–13]. As fetal cardiac growth is promoted by binding of insulin to the cardiac insulin-like-growth-factor- (IGF-) 1 receptor, HCM is believed to resolve within weeks after birth due to normalization of fetal hyperinsulinaemia [30]. Indeed cardiac dimensions and function parameters in the three children with previous neonatal HCM were normal at 7 years of age, but a larger prospective follow-up study of ODM with HCM should substantiate these results.

We previously showed that systolic blood pressure was significantly higher in ODM compared with controls [22]. In this subgroup of children who underwent additional echocardiography, the difference in systolic blood pressure did not reach statistical significance, most likely due to the fact that the groups were smaller. Despite a slightly higher mean SBP in ODM there were no differences in left ventricular function parameters between controls and ODM jet. Larger follow-up studies are necessary to investigate whether the difference in systolic blood pressure persists throughout childhood and may have consequences for cardiac function in later life.

Previous studies have shown that offspring of diabetic women who were macrosomic at birth are at increased risk of developing overweight and other cardiovascular risk factors [3, 4]. Therefore, we investigated the possible influence of neonatal macrosomia on cardiac outcome in ODM. We found that neither cardiac dimensions nor cardiac function significantly differed between macrosomic ODM and those with an appropriate-for-date birth weight. As some studies have shown more cardiac alterations in macrosomic newborns of diabetic mothers when compared with macrosomic newborns of nondiabetic mothers [31, 32], we compared cardiac outcome of macrosomic ODM with that of macrosomic

controls. No significant differences between those subgroups were found, indicating that neonatal macrosomia in ODM has no adverse effects on cardiac function at 7-8 years of age.

Extrapolating Freinkel's theory on "fuel-mediated teratogenesis," which states that high glucose concentrations during diabetic pregnancy make the developing tissues in the offspring vulnerable to alterations later in life [33], one might expect less favorable cardiovascular outcome in offspring of diabetic mothers with poorer glycemic control during pregnancy. However, maternal glycemic control during pregnancy did not significantly correlate with cardiac dimensions or function parameters in ODM at 7-8 years of age. It should be noted that maternal HbA1c may not be an accurate tool for the classification of level of glycemic control as it does not reflect the complexities of glycemic control in pregnant diabetic women [34].

As we are the first to describe cardiac dimensions and function in ODM at school age, this study should be a valuable addition to previous studies on long-term effects of a diabetic pregnancy on the development in the offspring. A limitation of this study is the relatively small sample size. Larger, ideally prospective follow-up studies should substantiate our results.

5. Conclusions

Cardiac function at 7-8 years of age in offspring of type 1 diabetic women is reassuring and comparable with that in children of nondiabetic women. Neonatal macrosomia and poorer maternal glycemic control during pregnancy were not related to adverse cardiac outcome in ODM.

Abbreviations

BMI: Body mass index
CO: Cardiac output
′Da: Peak wall motion velocity during late diastole (atrial contraction)
DBP: Diastolic blood pressure
′De: Peak wall motion velocity during early diastole
E/A: Ratio of early and late (atrial contraction) left ventricular filling speed
E/E′ ratio: Ratio of early diastolic peak E to E′ velocity
IVS: Interventricular septum
IVSd: Interventricular septal end diastolic dimension
LVEDd: Left ventricular end diastolic dimension
LVPW: Left ventricular posterior wall
LVPWd: Left ventricular posterior wall end diastolic dimension
MV DecT: Mitral valve deceleration time
ODM: Offspring of type 1 diabetic mothers
′S: Peak wall motion velocity during systole
SBP: Systolic blood pressure
S/D: Ratio of systolic and diastolic pulmonary vein filling speed
SF: Shortening fraction
TAPSE: Tricuspid annular plane systolic excursion
TR max PG: Maximum tricuspid regurgitation pressure gradient.

Acknowledgments

This study was funded by a grant from the Dutch Diabetes Research Foundation (Project no. 2004.00.038). All authors state that they have no conflict of interests to disclose and they declare that the Dutch Diabetes Research Foundation had no involvement in any part of the study.

References

[1] I. M. Evers, H. W. de Valk, and G. H. A. Visser, "Risk of complications of pregnancy in women with type 1 diabetes-nationwide prospective study in the Netherlands," *British Medical Journal*, vol. 328, no. 7445, pp. 915–918, 2004.

[2] U. Simeoni and D. J. Barker, "Offspring of diabetic pregnancy: long-term outcomes," *Seminars in Fetal and Neonatal Medicine*, vol. 14, no. 2, pp. 119–124, 2009.

[3] A. Plagemann, T. Harder, R. Kohlhoff, W. Rohde, and G. Dörner, "Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes," *International Journal of Obesity*, vol. 21, no. 6, pp. 451–456, 1997.

[4] C. M. Boney, A. Verma, R. Tucker, and B. R. Vohr, "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus," *Pediatrics*, vol. 115, no. 3, pp. e290–e296, 2005.

[5] P. A. M. Roest, L. van Iperen, S. Vis et al., "Exposure of neural crest cells to elevated glucose leads to congenital heart defects, an effect that can be prevented by N-acetylcysteine," *Birth Defects Research Part A—Clinical and Molecular Teratology*, vol. 79, no. 3, pp. 231–235, 2007.

[6] D. G. M. Molin, P. A. M. Roest, H. Nordstrand et al., "Disturbed morphogenesis of cardiac outflow tract and increased rate of aortic arch anomalies in the offspring of diabetic rats," *Birth Defects Research Part A—Clinical and Molecular Teratology*, vol. 70, no. 12, pp. 927–938, 2004.

[7] D. M. Jensen, P. Damm, L. Moelsted-Pedersen et al., "Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study," *Diabetes Care*, vol. 27, no. 12, pp. 2819–2823, 2004.

[8] M. C. M. Macintosh, K. M. Fleming, J. A. Bailey et al., "Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study," *British Medical Journal*, vol. 333, no. 7560, pp. 177–180, 2006.

[9] R. M. Abu-Sulaiman and B. Subaih, "Congenital heart disease in infants of diabetic mothers: echocardiographic study," *Pediatric Cardiology*, vol. 25, no. 2, pp. 137–140, 2004.

[10] F. J. Walther, B. Siassi, J. King, and P. Y. K. Wu, "Cardiac output in infants of insulin-dependent diabetic mothers," *Journal of Pediatrics*, vol. 107, no. 1, pp. 109–114, 1985.

[11] M. D. Reller and S. Kaplan, "Hypertrophic cardiomyopathy in infants of diabetic mothers: an update," *American Journal of Perinatology*, vol. 5, no. 4, pp. 353–358, 1988.

[12] R. Oberhoffer, J. Högel, F. Stoz, E. Kohne, and D. Lang, "Cardiac and extracardiac complications in infants of diabetic mothers and their relation to parameters of carbohydrate

metaholism," *European Journal of Pediatrics*, vol. 156, no. 4, pp. 262–265, 1997.

[13] S. Ullmo, Y. Vial, S. Di Bernardo et al., "Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study," *European Heart Journal*, vol. 28, no. 11, pp. 1319–1325, 2007.

[14] A. K. Deorari, A. Saxena, M. Singh, and S. Shrivastava, "Echocardiographic assessment of infants born to diabetic mothers," *Archives of Disease in Childhood*, vol. 64, no. 5, pp. 721–724, 1989.

[15] G. Rizzo, D. Arduini, and C. Romanini, "Cardiac function in fetuses of type I diabetic mothers," *American Journal of Obstetrics and Gynecology*, vol. 164, no. 3, pp. 837–843, 1991.

[16] L. A. Lisowski, P. M. Verheijen, M. M. C. de Smedt, G. H. A. Visser, and E. J. Meijboom, "Altered fetal circulation in type-1 diabetic pregnancies," *Ultrasound in Obstetrics and Gynecology*, vol. 21, no. 4, pp. 365–369, 2003.

[17] A. Kozák-Bárány, E. Jokinen, P. Kero, J. Tuominen, T. Rönnemaa, and I. Välimäki, "Impaired left ventricular diastolic function in newborn infants of mothers with pregestational or gestational diabetes with good glycemic control," *Early Human Development*, vol. 77, no. 1-2, pp. 13–22, 2004.

[18] N. E. Russell, M. Foley, B. T. Kinsley, R. G. Firth, M. Coffey, and F. M. McAuliffe, "Effect of pregestational diabetes mellitus on fetal cardiac function and structure," *American Journal of Obstetrics and Gynecology*, vol. 199, no. 3, pp. 312.e1–312.e7, 2008.

[19] B. E. Reinking, E. W. Wedemeyer, R. M. Weiss, J. L. Segar, and T. D. Scholz, "Cardiomyopathy in offspring of diabetic rats is associated with activation of the MAPK and apoptotic pathways," *Cardiovascular Diabetology*, vol. 8, article 43, 2009.

[20] M. L. S. Lindegaard, E. M. M. Svarrer, P. Damm, E. R. Mathiesen, and L. B. Nielsen, "Increased LDL cholesterol and CRP in infants of mothers with type 1 diabetes," *Diabetes/Metabolism Research and Reviews*, vol. 24, no. 6, pp. 465–471, 2008.

[21] M. Rijpert, I. M. Evers, M. A. M. J. de Vroede, H. W. de Valk, C. J. Heijnen, and G. H. A. Visser, "Risk factors for childhood overweight in offspring of type 1 diabetic women with adequate glycemic control during pregnancy: nationwide follow-up study in the Netherlands," *Diabetes Care*, vol. 32, no. 11, pp. 2099–2104, 2009.

[22] M. Rijpert, I. M. Evers, H. W. de Valk et al., "Cardiovascular and metabolic outcome in 6-8year old offspring of women with type 1 diabetes with near-optimal glycaemic control during pregnancy," *Early Human Development*, vol. 87, no. 1, pp. 49–54, 2011.

[23] G. H. A. Visser, P. H. C. Eilers, P. M. Elferink-Stinkens, H. M. W. M. Merkus, and J. M. Wit, "New Dutch reference curves for birthweight by gestational age," *Early Human Development*, vol. 85, no. 12, pp. 737–744, 2009.

[24] M. D. Pettersen, W. Du, M. E. Skeens, and R. A. Humes, "Regression equations for calculation of Z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study," *Journal of the American Society of Echocardiography*, vol. 21, no. 8, pp. 922–934, 2008.

[25] B. W. Eidem, C. J. McMahon, R. R. Cohen et al., "Impact of cardiac growth on doppler tissue imaging velocities: a study in healthy children," *Journal of the American Society of Echocardiography*, vol. 17, no. 3, pp. 212–221, 2004.

[26] L. Kapusta, J. M. Thijssen, J. Groot-Loonen, T. Antonius, J. Mulder, and O. Daniëls, "Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines," *Ultrasound in Medicine and Biology*, vol. 26, no. 7, pp. 1099–1108, 2000.

[27] D. A. Roberson, W. Cui, Z. Chen, L. F. Madronero, and B. F. Cuneo, "Annular and septal doppler tissue imaging in children: normal z-score tables and effects of age, heart rate, and body surface area," *Journal of the American Society of Echocardiography*, vol. 20, no. 11, pp. 1276–1284, 2007.

[28] J. K. Oh, C. P. Appleton, L. K. Hatle, R. A. Nishimura, J. B. Seward, and A. J. Tajik, "The noninvasive assessment of left ventricular diastolic function with two-dimensional and doppler echocardiography," *Journal of the American Society of Echocardiography*, vol. 10, no. 3, pp. 246–270, 1997.

[29] S. F. Nagueh, C. P. Appleton, T. C. Gillebert et al., "Recommendations for the evaluation of left ventricular diastolic function by echocardiography," *Journal of the American Society of Echocardiography*, vol. 22, no. 2, pp. 107–133, 2009.

[30] J. L. Nold and M. K. Georgieff, "Infants of diabetic mothers," *Pediatric Clinics of North America*, vol. 51, no. 3, pp. 619–637, 2004.

[31] K. Demiroren, L. Cam, B. Oran et al., "Echocardiographic measurements in infants of diabetic mothers and macrosomic infants of nondiabetic mothers," *Journal of Perinatal Medicine*, vol. 33, no. 3, pp. 232–235, 2005.

[32] M. M. Vela-Huerta, A. Vargas-Origel, and A. Olvera-Lopez, "Asymmetrical septal hypertrophy in newborn infants of diabetic mothers," *American Journal of Perinatology*, vol. 17, no. 2, pp. 89–94, 2000.

[33] N. Freinkel, "Of pregnancy and progeny," *Diabetes*, vol. 29, no. 12, pp. 1023–1035, 1980.

[34] A. Kerssen, H. W. de Valk, and G. H. A. Visser, "Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus?" *Diabetologia*, vol. 49, no. 1, pp. 25–28, 2006.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 105076, 16 pages
doi:10.1155/2011/105076

Review Article

Early-Life Origins of Type 2 Diabetes: Fetal Programming of the Beta-Cell Mass

Bernard Portha, Audrey Chavey, and Jamileh Movassat

Université Paris-Diderot, Sorbonne-Paris-Cité, Laboratoire B2PE (Biologie et Pathologie du Pancréas Endocrine), Unité BFA (Biologie Fonctionnelle et Adaptive), EAC 4413 Centre National de la Recherche Scientifique, 75205 Paris, France

Correspondence should be addressed to Bernard Portha, portha@univ-paris-diderot.fr

Received 30 May 2011; Revised 2 August 2011; Accepted 2 August 2011

Academic Editor: Christine Maric-Bilkan

A substantial body of evidence suggests that an abnormal intrauterine milieu elicited by maternal metabolic disturbances as diverse as undernutrition, placental insufficiency, diabetes or obesity, may program susceptibility in the fetus to later develop chronic degenerative diseases, such as obesity, hypertension, cardiovascular diseases and diabetes. This paper examines the developmental programming of glucose intolerance/diabetes by disturbed intrauterine metabolic condition experimentally obtained in various rodent models of maternal protein restriction, caloric restriction, overnutrition or diabetes, with a focus on the alteration of the developing beta-cell mass. In most of the cases, whatever the type of initial maternal metabolic stress, the beta-cell adaptive growth which normally occurs during gestation, does not take place in the pregnant offspring and this results in the development of gestational diabetes. Therefore gestational diabetes turns to be the ultimate insult targeting the offspring beta-cell mass and propagates diabetes risk to the next generation again. The aetiology and the transmission of spontaneous diabetes as encountered in the GK/Par rat model of type 2 diabetes, are discussed in such a perspective. This review also discusses the non-genomic mechanisms involved in the installation of the programmed effect as well as in its intergenerational transmission.

1. Perinatal Risk Factors for Diabetes in Later Life

Type 2 diabetes mellitus (T2D) is a complex polygenic disease that often manifests years before eventual clinical diagnosis [1]. T2D develops as a result of a failure to adequately increase beta-cell function and mass to meet the demands of prevailing insulin resistance [2]. The contribution of beta-cell failure to the pathophysiology of T2D is supported by islet pathology that reveals a beta-cell deficit of approximately 50 and 65% in individuals with impaired fasting glucose and T2D, respectively [3]. Consistent with these observations, most genes linked to T2D by genome-wide association scans have been shown to influence some aspects of beta-cell biology, such as regulation of beta-cell secretory function and development and growth of beta-cell mass [4]. It has long been recognized that nutrient availability during fetal and early postnatal life is an important determinant of adult health [5].

There are strong arguments showing that T2D is more prevalent among subjects that were in utero exposed to maternal diabetes (IUED). The role of maternal inheritance in T2D has been reported in a majority of epidemiological studies [6, 7]. To determine the role of the intrauterine diabetic environment per se, the prevalence of diabetes was compared in Pima nuclear families in which at least one sibling was born before and one after the mother was diagnosed with T2D. Offspring born after their mother displayed diabetes had a fourfold higher risk of diabetes and a higher body mass index (BMI) than their full siblings born before their mother developed diabetes [8]. These findings indicate that intrauterine exposure to a diabetic environment increases risk of obesity and T2D beyond that attributable to genetic factors, at least in Pima Indians. To circumvent the confounding effect of genes linked to early onset T2D and transmitted by the pregnant T2D mother, the effect of fetal exposure to T1D was evaluated in adult offspring lacking T1D immunological markers. A 33% prevalence of

IGT was reported in offspring of T1D mothers compared with none in offspring of T1D fathers (control group) [9]. Altogether, these findings suggest that fetal exposure to maternal diabetes is indeed associated with abnormal glucose homeostasis in offspring and may participate in the excess of maternal transmission in T2D. In adult Pima Indians with normal glucose tolerance and who had been exposed to an intrauterine diabetic environment, acute insulin response to i.v. glucose was found reduced in those offspring whose mother was diabetic before pregnancy while it remained normal in those whose mother developed diabetes after pregnancy, [10]. Body fat and insulin sensitivity (euglycemic hyperinsulinemic clamp) were similar in the two groups of subjects [10]. In the same study, acute insulin response was found reduced in offspring of parents (mother or father) with early onset of T2D [10], suggesting that gene(s) linked to early-onset diabetes is(are) associated with reduced insulin secretory response to glucose [11]. Offspring of T1D mothers had reduced insulin secretion, more pronounced in IGT subjects, but similar fat mass and insulin action compared with offspring of T1D fathers [9]. Also in nondiabetic offspring of mothers with young-onset T2D (diagnosed under age 50), beta-cell function (early insulin release after oral glucose) was found decreased as compared to that of offspring of fathers with young-onset T2D [12]. Therefore, human studies suggest that insulin secretion defect participates in the abnormal glucose tolerance observed in adult offspring exposed to maternal diabetes during fetal life. Importantly, they showed that insulin secretion may be reduced even in normal glucose-tolerant offspring. Nevertheless, in children and adolescent offspring, insulin resistance involvement was suggested and may be related, at least in part, to their higher body weight.

Beside studies in IUED populations, prenatal nutrient insufficiency resulting in low birth weight is also associated with increased risk for development of obesity, cardiovascular disease, and T2D [13–15]. The association between low birth weight and development of T2D was first reported in classic studies by Hales et al. [15] that demonstrated a severalfold increase in the incidence of glucose intolerance and T2D in adult males that were born small compared with those who were born at a normal birth weight. These seminal observations since have been consistently reproduced by numerous investigators worldwide [16]. Although epidemiological evidence linking low birth weight with increased susceptibility to T2DM is strong [16], the molecular and physiological mechanisms underlying this association are still under investigation [17]. It has long been appreciated that low birth weight is associated with adult insulin resistance, which can contribute to the increased risk in development of T2D [18]. However, susceptibility to T2D in low-birth-weight individuals has also been hypothesized to be attributed to inadequate beta-cell mass formation [15]. Because it is not possible to measure beta-cell mass in vivo, this hypothesis cannot yet be tested directly in humans. However, evidence suggests that inadequate beta-cell formation in utero may underlie subsequent susceptibility for T2D. First, the fetal period is critical for endocrine pancreatic development in rodents and humans [19]. Second, clinical data show that children and adults with low birth weight demonstrate impaired beta-cell function compared with their normal birth-weight counterparts [20, 21] and human fetuses with severe growth retardation, have a reduction in pancreatic endocrine cell mass [22].

In this paper, we discuss the evidence for beta-cell dysfunction in IUED (in utero exposed to maternal diabetes), IUEO (in utero exposed to maternal overnutrition) and IUGR (in utero growth restriction) animal models, focusing on the strengths and limits of each, in order to define critical periods and types of alterations that can lead to impaired beta-cell function. We also discuss several potential mechanisms dissected in relevant animal models that begin to explain this outcome.

2. Compromised Intrauterine Environment and Risk for Diabetes in Later Life

Thanks to abundant studies mostly in rodents in which the foetal environment can be manipulated, a substantial body of data now addresses the mechanisms involved in the developmental programming of glucose intolerance and T2D.

IUED Models. In rat, maternal diabetes may be induced experimentally by streptozotocin (STZ) injection that selectively destroys beta-cells. Mild or severe diabetes ensue depending on the dose used. At birth, the progeny of mild diabetic mothers had normal weight or slight macrosomia and an enhanced percentage of pancreatic endocrine tissue due to hyperplasia and hypertrophy of the islet cells [24, 25], leading to a higher beta-cell mass that was hypervascularized [26]. The pancreatic insulin content and insulin secretion were raised in these fetuses [27]. On the other hand, fetuses from severe diabetic dams were small at birth and had decreased pancreatic weight [28]. Their beta-cells were almost degranulated, leading to low pancreatic insulin content and low plasma insulin [27]. Similar endocrine pancreas/beta-cell alterations with low beta-cell mass have been reported in fetuses from spontaneous diabetic BB rats [29] or spontaneous diabetic GK rats [30, 31]. The long-term consequences have been evaluated in the progeny of these models. Impaired glucose tolerance was observed in the offspring of mild STZ diabetic rats due to lower insulin secretion in response to glucose, while insulin resistance was reported in the offspring of the severe STZ diabetic mothers [32–34]. Glucose tolerance was also impaired in offspring of normal mothers receiving glucose infusion during late gestation, and it was associated with decreased glucose-induced insulin secretion [24, 35–37].

The greatest difficulty in most animal models of diabetic pregnancy has been the attainment of a stable degree of mild hyperglycemia during gestation. Though useful, most techniques used to achieve models of diabetes in pregnancy have some drawbacks. Maternal glucose infusions limited to the last trimester of pregnancy result in hyperglycemia and hyperinsulinemia and do not mimic the relative insulin deficiency of gestational diabetes [38]. The multiple lipid

and protein abnormalities associated with diabetes may be as important in the induction of fetal abnormalities as hyperglycemia, but they are not replicated by the maternal glucose infusion model. A concern of studies using STZ during pregnancy is the possibility that the toxin might cross the placenta and be directly harmful to the fetal pancreas and other fetal tissues, and thus make any analysis of the long-term effects of hyperglycemia in utero difficult [39]. The problem may be circumvented by giving STZ to female neonates who will later become pregnant: this will result in moderate gestational hyperglycemia [40]. Finally it must be recognized that none of the previously mentioned models will serve directly as a model of human gestational diabetes.

An ideal animal model to test the isolated impact of diabetic pregnancy would enter the pregnancy in a euglycemic state, become exposed to hyperglycaemic during whole pregnancy, and return postpartum to normoglycemic environment. Such a model also would allow study of the long-term effects of diabetes independent of any genetic influence. It was recently proposed that the pregnant GK rat being transferred normal Wistar (W) rat embryo represents a more relevant paradigm in such a perspective [41]. Using the GK/Par rat (Figure 1) we have transferred W rat oocytes to diabetic GK/Par females, and at their birth the W neonates were suckled by nondiabetic W foster mothers. Under these unique conditions, we have found that maternal diabetes negatively imprints the growth of a genetically normal (Wistar) beta-cell mass in a way as the insult is still present later at adult age as a decreased beta-cell population [42, 43]. Not only maternal diabetes but also intrauterine undernutrition induced by several means such as protein (IUPR) or calorie (IUCR) restriction, or alteration in the availability of the nutrients by uterine/placental insufficiency (UPI) induced by uterine artery ligation, alter early islet development and provoke lasting consequences in rodents.

IUCR Models. Global restrictions (to 40–50% of normal intake) (IUCR) in the last week of rat pregnancy results in low birth weight offspring with decreased beta-cell mass. Although these animals can regain their body and pancreatic weights upon normal postnatal feeding, they still demonstrate a reduced beta-cell mass and insulin content in adulthood [44, 45]. Extending this level of nutrient restriction during suckling results in a permanent reduction of beta-cell mass [46, 47] and subsequent age-dependent loss of glucose tolerance in the offspring [48]. Underfeeding the rat mothers during the first two weeks of gestation exerts no adverse effect upon insulin secretion and insulin action in the adult male offspring [49].

IUPR Models. The maternal protein restriction (5–8% as compared to 20% in normal diet) (IUPR) model has been one of the most extensively studied models. The low-protein-fed mothers give birth to growth-restricted offspring [50–54], and when suckled by their mothers maintained on the same low-protein fed, they remain permanently growth restricted, despite being weaned on a normal diet [53]. Reduced placental weight and endocrine and metabolic abnormalities are also observed [50, 55, 56]. Despite young offspring of low-protein-fed dams demonstrating improved glucose tolerance [56, 57], the male offspring undergo an age-dependent loss in glucose tolerance, such that by 17 months of age they develop T2D and insulin resistance [58]. Female offspring only develop hyperinsulinemia and impaired glucose tolerance at a much later age (21 months) [54]. Studies in this model have also demonstrated reductions in beta-cell mass [51], skeletal muscle mass [53], central adipose deposit weights [57, 59], and insulin signalling defects in muscle, adipocytes, and liver [59–61]. This IUPR model has also been associated with the development of hypertension with the kidney and the rennin-angiotensin system as playing a role [62].

UPI Models. Fetal growth retardation may also result from experimental uteroplacental insufficiency (UPI). Fetal UPI rats have decreased levels of glucose, insulin, IGF1, amino acids, and oxygen [63–65]. UPI offspring develop diabetes in later life [66, 67] with a phenotype that is similar to that observed in T2D humans with alterations in insulin secretion and action and a failure of beta-cell function and growth [68, 69].

IUEO Models. There are several reports on the consequences of a high-fat diet (during gestation only or both gestation and lactation) on the adult progeny. High-fat diet consumption by female rats malprograms the male offspring for glucose intolerance and increased body weight in adulthood [70]. Some of the observed consequences include reduced whole-body insulin sensitivity, impaired or normal insulin secretion and changes in the structure of pancreas [71–74], defective mesenteric artery endothelial function [75], hypertension [76, 77], alterations in renal functions [78], increased body adiposity [72, 76], deranged blood lipid profile [71, 76, 78], hyperleptinemia [72], and proatherogenic lesions [79]. There are not many reports on fetal islet adaptations due to a high-fat dietary modification in the dam. Cerf et al. [80] demonstrated that feeding rat female with a high-fat diet throughout gestation resulted in significant decreases in beta-cell volume and number resulting in hyperglycemia in 1-day-old newborn rat pups without changes in serum insulin concentrations. However, the report of fetal hyperinsulinemia in the high-fat term rat fetus [70] is not consistent with this finding.

Maternal obesity in mice, in the absence of diabetes, can also impair glucose tolerance in genetically normal offspring. This was shown using mothers carrying the Agouti (Ay) mutation on a C57BL/6 background. On this background, the Ay mutation produces marked obesity without diabetes. At adult age while maintained on normal diet, genetically normal, adult female offspring of Ay-positive mothers exhibited reduced glucose-induced insulin secretion in vivo [81].

Also male mice whose mothers consumed a high-fat diet were heavier, glucose intolerant, and insulin resistant and produced second-generation offspring who were insulin resistant, although not obese [82]. Whether this is

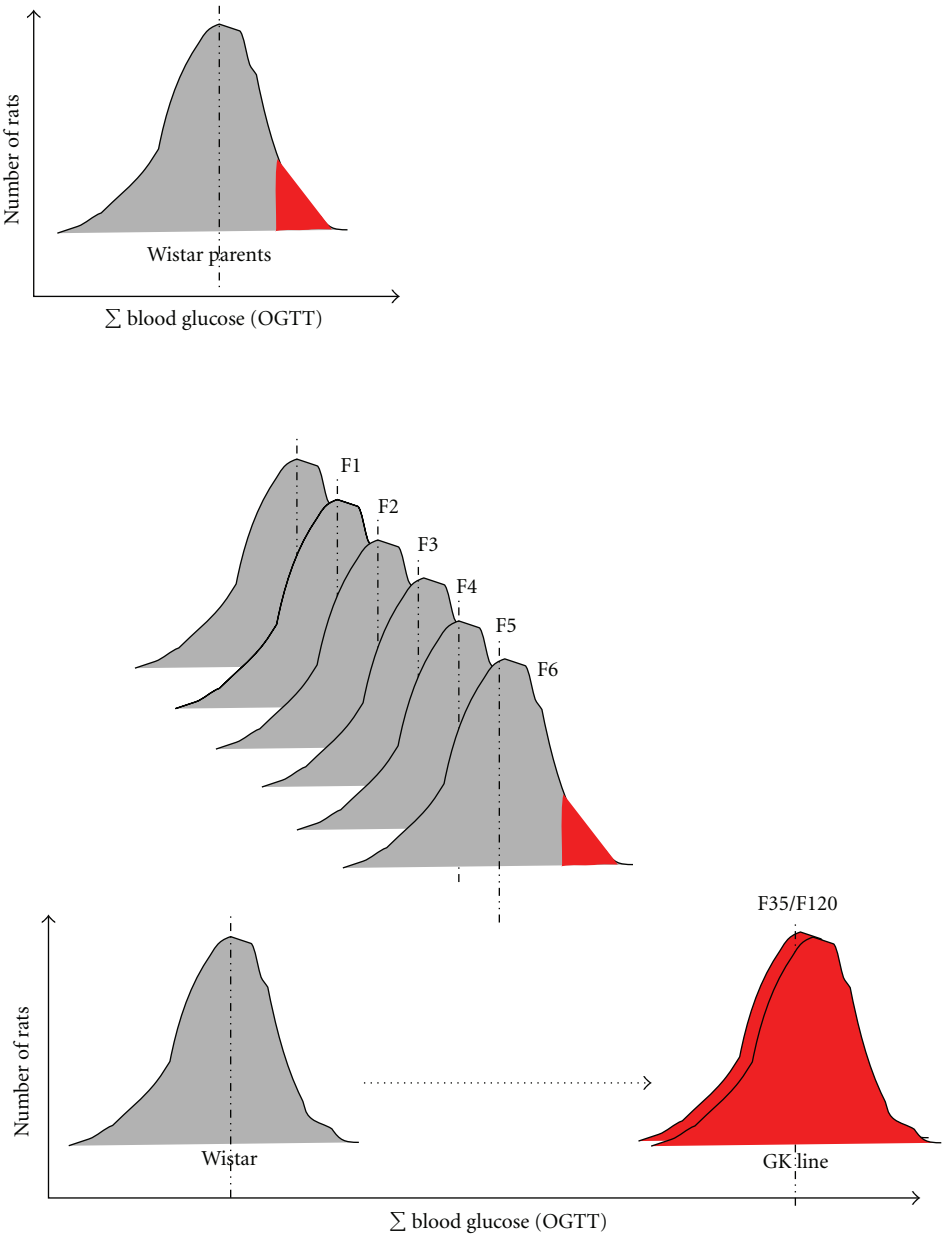


Figure 1: From the nondiabetic Wistar rat to the spontaneously diabetic GK (Goto-Kakizaki) rat. The inbred GK rat line (Wistar strain) was produced by Goto et al. at Tohoku University, Sendaï, Japan, by selective breeding of normal Wistar rats over many generations using glucose tolerance value (and not basal glucose value only) as a discriminant phenotype [23]. Only W rats selected at the upper limit of normal distribution for glucose tolerance were used. The diabetic state (basal hyperglycemia) was reported to become stable after the 30 generations of selective crosses in the original Japanese colony. Here is illustrated the distribution of the sum of blood glucose values ($\sum$ blood glucose) during standardised oral glucose tolerance tests (OGTTs) performed in original parent Wistar rats, in rats from generations F1 to F35 in the original Japanese colony and in rats from generations F35 to F120 bred under our conditions in Paris from 1989 until now (subline GK/Par). In the inbred GK/Par rat line, all rats are nonoverweight, nonketotic, and display moderate fasting hyperglycemia with strong postprandial glucose intolerance. No attenuation, nor aggravation, of the diabetic phenotype overtime (more than 20 years and 80 generations) was registered in the GK/Par line.

a consequence of paternal in utero exposure or their adult sequelae of obesity and diabetes is unclear. It was recently reported that chronic high-fat diet consumption in father rats induced increased body weight, adiposity, impaired glucose tolerance, and insulin sensitivity in their offspring [83]. Relative to controls, their female offspring had an early onset of impaired insulin secretion and glucose tolerance that worsened with time and normal adiposity. Among the differentially expressed islet genes, hypomethylation of the Il13ra2 gene was demonstrated. This is a proof of

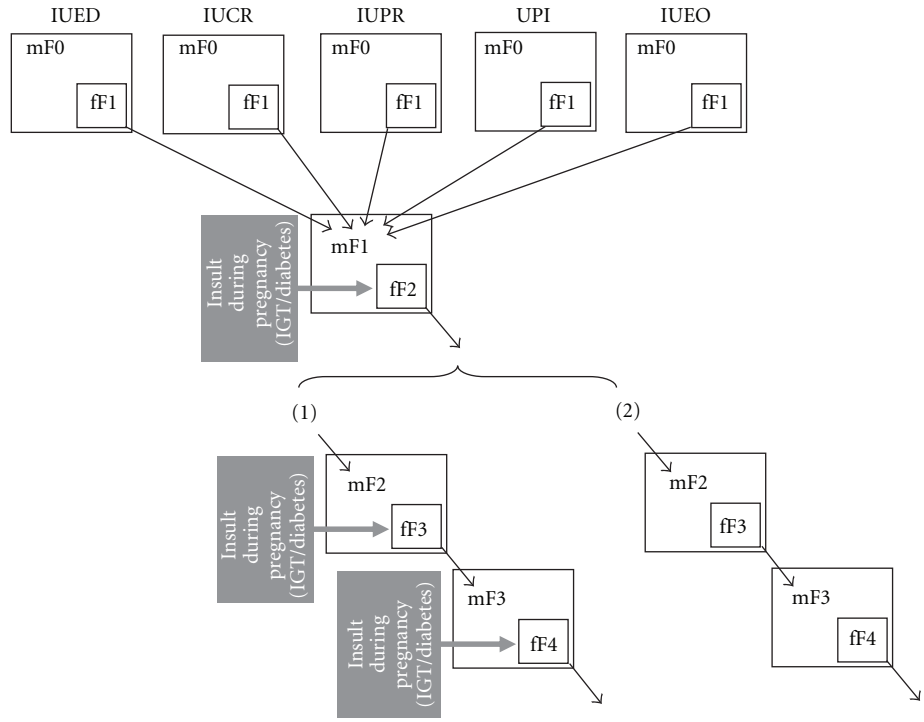


Figure 2: Mechanisms for the installation and intergenerational transmission of programmed beta cell mass (BCM) disruption in response to compromised intrauterine environment. The initial insults in F0 mother (mF0) impact the developing BCM of the fetuses (fF1). Diverse initial insults (IUED, IUCR, IUPR, UPI, IUEO), alone or in combination, give rise to the same programmed BCM outcome. Altered BCM phenotype in F1 females does not allow normal BCM adaptation during pregnancy and IGT/diabetes ensues (gestational diabetes). Gestational diabetes in the F1 pregnant mother (mF1) acting as an ultimate insult impacts the developing BCM of the F2 fetuses (fF2). Altered BCM phenotype in F2 females does not allow normal BCM adaptation during pregnancy and IGT/diabetes ensues (gestational diabetes). Gestational diabetes in the F2 pregnant mother (mF2) acting as an ultimate insult impacts the developing BCM of the F3 fetuses (fF3), therefore perpetuating similar BCM programming across generations. There are at least two potential scenarii for the transmission of BCM programming to subsequent generations: (1) the insult as seen in the F1 mother (IGT/diabetes insult during pregnancy) directly impairs BCM development, but BCM malprogramming is not necessarily irreversible. However, as the environmental insult (gestational diabetes) persists across generations, it recreates the same gestational phenotype in each subsequent generation (panel 1 in Figure 2); (2) the insult as seen in the F1 mother permanently affects BCM and results in the perpetuation of BCM malprogramming in the subsequent generations, in the absence of a further gestational insult (panel 2 in Figure 2). M: mother; f: fetus; F1: first-generation animals procreated by parent (F0) females submitted to experimentally disturbed metabolism during their pregnancy; F2: second-generation animals procreated by F1 females exposed to intrauterine-disturbed metabolism; IUED: in utero exposed to maternal diabetes; IUCR: in utero exposed to maternal calorie restriction; IUPR: in utero exposed to maternal protein restriction; UPI: uteroplacental insufficiency; IUEO: in utero exposed to maternal overnutrition or obesity.

concept that paternal high-fat-diet exposure programs beta-cell dysfunction in rat F1 female offspring. This is the first report in mammals of nongenetic, intergenerational transmission of metabolic sequelae of a high-fat diet from father to offspring [83].

Among the many types of maternal metabolic stress used to produce IUGR, hypercholesterolemia combined to high fat diet was recently added since feeding LDL receptor null ($LDLR^{-/-}$) mice with a high-fat resulted in litters with significant growth retardation. The $LDLR^{-/-}$ high-fat diet offspring developed significantly larger atherosclerotic lesions by 90 days compared with chow diet offspring [84]. Importantly, maternal hypoaminoacidemia proved to be an important antecedent in this hypercholesterolemic IUGR mouse [84] as in a protein-deficient IUGR mouse model [84] and an IUED rat model [85]. It may be an important link in the mechanisms that contribute to adult-onset glucose intolerance, obesity, and atherosclerosis. In this study beta-cell mass was not investigated.

To sum up, it turns to be manifest that, despite differences in the type, timing, and duration of intrauterine insult, most animal models of IUED, IUCR, IUPR, or IUEO have outcomes of impaired glucose tolerance or T2D (Figure 2).

3. Various Early-Life Stressors, the Same Target: The Developing Beta-Cell Mass

As abundantly illustrated in animal models, many early-life stressors such as maternal hyperglycaemia, undernutrition, overnutrition, hypercholesterolemia, corticosteroid therapy, uteroplacental insufficiency, or hypoxia trigger a beta-cell mass adaptive response in the fetus (Figure 2, Table 1).

Table 1: Beta-cell (BC) mass characteristics in rodent models of compromised intrauterine environment.

Rodent models	BC phenotype		
	fetal	neonatal/suckling	adult
IUED, mild STZD (F1)	Increased BC mass, high BC proliferation [24–27]	Increased BC mass, high BC proliferation, high islet vascularisation [24, 25]	Normal BC mass, low GSIS, low GT [24]
F2 issued from mild STZD F1	NR	NR	Low GSIS, low GT [26, 32]
IUED, severe STZD (F1)	low BC mass [27, 28]	NR	Increased BC mass, high GSIS, low GT [32–34, 39]
IUED, GI (F1)	Slightly increased BC mass, high BC proliferation [35]	NR	Low GSIS, low GT [24, 35–38]
F2 issued from GI F1	NR	NR	Low GSIS, low GT [35]
IUED, GK/Par	Low BC mass, low BC neogenesis [30, 31, 42, 86, 87]	Low BC mass, low BC neogenesis [88]	Low BC mass, low BC proliferation, low GSIS [23, 88, 89]
Severe IUCR (F1)	Increased BC mass, high BC neogenesis, high BC proliferation [46, 90–92]	NR	Low BC mass, low BC proliferation, low GSIS [46]
IUCR (F1)	Low BC mass, low BC neogenesis [44, 45, 93]	Low BC mass [47]	Low BC mass, low GSIS, low GT [44–49]
F2 issued from IUCR F1	Low BC mass, low BC neogenesis [94]	NR	Low GSIS, low GT [32]
IUPR (F1)	Low BC mass, low BC proliferation, low islet vascularization [50, 51, 93, 95]	Low BC mass [93]	Low BC mass, low GSIS, low GT [51, 53, 54, 56–62, 96–98]
F2 issued from IUPR F1	Low BC mass [26]	NR	Normal GT [99]
UPI (F1)	Normal BC mass, low BC proliferation, low islet vascularization [63–65]	Normal BC mass [65–67]	Low BC mass, low GSIS, low GT [66, 67, 100, 101]
F2 issued from UPI F1	NR	NR	Low BC mass, low BC proliferation, low GSIS, low GT [32]
IUEO (F1)	NR	Slightly reduced BC mass [80]	Normal or decreased GSIS, low GT [70–76, 81–84]
F2 issued from IUEO F1	NR	NR	Normal GT [82]

NR: not reported in the literature to the author's knowledge; GSIS: glucose-stimulated insulin secretion; GT: glucose tolerance; STZD: diabetes obtained after streptozotocin administration to adult females several days before mating or during pregnancy; GI: continuous glucose infusion in unrestrained normal pregnant rat during the last week of pregnancy; F1: first-generation animals procreated by parent (F0) females submitted to experimentally disturbed metabolism during their pregnancy; F2: second-generation animals procreated by F1 females exposed to intrauterine disturbed metabolism; IUED: in utero exposed to maternal diabetes; IUCR: in utero exposed to maternal calorie restriction; IUPR: in utero exposed to maternal protein restriction; UPI: uteroplacental insufficiency; IUEO: in utero exposed to maternal overnutrition or obesity.

3.1. Critical Windows for Adaptive Response to Early-Life Stressors. The development of the endocrine pancreas starts from a pool of common precursor cells that become progressively committed to the endocrine lineage under the control of a hierarchical network of transcription factors. During late fetal and early postnatal life, the beta-cell mass is determined by the recruitment of undifferentiated precursors, as well as the replication and apoptosis rates of the beta cells. Obviously, any disturbance of the environment of the endocrine cells at a specific developmental time-point, as it occurs in a perturbed intrauterine milieu, may modify the balance of controlling factors, thereby contributing to an adaptive beta-cell growth response which is metabolically appropriate on the short term. However, this adaptive response may turn to be detrimental if maintained on the long term, as it may foster beta-cell failure and diabetes later in life. We are largely ignorant of when programming may be initiated during development.

Preimplantatio. An early onset for programming was indicated, as maternal low-protein diet during only the preimplantation period of rat development (0–4 days after

mating), before return to control diet for the remainder of the gestation, induced blastocyst abnormalities, and programming of postnatal growth rate and hypertension [102]. More specifically it was shown that preimplantation embryos collected from dams after 0–4 days of maternal low-protein diet displayed significantly reduced cell numbers, within the inner cell mass and trophectoderm lineages, apparently induced by a slower rate of cellular proliferation. The low-protein diet significantly reduced insulin and essential amino acid levels and increased glucose levels within maternal serum by day 4 of development. These data indicate that the mildly hyperglycemic and amino-acid-depleted maternal environment generated by undernutrition may act as an early mechanism of programming and initiate conditions of "metabolic stress," restricting early embryonic proliferation and the generation of appropriately sized stem-cell lineages. In chemically or genetically obtained rat diabetes models in which maternal serum insulin depletion and hyperglycemia are induced, proliferation of inner cell mass or total cell numbers within blastocysts is inhibited [103, 104]. Therefore, the preimplantation embryo is particularly sensitive to metabolic modifications that may have programming consequences [105, 106], and one possibility is that it is the preimplantation embryo itself that is programmed.

Postimplantation. Embryo transfer experiments may also help to dissociate the impact of the maternal environment in early (preimplantation) versus late gestation (postimplantation). We recently found that embryos (blastocysts) from a nondiabetic Wistar strain placed into a diabetic GK/Par uterus develop a reduced beta-cell mass which remains low on the long term [42]. Data with rat models of prenatal undernutrition [95] also illustrate that low-energy and low-protein diets that reduce the development of the beta-cell mass in both cases act at different critical time windows. The beta-cell mass is deficient in the low-energy pancreas because this diet reduces neogenesis, probably because of high glucocorticoid levels, rather than by impairing vascularisation and proliferation. Early gestation is thus a very sensitive period in this model. By contrast, pancreatic alterations take place at a later fetal stage in the low-protein model, and the beta-cell mass is deficient in this case because this diet reduces beta-cell vascularisation and proliferation without altering beta-cell differentiation [95].

Postnatal versus Prenata. Further support for the crucial impact of prenatal nutritional environment is the recent report that prenatal nutrient restriction in both male and female rats led to an inappropriate postnatal beta-cell mass formation attributed to a decrease in the rate of beta-cell replication and beta-cell neogenesis [93]. In contrast, male and female rats exposed to postnatal nutrient restriction alone (with normal prenatal nutrient exposure) were characterized by decreased pancreatic and body weights, but a weight-adjusted beta-cell mass higher compared to control animals [93]. Another illustration is offered by observations in normal rat pups reared artificially on a high-carbohydrate milk formula [107]: such alteration of nutrition, during the suckling period only, induced persistent adaptation of energy metabolism in adulthood (obesity, glucose intolerance, and impaired insulin secretion).

3.2. Molecular Mechanisms Mediating the Perinatal Beta-Cell Adaptive Response to Early-Life Stressors. Molecular mechanisms responsible for impaired beta-cell mass formation after IUCR or IUPR have come under investigation.

First, it has been proposed that IUCR can result in a reduction of the embryonic beta-cell progenitor pool leading to inappropriate postnatal beta-cell formation. Stanger et al. [108] demonstrated that selective genetic reduction in the size of PDX-1+ pancreatic progenitors during the fetal period results in impaired beta-cell formation during the postnatal period with consequent development of glucose intolerance during adulthood. Consistent with this, maternal food restriction leads to significant reduction in PDX-1+ and neurogenin-3+ pancreatic precursors during embryonic development in rats, diminished postnatal beta-cell formation, and inability to expand beta-cell mass in response to pregnancy [47, 94]. The UPI model is also characterized by a permanent decrease in islet PDX-1 mRNA expression. This decrease has recently been shown to be due to progressive epigenetic silencing of the Pdx1 gene locus secondary to proximal promoter methylation [69, 109], and it may be responsible for the decreased rate of beta-cell replication and inappropriate postnatal beta-cell mass development [69, 110]. In the same way of thinking, studies have demonstrated that the maintenance of methylated histone H3 Lys4 by Set7/9, a member of the SET methyltransferase family, is crucial to Pdx1 activity in beta-cell lines [111–113]. This led to the hypothesis that Set7/9 may represent a novel chromatin-modifying protein that functions in part through its recruitment to target genes by cell-specific transcription factors such as Pdx1. Since then, a role of histone methyl transferases, particularly set7, has also been demonstrated in the sustained deleterious effects of chronic hyperglycemia on human microvascular endothelial cells [114]. Such an epigenetic change could potentially be involved in the deleterious effect of high glucose upon the fetal pancreas in the IUED models.

Another mechanism proposed to explain reduced beta-cell formation after IUCR is related to prenatal glucocorticoid exposure. Administration of either dexamethasone or carbenoxolone (to inhibit 11 β-hydroxysteroid dehydrogenase type 2) to normal pregnant rats also causes fetal growth retardation and the adult offspring are hypertensive and hyperglycemic, with hyperactive hypothalamic-pituitary-adrenal axis [115]. Maternal undernutrition significantly increased both fetal and maternal corticosterone concentrations in rats [116]. Subsequently, maternal and/or fetal overexposure to glucocorticoids (via administration of dexamethasone) impairs both fetal and postnatal beta-cell formation in rodents and nonhuman primates [94, 117–119]. Seckl et al. [115] have shown that fetal corticosterone concentrations are inversely correlated with fetal insulin content and postnatal beta-cell formation in rats. Evidence suggests that glucocorticoids can exert a direct effect on

the developing fetal pancreas via transcriptional modulation of transcription factors involved in beta-cell formation and differentiation [117]. Glucocorticoid receptors are present in the pancreas during embryonic development of rodents and humans [117], and glucocorticoids can bind to the Pdx1 promoter and thus suppress fetal endocrine cell differentiation [117]. Glucocorticoid treatment has been shown to significantly reduce fetal expression of key endocrine transcription factors such as Pdx1 and Pax6 but simultaneously increase expression of transcription factors that regulate development of the exocrine pancreas [119].

It has also been demonstrated that the UPI or the low-protein IUPR offspring experience increased oxidative stress and impaired mitochondrial function [96, 120]. The mitochondrial dysfunction was not limited to just the beta cell, as mitochondria from both the liver and skeletal muscle exhibit decreased oxidation of pyruvate, subsequently leading to the development of features commonly found in T2D [100, 121]. Also exposure to a Western-style diet before and during pregnancy (an IUEO model) alters the redox state as early as preimplantation development, leading to mild oxidative stress associated with inflammation. The finding that administration of antioxidants to the dam reverses oxidative stress and completely prevents the development of glucose intolerance and increased adiposity in the adult offspring suggests that oxidative stress plays an important role in the development of adiposity in this case [122]. Some studies in the low-protein IUPR model have demonstrated that oxidative stress is not limited to just mitochondrial DNA damage, but also to genomic DNA, impacting cell-cycle regulation and gene expression [123]. While DNA is being targeted throughout by ROS, there are particular regions that are known to be more sensitive to ROS-mediated damage, for example, telomeres. Telomeres comprise GC-rich repeats and are found at the ends of each chromosome. They are known to shorten with each cellular division and, hence, can act as a mitotic clock, registering the number of replicative divisions to have taken place within the cell. Investigations using an IUPR model have indeed reported a decrease in longevity in the offspring [123, 124] accompanied by reduction in mitochondrial antioxidant defences [96, 125] and telomere length in islets [125].

Pancreatic islet development has been shown to be influenced by a number of growth factors including the insulin-like growth factors, IGF-I and IGF-II whose expression in utero is regulated by nutrient and hormone concentrations. IUPR modifies expression of both IGF genes in a variety of fetal tissues. In an IUPR rat model with a decreased beta-cell mass and beta-cell replication and an increased rate of beta-cell apoptosis, gene expression for IGF-II but not IGF-I was found reduced in the fetal pancreas [126]. In a different IUPR model with more severe global food restriction which induced hyperinsulinemia and an increase in beta-cell mass in their fetuses [90], the fetal phenotype was unexpectedly associated with an increase in pancreatic IGF-I expression, islet IGF-1R [91], and IRS-2 [92]. In the fetal GK/Par rat exposed to mild hyperglycemia during gestation (a model of IUED), data from our group suggest that the beta-cell deficit (reduced by more than 50%) starts as early as fetal age E16 and reflects decreased beta-cell proliferation, a limitation of beta-cell neogenesis from precursors, and increased apoptosis of both beta cells and their precursors [86]. Notably, Pdx1 and Neurogenin3 expression were decreased on E18 but normally expressed on E13 [86]. Defective signalling through the Igf2/Igf1-R pathway may represent the primary instrumental anomaly since Igf2 and Igf1-R protein expressions are already decreased within the GK/Par pancreatic rudiment at E13, at a time when beta-cell mass (first wave of beta-cell expansion) is in fact normal [31]. Low levels of pancreatic Igf2 associated with beta-cell mass deficiency are maintained thereafter within the fetal pancreas [87]. Crossbreeding protocols between nondiabetic W and diabetic GK rats showed that, in late gestation (E18), pancreatic Igf2 protein expression was as low in GKmother/GKfather and Wmother/GKfather crosses as in GKmother/GKfather crosses [87]. These findings rather support the hypothesis that the pancreatic Igf2 anomaly in the GK diabetic model is linked to a genetic determinism. This view is also consistent with the results of genetic analyses that linked a locus containing the gene encoding Igf2 to diabetes in the GK rat [127]. The Igf2 gene is subjected to paternal genomic imprinting. However, because the Igf2 expression is similarly affected in fetuses, regardless of whether the father is W or GK [87], we cannot conclude with a simple change of Igf2 gene imprinting in the GK rat.

Finally, our understanding of the underlying mechanisms for reduced BCM in response to inappropriate perinatal nutrition is growing rapidly. However, the relative contribution of the many intrinsic and extrinsic factors which contribute to the adaptive response of the developing endocrine pancreas is still to be established.

4. Various Early-Life Stressors: One Ultimate Programming Inducer—Perinatal Hyperglycemia

As abundantly illustrated in animal models, early-life stressors such as maternal undernutrition, overnutrition, hypercholesterolemia, corticosteroid therapy, uteroplacental insufficiency, or hypoxia program metabolic adaptations that initially favour survival but are ultimately detrimental to adult health. Interestingly, there exists in fact one crucial commonality between these models with quite different etiologies: in most of the cases, the altered maternal/fetal metabolism appears to be associated with a diabetogenic effect in the adult offspring either male or female, resulting in a permanent deficiency of the endocrine pancreatic function (F1). In females, the combination of a latent diabetogenic tendency (low insulin response) and the metabolic stress of pregnancy promotes gestational diabetes. F1 gestational diabetes per se is an inducing factor for impaired glucose tolerance and gestational diabetes again in the next female generation (F2).

Finally, the relevant message is that programming of the endocrine pancreas ultimately originates from hyperglycemia experienced during the fetal and/or early postnatal life, whatever the etiology of maternal hyperglycemia,

primary (in F0 diabetic mothers) or secondary (in F1 diabetic mothers issued from F0 mothers exposed to undernutrition, UPI, or high glucocorticoid) (Figure 2).

5. Transgenerational Inheritance of Beta-Cell Mass Programming

While a large number of animal studies have shown the effects of undernutrition during foetal/perinatal development on the glucose metabolism of offspring (F1) in adulthood, several studies have shown that glucose metabolism is also altered in the offspring (F2) as well as grand offspring (F3) of fetally malnourished F1 females, even when the F1 and F2 females have been well nourished since weaning [32, 128] (Figure 1, Table 1). With an aim to dissect the relative parental contributions that lead to F2 offspring outcomes in these models of maternal (F0) undernutrition, it was recently reported that F1 males exhibit moderate hyperglycemia and IGT with aging and impaired glucose-stimulated insulin secretion and that all F2 offspring of F1 males or F1 females develop glucose intolerance [99]. Therefore, intergenerational progression of glucose intolerance can derive from both the maternal and paternal lines. This is an experimental proof that transgenerational transmission of IGT may also occur through the paternal lineage, beside the more widely accepted maternal and grandmaternal inheritance of diabetes [94, 99, 128, 129].

Conceptually, transgenerational inheritance of disease risk may be mediated by nongenomic mechanisms, including either (1) epigenetic mechanisms [130–133] or (2) other broader indirect mechanisms associated with parental physiology [134]. First, alterations in nutrition during development can alter epigenetic marks, thus regulating gene expression through DNA methylation and/or histone modifications. Interestingly, such epigenetic modifications may progress with aging during postnatal life, in association with metabolic phenotypes, as recently observed at the Pdx1 and GLUT4 loci in UPI rats [109, 135]. If these epigenetic changes occur in the germ line, they can be inherited through meiosis [136], thus providing a plausible explanation for intergenerational effects, transmitted via either maternal or paternal lines. In addition, other indirect biological processes may influence phenotypes in subsequent generations. For example, physical constraints may alter birth size through the maternal lineage: since uterine size is reduced in girls that are born small and remain short, this may influence fetal growth and reduce weight in their progeny [134].

Furthermore, maternal metabolism may also influence cross-generational phenotypes [32]. Maternal undernutrition during pregnancy (F0) increases risk for developing diabetes and obesity in her offspring (F1). When these high-risk adult F1 females become pregnant, the metabolic stress of pregnancy may result in hyperglycemia and/or overt gestational diabetes that may, in turn, contribute to defective beta-cell mass and increased diabetes risk in F2 offspring [32]. By this mechanism gestational diabetes may pass from one generation to the next one. In these last examples, intergenerational transmission of phenotypes would occur exclusively through the maternal lineage, as opposed to the epigenetic mechanisms mentioned above. Such a scenario is relevant to the GK/Par rat (Figure 3), since the GK/Par mothers are mildly hyperglycemic through their gestation and during the suckling period. It offers a rationale to elucidate several clues: (1) the initiation of pancreas programming in the F1 offspring of the first founders (F0), since the GK line is issued from intercrosses between Wistar females and males with borderline IGT but otherwise normal basal blood glucose level [23]; (2) the progression of the IGT phenotype until a stable mild diabetic phenotype was reached among the generations $n = 30$ [23]; (3) the lack of attenuation of the diabetic GK phenotype overtime (along more than 20 years and 80 generations), since offspring of GK female/W male crosses were more hyperglycemic than those of W female/GK male crosses [89].

6. Epigenetic Mechanisms Mediating the Diabetes Risk Associated with Beta-Cell Mass Programming

Several lines of evidence indicate that epigenetic modification may be a key unifying mechanism mediating risk associated with a perturbed intrauterine environment. First, disruption of physiologic responses and functional capacity as observed in multiple tissues of IUED or IUGR animals and humans, including muscle, adipose, pancreas, liver, and CNS may be related to histone modification and DNA methylation, thereby altering related gene expression [133].

The preimplantation embryo is particularly sensitive to epigenetic modifications that might permanently alter the phenotype in the adult [105, 137]. For example, in the agouti mouse model, folate supplementation of the maternal diet at conception increases DNA methylation of the agouti gene and increases longevity of the offspring [138]. Maternal protein restriction has been shown to alter the methylation status of the promoters of the glucocorticoid receptor [97], PPARα [98], and the angiotensin receptor [139] with parallel changes in gene expression. More recent studies have shown that histone modifications can also be influenced by the early environment. Alterations in histone modifications have also been implicated in mediating the effect of caloric restriction during the second half of pregnancy on the programmed reduction of GLUT4 expression in the offspring [135]. In the case of the UPI rat model and the pancreatic tissue, Stoffers and colleagues have reported a progressive reduction in expression of Pdx1, a key transcription factor regulating pancreatic development and function [69]. Pdx1 expression is reduced by 50% in UPI fetuses and by 80% in adult UPI offspring. Notably, these changes precede the onset of beta-cell dysfunction, suggesting a primary pathogenic role. Since the Pdx1 promoter is a target for epigenetic modification, as it contains a conserved CpG islands and is associated with high levels of histone acetylation. Interestingly, binding of both acetylated histone H3/H4 and the transcription factor USF1 was found abolished in UPI fetuses [109]. While there

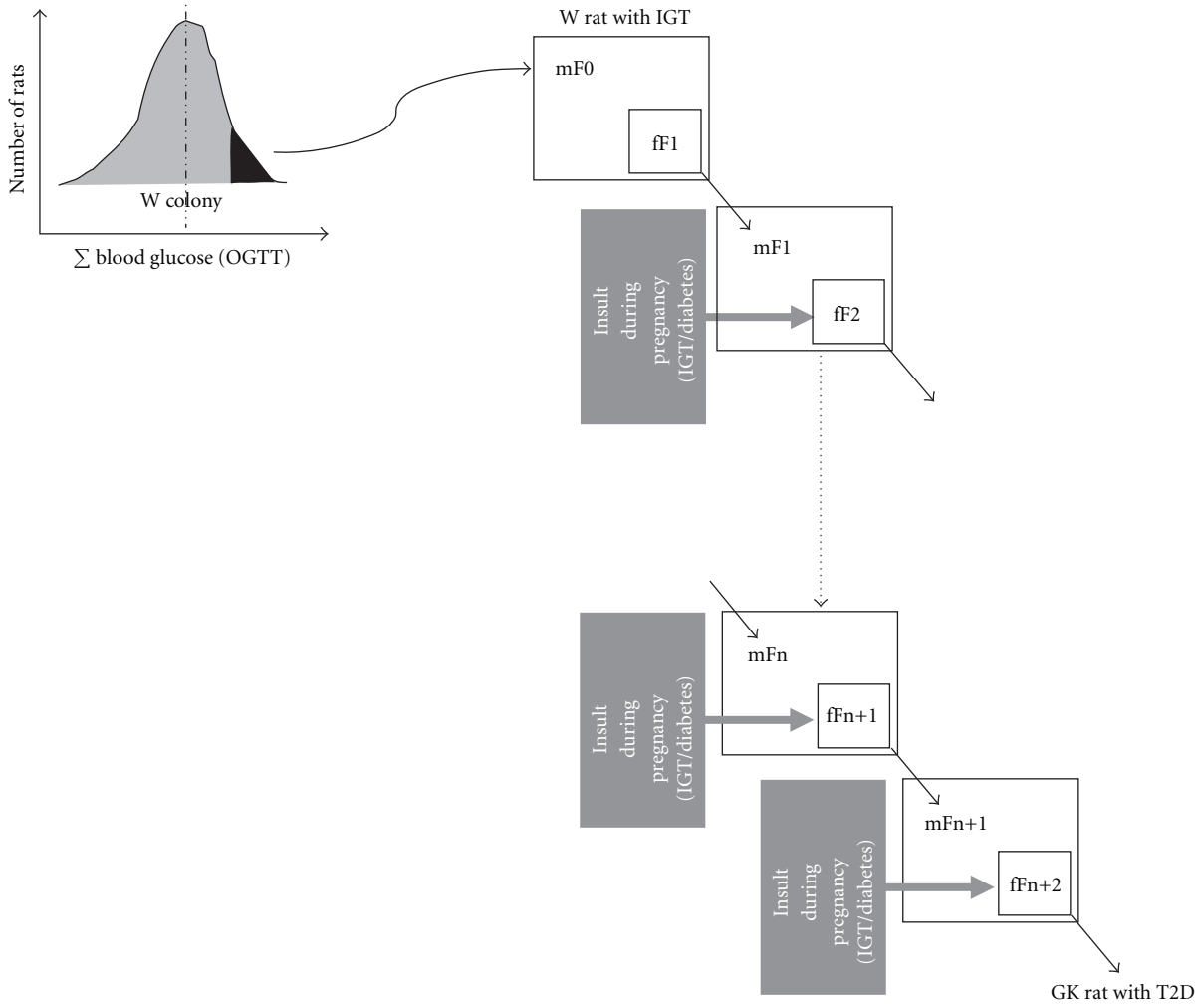


Figure 3: Mechanisms for the installation and intergenerational transmission of programmed beta-cell mass (BCM) disruption in the GK/Par rat model of type 2 diabetes. Maternal IGT/diabetes during gestation induces BCM programming in the first (F1) and the subsequent rat generations. Metabolic modifications in the pups during the in utero and suckling periods are followed by the onset of pathological conditions in adulthood (glucose intolerance and type 2 diabetes) and the transmission of programmed endocrine/metabolic capacities to the next generation. W: Wistar strain.

was methylation at multiple CpGs in UPI adult offspring, no methylation was detected in UPI neonates, indicating that methylation was unlikely to explain Pdx1 repression early in life. Together, these data indicate that progressive silencing of gene expression is largely initiated by early epigenetic changes and is maintained thereafter even in the absence of further experimental insults during postnatal life. UPI also increases histone acetylation of the PPARγ coactivator PGC-1 and carnitine-palmitoyltransferase I (CPT1) promoters in newborn and young rats, and these changes are associated with increased PGC-1 and CPT1 mRNAs [101]. Finally, there is now little doubt that epigenetic regulation of gene expression also occurs in humans as a response to early nutritional insult: a recent study has revealed that individuals who were exposed to famine in utero during the Dutch Hunger Winter had altered methylation of the Igf2 gene in white blood cells in adulthood [140].

7. Implications for Public Health

Although the focus of most studies in the metabolic programming field has been on delineating the effects of reduced maternal nutrition, there is now a growing interest in the role of maternal overnutrition in the programming of diabetes risk. The worldwide prevalence of obesity continues to increase, in association with an increase in the risk of metabolic T2D. Indeed, a recent study estimated that the number of people worldwide with diabetes would increase from 171 million in 2000 to 366 million by 2030 if the prevalence of obesity remained constant [141], which has major implications for public health strategies worldwide [142]. This global trend to increasing obesity is reflected in the increasing numbers of women who are obese during pregnancy [143]. Given that the offspring of obese mothers have an increased risk of developing obesity and T2D

themselves [144, 145], the potential impact of the intergenerational consequences of maternal obesity is of great concern for public health policy makers.

Moreover, maternal hyperglycemia per se increases the probability of adolescent obesity and future T2D. To what extent maternal hyperglycemia is fuelling the global rise in obesity and T2D is unknown, but its contribution is highly significant. The exact degree of hyperglycemia that has this effect and the exact timing in pregnancy that hyperglycemia is impressionable on fetal programming is unknown. The need to identify and treat all women with gestational diabetes is very much dependent on us knowing this. Meanwhile, achieving rigorous glycemic control in women with diabetic pregnancy has to remain a major therapeutic goal.

Several interventions (dietary or pharmacological) to reduce the long-term sequelae of early-life programming effects have been used in animal models. For example, the administration of folic acid with a low-protein diet during pregnancy prevents the altered phenotype and epigenotype in rat offspring [97], and administration of a diet rich in methyl donors prevents the transgenerational increase in obesity in agouti yellow mice [146]. Importantly, the timing of such interventions can be crucial. Examples include neonatal leptin treatment which reverses the programming effects of prenatal undernutrition [147]. In the UPI rat model, epigenetic silencing of the Pdx1 gene can be reversed during a critical developmental window in the neonatal period, using trichostatin A which inhibit HDACs [109]. In the same model, exposure to exendin-4 in the neonatal period reversed the detrimental fetal programming of the beta-cell mass and prevented the development of diabetes in adulthood: this was closely related to restoration of pdx1 expression and beta-cell proliferation rate [69]. A GLP-1 or exendin-4 treatment limited to the neonatal prediabetic period was also shown to delay the installation and limit the severity of T2D in the GK/Par model [88]. In such context, it is important to note that GLP1-derived drugs that are currently used to treat patients with T2D may target chromatin remodelling. Treating beta cells from the INS1 cell line or dispersed mouse islet cells with GLP-1 increased global acetylation of histone H3 and increased its phosphorylation in a concentration-dependent manner [148]. Such histone modifications increased association with the transcription factor phospho-CREB and with cAMP-response CREB coactivator 2. Taken as a whole, these data may provoke optimism—that there may be a window for potential postnatal therapeutic interventions to prevent/modify the "programmed" diabetes risk.

Abbreviations

m: Mother
f: Fetus
F1: First-generation animals procreated by parent (F0) females submitted to experimentally disturbed metabolism during their pregnancy
F2: Second-generation animals procreated by F1 females exposed to intrauterine-disturbed metabolism
IUED: In utero exposed to maternal diabetes
IUCR: In utero exposed to maternal calorie restriction
IUPR: In utero exposed to maternal protein restriction
UPI: Uteroplacental insufficiency
IUEO: In utero exposed to maternal overnutrition or obesity
BCM: Beta-cell mass.

Acknowledgments

The studies from our laboratory and referred to in this paper have been funded by the French ANR (programme Physio 2006—Prograbeta—ref. ANR-06-PHYSIO-028), EGIDE (PHC franco-espagnol PICASSO 2008-2009), and NEB Association. A. Chavey received a CNRS postdoctoral fellowship and was granted by NESTLE-France and Alfediam/SFD.

References

[1] M. I. Harris, R. Klein, T. A. Welborn, and M. W. Knuiman, "Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis," *Diabetes Care*, vol. 15, no. 7, pp. 815–819, 1992.

[2] R. A. Defronzo, "From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus," *Diabetes*, vol. 58, no. 4, pp. 773–795, 2009.

[3] A. E. Butler, J. Janson, S. Bonner-Weir, R. Ritzel, R. A. Rizza, and P. C. Butler, "β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes," *Diabetes*, vol. 52, no. 1, pp. 102–110, 2003.

[4] J. C. Florez, "Newly identified loci highlight β-cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes?" *Diabetologia*, vol. 51, no. 7, pp. 1100–1110, 2008.

[5] P. Saenger, P. Czernichow, I. Hughes, and E. O. Reiter, "Small for gestational age: short stature and beyond," *Endocrine Reviews*, vol. 28, no. 2, pp. 219–251, 2007.

[6] A. O. Martin, J. L. Simpson, C. Ober, and N. Freinkel, "Frequency of diabetes mellitus in mothers of probands with gestational diabetes: possible maternal influence on the predisposition to gestational diabetes," *American Journal of Obstetrics and Gynecology*, vol. 151, no. 4, pp. 471–475, 1985.

[7] J. C. Alcolado, K. Laji, and R. Gill-Randall, "Maternal transmission of diabetes," *Diabetic Medicine*, vol. 19, no. 2, pp. 89–98, 2002.

[8] D. Dabelea, R. L. Hanson, R. S. Lindsay et al., "Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships," *Diabetes*, vol. 49, no. 12, pp. 2208–2211, 2000.

[9] E. Sobngwi, P. Boudou, F. Mauvais-Jarvis et al., "Effect of a diabetic environment in utero on predisposition to type 2 diabetes," *The Lancet*, vol. 361, no. 9372, pp. 1861–1865, 2003.

[10] J. F. Gautier, C. Wilson, C. Weyer et al., "Low acute insulin secretory responses in adult offspring of people with early

onset type 2 diabetes," *Diabetes*, vol. 50, no. 8, pp. 1828–1833, 2001.

[11] R. L. Hanson, R. C. Elston, D. J. Pettitt, P. H. Bennett, and W. C. Knowler, "Segregation analysis of non-insulin-dependent diabetes mellitus in Pima Indians: evidence for a major-gene effect," *American Journal of Human Genetics*, vol. 57, no. 1, pp. 160–170, 1995.

[12] R. Singh, E. Pearson, P. J. Avery et al., "Reduced β-cell function in offspring of mothers with young-onset type 2 diabetes," *Diabetologia*, vol. 49, no. 8, pp. 1876–1880, 2006.

[13] D. J. Barker, C. N. Hales, C. H. Fall, C. Osmond, K. Phipps, and P. M. Clark, "Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth," *Diabetologia*, vol. 36, no. 1, pp. 62–67, 1993.

[14] D. J. P. Barker, "The developmental origins of adult disease," *Journal of the American College of Nutrition*, vol. 23, supplement 6, pp. 588S–595S, 2004.

[15] C. N. Hales, D. J. Barker, P. M. Clark et al., "Fetal and infant growth and impaired glucose tolerance at age 64," *British Medical Journal*, vol. 303, no. 6809, pp. 1019–1022, 1991.

[16] P. H. Whincup, S. J. Kaye, C. G. Owen et al., "Birth weight and risk of type 2 diabetes: a systematic review," *Journal of the American Medical Association*, vol. 300, no. 24, pp. 2886–2897, 2008.

[17] R. H. Jones and S. E. Ozanne, "Intra-uterine origins of type 2 diabetes," *Archives of Physiology and Biochemistry*, vol. 113, no. 1, pp. 25–29, 2007.

[18] D. I. Phillips, D. J. Barker, C. N. Hales, S. Hirst, and C. Osmond, "Thinness at birth and insulin resistance in adult life," *Diabetologia*, vol. 37, no. 2, pp. 150–154, 1994.

[19] J. Rahier, J. Wallon, and J. C. Henquin, "Cell populations in the endocrine pancreas of human neonates and infants," *Diabetologia*, vol. 20, no. 5, pp. 540–546, 1981.

[20] D. L. Economides, K. H. Nicolaides, W. A. Gahl, I. Bernardini, and M. I. Evans, "Plasma insulin in appropriate and small for gestational age fetuses," *American Journal of Obstetrics and Gynecology*, vol. 160, no. 5 I, pp. 1091–1094, 1989.

[21] C. Brufani, A. Grossi, D. Fintini et al., "Obese children with low birth weight demonstrate impaired β-cell function during oral glucose tolerance test," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 11, pp. 4448–4452, 2009.

[22] F. A. van Assche, F. de Prins, L. Aerts, and M. Verjans, "The endocrine pancreas in small-for-dates infants," *British Journal of Obstetrics and Gynaecology*, vol. 84, no. 10, pp. 751–753, 1977.

[23] Y. Goto, M. Kakizaki, and N. Masaki, "Spontaneous diabetes produced by selective breeding of normal Wistar rats," *Proceedings of the Japan Academy*, vol. 51, pp. 80–85, 1975.

[24] L. Aerts, K. Holemans, and F. A. van Assche, "Maternal diabetes during pregnancy: consequences for the offspring," *Diabetes/Metabolism Reviews*, vol. 16, no. 3, pp. 147–197, 1990.

[25] B. Reusens-Billen, C. Remacle, J. Daniline, and J. J. Hoet, "Cell proliferation in pancreatic islets of rat fetuses and neonates from normal and diabetic mothers. An in vitro and in vivo study," *Hormone and Metabolic Research*, vol. 16, no. 11, pp. 565–571, 1984.

[26] B. Reusens and C. Remacle, "Intergenerational effect of an adverse intrauterine environment on perturbation of glucose metabolism," *Twin Research*, vol. 4, no. 5, pp. 406–411, 2001.

[27] A. Kervran, M. Guillaume, and A. Jost, "The endocrine pancreas of the fetus from diabetic pregnant rat," *Diabetologia*, vol. 15, no. 5, pp. 387–393, 1978.

[28] L. Aerts, L. Vercruysse, and F. A. van Assche, "The endocrine pancreas in virgin and pregnant offspring of diabetic pregnant rats," *Diabetes Research and Clinical Practice*, vol. 38, no. 1, pp. 9–19, 1997.

[29] J. Verhaeghe, T. L. Peeters, M. Vandeputte, W. Rombauts, R. Bouillon, and F. A. van Assche, "Maternal and fetal endocrine pancreas in the spontaneously diabetic BB rat," *Biology of the Neonate*, vol. 55, no. 4-5, pp. 298–308, 1989.

[30] P. Serradas, M. N. Gangnerau, M. H. Giroix, C. Saulnier, and B. Portha, "Impaired pancreatic β-cell function in the fetal GK rat. Impact of diabetic inheritance," *Journal of Clinical Investigation*, vol. 101, no. 4, pp. 899–904, 1998.

[31] F. Miralles and B. Portha, "Early development of β-cells is impaired in the GK rat model of type 2 diabetes," *Diabetes*, vol. 50, supplement 1, pp. S84–S88, 2001.

[32] L. Aerts and F. A. van Assche, "Animal evidence for the transgenerational development of diabetes mellitus," *International Journal of Biochemistry and Cell Biology*, vol. 38, no. 5-6, pp. 894–903, 2006.

[33] J. Han, J. Xu, Y. S. Long, P. N. Epstein, and Y. Q. Liu, "Rat maternal diabetes impairs pancreatic β-cell function in the offspring," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 293, no. 1, pp. E228–E236, 2007.

[34] V. Grill, B. Johansson, P. Jalkanen, and U. J. Eriksson, "Influence of severe diabetes mellitus early in pregnancy in the rat: effects on insulin sensitivity and insulin secretion in the offspring," *Diabetologia*, vol. 34, no. 6, pp. 373–378, 1991.

[35] A. Ktorza, D. Gauguier, M. T. Bihoreau, M. F. Berthault, and L. Picon, "Adult offspring from mildly hyperglycemic rats show impairment of glucose regulation and insulin secretion which is transmissible to the next generation," in *Frontiers in Diabetic Research. Lessons from Animal Diabetes*, E. Shafrir, Ed., pp. 555–560, Smith-Gordon and Company, London, UK, 1990.

[36] W. Oh, N. L. Gelardi, and C. J. Cha, "Maternal hyperglycemia in pregnant rats: its effect on growth and carbohydrate metabolism in the offspring," *Metabolism*, vol. 37, no. 12, pp. 1146–1151, 1988.

[37] D. Gauguier, M. T. Bihoreau, L. Picon, and A. Ktorza, "Insulin secretion in adult rats after intrauterine exposure to mild hyperglycemia during late gestation," *Diabetes*, vol. 40, supplement 2, pp. 109–114, 1991.

[38] M. T. Bihoreau, A. Ktorza, M. F. Kinebanyan, and L. Picon, "Impaired glucose homeostasis in adult rats from hyperglycemic mothers," *Diabetes*, vol. 35, no. 9, pp. 979–984, 1986.

[39] E. A. Ryan, D. Liu, R. C. Bell, D. T. Finegood, and J. Crawford, "Long term consequences in offspring of diabetes in pregnancy: studies with syngeneic islet-transplanted streptozotocin-diabetic rats," *Endocrinology*, vol. 136, no. 12, pp. 5587–5592, 1995.

[40] N. Triadou, B. Portha, L. Picon, and G. Rosselin, "Experimental chemical diabetes and pregnancy in the rat. Evolution of glucose tolerance and insulin response," *Diabetes*, vol. 31, no. 1, pp. 75–79, 1982.

[41] R. Gill-Randall, D. Adams, R. L. Ollerton, M. Lewis, and J. C. Alcolado, "Type 2 diabetes mellitus-genes or intrauterine environment? An embryo transfer paradigm in rats," *Diabetologia*, vol. 47, no. 8, pp. 1354–1359, 2004.

[42] A. Chavey, M. N. Gangnerau, L. Maulny et al., "Intrauterine programming of β-cell development and function by

maternal diabetes. What does embryo-transfer experiments in GK/Par rats tell us?" *Diabetologia*, vol. 51, supplement 1, p. 151A, 2008.

[43] B. Portha, A. Chavey, L. Maulny et al., "Des modèles animaux pour étudier l'origine développementale des maladies métaboliques de l'adulte: application à l'étude du risque de diabète," *Cahiers de Nutrition et de Diététique*, vol. 44, no. 2, pp. 77–84, 2009.

[44] A. Garofano, P. Czernichow, and B. Bréant, "In utero undernutrition impairs rat β-cell development," *Diabetologia*, vol. 40, no. 10, pp. 1231–1234, 1997.

[45] E. Bertin, M. N. Gangnerau, G. Bellon, D. Bailbe, A. A. de Vacqueur, and B. Portha, "Development of β-cell mass in fetuses of rats deprived of protein and/or energy in last trimester of pregnancy," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 283, no. 3, pp. R623–R630, 2002.

[46] M. A. Martín, C. Alvarez, L. Goya, B. Portha, and A. M. Pascual-Leone, "Insulin secretion in adult rats that had experienced different underfeeding patterns during their development," *American Journal of Physiology*, vol. 272, no. 4, pp. E634–E640, 1997.

[47] A. Garofano, P. Czernichow, and B. Bréant, "β-cell mass and proliferation following late fetal and early postnatal malnutrition in the rat," *Diabetologia*, vol. 41, no. 9, pp. 1114–1120, 1998.

[48] A. Garofano, P. Czernichow, and B. Bréant, "Effect of ageing on β-cell mass and function in rats malnourished during the perinatal period," *Diabetologia*, vol. 42, no. 6, pp. 711–718, 1999.

[49] B. Portha, M. Kergoat, O. Blondel, and D. Bailbé, "Underfeeding of rat mothers during the first two trimesters of gestation does not alter insulin action and insulin secretion in the progeny," *European Journal of Endocrinology*, vol. 133, no. 4, pp. 475–482, 1995.

[50] A. Snoeck, C. Remacle, B. Reusens, and J. J. Hoet, "Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas," *Biology of the Neonate*, vol. 57, no. 2, pp. 107–118, 1990.

[51] S. Dahri, A. Snoeck, B. Reusens-Billen, C. Remacle, and J. J. Hoet, "Islet function in offspring of mothers on low-protein diet during gestation," *Diabetes*, vol. 40, no. 2, pp. 115–120, 1991.

[52] S. C. Langley-Evans and M. Nwagwu, "Impaired growth and increased glucocorticoid-sensitive enzyme activities in tissues of rat fetuses exposed to maternal low protein diets," *Life Sciences*, vol. 63, no. 7, pp. 605–615, 1998.

[53] M. Desai, N. J. Crowther, A. Lucas, and C. N. Hales, "Organ-selective growth in the offspring of protein-restricted mothers," *British Journal of Nutrition*, vol. 76, no. 4, pp. 591–603, 1996.

[54] D. S. Fernandez-Twinn, A. Wayman, S. Ekizoglou, M. S. Martin, C. N. Hales, and S. E. Ozanne, "Maternal protein restriction leads to hyperinsulinaemia and reduced insulin-signaling protein expression in 21-mo-old female rat offspring," *American journal of physiology Regulatory integrative and comparative physiology*, vol. 288, no. 2, pp. R368–R373, 2005.

[55] D. S. Fernandez-Twinn, S. E. Ozanne, S. Ekizoglou et al., "The maternal endocrine environment in the low-protein model of intra-uterine restriction," *British Journal of Nutrition*, vol. 90, no. 4, pp. 815–822, 2003.

[56] S. E. Ozanne, C. L. Wang, C. J. Petry, J. M. Smith, and C. N. Hales, "Ketosis resistance in the male offspring of protein-malnourished rat dams," *Metabolism: Clinical and Experimental*, vol. 47, no. 12, pp. 1450–1454, 1998.

[57] P. R. Shepherd, N. J. Crowther, M. Desai, C. N. Hales, and S. E. Ozanne, "Altered adipocyte properties in the offspring of protein malnourished rats," *British Journal of Nutrition*, vol. 78, no. 1, pp. 121–129, 1997.

[58] C. J. Petry, M. W. Dorling, D. B. Pawlak, S. E. Ozanne, and C. N. Hales, "Diabetes in old male offspring of rat dams fed a reduced protein diet," *International Journal of Experimental Diabetes Research*, vol. 2, no. 2, pp. 139–143, 2001.

[59] S. E. Ozanne, M. W. Dorling, C. L. Wang, and C. J. Petry, "Depot-specific effects of early growth retardation on adipocyte insulin action," *Hormone and Metabolic Research*, vol. 32, no. 2, pp. 71–75, 2000.

[60] S. E. Ozanne, G. D. Smith, J. Tikerpae, and C. N. Hales, "Altered regulation of hepatic glucose output in the male offspring of protein-malnourished rat dams," *American Journal of Physiology*, vol. 270, no. 4, pp. E559–E564, 1996.

[61] S. E. Ozanne, C. B. Jensen, K. J. Tingey, H. Storgaard, S. Madsbad, and A. A. Vaag, "Low birthweight is associated with specific changes in muscle insulin-signalling protein expression," *Diabetologia*, vol. 48, no. 3, pp. 547–552, 2005.

[62] S. C. Langley-Evans, A. J. Langley-Evans, and M. C. Marchand, "Nutritional programming of blood pressure and renal morphology," *Archives of Physiology and Biochemistry*, vol. 111, no. 1, pp. 8–16, 2003.

[63] E. S. Ogata, M. Bussey, and S. Finley, "Altered gas exchange, limited glucose and branched chain amino acids, and hypoinsulinism retard fetal growth in the rat," *Metabolism*, vol. 35, no. 10, pp. 970–977, 1986.

[64] R. A. Simmons, A. S. Gounis, S. A. Bangalore, and E. S. Ogata, "Intrauterine growth retardation: fetal glucose transport is diminished in lung but spared in brain," *Pediatric Research*, vol. 31, no. 1, pp. 59–63, 1992.

[65] T. Unterman, R. Lascon, M. B. Gotway et al., "Circulating levels of insulin-like growth factor binding protein-1 (IGFBP-1) and hepatic mRNA are increased in the small for gestational age (SGA) fetal rat," *Endocrinology*, vol. 127, no. 4, pp. 2035–2037, 1990.

[66] R. A. Simmons, L. J. Templeton, and S. J. Gertz, "Intrauterine growth retardation leads to the development of type 2 diabetes in the rat," *Diabetes*, vol. 50, no. 10, pp. 2279–2286, 2001.

[67] J. Boloker, S. J. Gertz, and R. A. Simmons, "Gestational diabetes leads to the development of diabetes in adulthood in the rat," *Diabetes*, vol. 51, no. 5, pp. 1499–1506, 2002.

[68] K. Holemans, L. Aerts, and F. A. van Assche, "Lifetime consequences of abnormal fetal pancreatic development," *Journal of Physiology*, vol. 547, no. 1, pp. 11–20, 2003.

[69] D. A. Stoffers, B. M. Desai, D. D. DeLeon, and R. A. Simmons, "Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat," *Diabetes*, vol. 52, no. 3, pp. 734–740, 2003.

[70] M. Srinivasan, S. D. Karewa, A. Palaniyappan, J. D. Pandya, and M. S. Patel, "Maternal high-fat diet consumption results in fetal programming predisposing to the onset of metabolic syndrome-like phenotype in adulthood," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 291, no. 4, pp. E792–E799, 2006.

[71] F. Guo and K. L. Jen, "High-fat feeding during pregnancy and lactation affects offspring metabolism in rats," *Physiology and Behavior*, vol. 57, no. 4, pp. 681–686, 1995.

[72] P. D. Taylor, J. McConnell, I. Y. Khan et al., "Impaired glucose homeostasis and mitochondrial abnormalities in offspring of

rats fed a fat-rich diet in pregnancy," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 288, no. 1, pp. R134–R139, 2005.

[73] S. Dyrskog, S. Gregersen, and K. Hermansen, "High-fat feeding during gestation ans nursing period have diffrentail effects on the insulin secretory capacity in offspring from normal wistar rats," *Review of Diabetic Studies*, vol. 2, no. 3, pp. 136–145, 2005.

[74] P. Nivoit, C. Morens, F. A. van Assche et al., "Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance," *Diabetologia*, vol. 52, no. 6, pp. 1133–1142, 2009.

[75] I. Y. Khan, V. Dekou, G. Douglas et al., "A high-fat diet during rat pregnancy or suckling induces cardiovascular dysfunction in adult offspring," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 288, no. 1, pp. R127–R133, 2005.

[76] I. Y. Khan, P. D. Taylor, V. Dekou et al., "Gender-linked hypertension in offspring of lard-fed pregnant rats," *Hypertension*, vol. 41, no. 1, pp. 168–175, 2003.

[77] S. C. Langley-Evans, "Intrauterine programming of hypertension in the rat: nutrient interactions," *Comparative Biochemistry and Physiology A*, vol. 114, no. 4, pp. 327–333, 1996.

[78] H. B. Karnik, B. R. Sonawane, J. S. Adkins, and S. Mohla, "High dietary fat feeding during perinatal development of rats alters hepatic drug metabolism of progeny," *Developmental Pharmacology and Therapeutics*, vol. 14, no. 2, pp. 135–140, 1990.

[79] W. Palinski, F. P. D'Armiento, J. L. Witztum et al., "Maternal hypercholesterolemia and treatment during pregnancy influence the long-term progression of atherosclerosis in offspring of rabbits," *Circulation Research*, vol. 89, no. 11, pp. 991–996, 2001.

[80] M. E. Cerf, K. Williams, X. I. Nkomo et al., "Islet cell response in the neonatal rat after exposure to a high-fat diet during pregnancy," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 288, no. 5, pp. R1122–R1128, 2005.

[81] J. Han, J. Xu, P. N. Epstein, and Y. Q. Liu, "Long-term effect of maternal obesity on pancreatic β-cells of offspring: reduced beta cell adaptation to high glucose and high-fat diet challenges in adult female mouse offspring," *Diabetologia*, vol. 48, no. 9, pp. 1810–1818, 2005.

[82] G. A. Dunn and T. L. Bale, "Maternal high-fat diet promotes body length increases and insulin insensitivity in second-generation mice," *Endocrinology*, vol. 150, no. 11, pp. 4999–5009, 2009.

[83] S. F. Ng, R. Lin, D. R. Laybutt, R. Barres, J. A. Owens, and M. J. Morris, "Chronic high-fat diet in fathers programs β 2-cell dysfunction in female rat offspring," *Nature*, vol. 467, no. 7318, pp. 963–966, 2010.

[84] K. K. S. Bhasin, A. van Nas, L. J. Martin et al., "Maternal low-protein diet or hypercholesterolemia reduces circulating essential amino acids and leads to intrauterine growth restriction," *Diabetes*, vol. 58, no. 3, pp. 559–566, 2009.

[85] L. Aerts, R. van Bree, V. Feytons, W. Rombauts, and F. A. van Assche, "Plasma amino acids in diabetic pregnant rats and in their fetal and adult offspring," *Biology of the Neonate*, vol. 56, no. 1, pp. 31–39, 1989.

[86] S. Calderari, M. N. Gangnerau, M. Thibault et al., "Defective IGF-2 and IGF-1R protein production in embryonic pancreas precedes β-cell mass anomaly in the Goto-Kakizaki rat model of type 2 diabetes," *Diabetologia*, vol. 50, no. 7, pp. 1463–1471, 2007.

[87] P. Serradas, L. Goya, M. Lacorne et al., "Fetal insulin-like growth factor-2 production is impaired in the GK rat model of type 2 diabetes," *Diabetes*, vol. 51, no. 2, pp. 392–397, 2002.

[88] C. Tourrel, D. Bailbé, M. Lacorne, M. -J. Meile, M. Kergoat, and B. Portha, "Persistent improvement of type 2 diabetes in the Goto-Kakizaki rat model by expansion of the β-cell mass during the prediabetic period with glucagon-like peptide-1 or exendin-4," *Diabetes*, vol. 51, no. 5, pp. 1443–1452, 2002.

[89] D. Gauguier, I. Nelson, C. Bernard et al., "Higher maternal than paternal inheritance of diabetes in GK rats," *Diabetes*, vol. 43, no. 2, pp. 220–224, 1994.

[90] C. Alvarez, M. A. Martín, L. Goya, E. Bertin, B. Portha, and A. M. Pascual-Leone, "Contrasted impact of maternal rat food restriction on the fetal endocrine pancreas," *Endocrinology*, vol. 138, no. 6, pp. 2267–2273, 1997.

[91] M. A. Martin, P. Serradas, S. Ramos et al., "Protein-caloric food restriction affects insulin-like growth factor system in fetal Wistar rat," *Endocrinology*, vol. 146, no. 3, pp. 1364–1371, 2005.

[92] E. Fernandez, M. A. Martin, S. Fajardo, F. Escriva, and C. Alvarez, "Increased IRS-2 content and activation of IGF-1 pathway contribute to enhance beta-cell mass in fetuses from undernourished pregnant rats," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 292, no. 1, pp. E187–E195, 2007.

[93] A. V. Matveyenko, I. Singh, B. C. Shin, S. Georgia, and S. U. Devaskar, "Differential effects of prenatal and postnatal nutritional environment on β-cell mass development and turnover in male and female rats," *Endocrinology*, vol. 151, no. 12, pp. 5647–5656, 2010.

[94] B. Blondeau, I. Avril, B. Duchene, and B. Bréant, "Endocrine pancreas development is altered in foetuses from rats previously showing intra-uterine growth retardation in response to malnutrition," *Diabetologia*, vol. 45, no. 3, pp. 394–401, 2002.

[95] O. Dumortier, B. Blondeau, B. Duvillié, B. Reusens, B. Bréant, and C. Remacle, "Different mechanisms operating during different critical time-windows reduce rat fetal β-cell mass due to a maternal low-protein or low-energy diet," *Diabetologia*, vol. 50, no. 12, pp. 2495–2503, 2007.

[96] N. Theys, T. Bouckenooghe, M. T. Ahn, C. Remacle, and B. Reusens, "Maternal low-protein diet alters pancreatic islet mitochondrial function in a sex-specific manner in the adult rat," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 297, no. 5, pp. R1516–R1525, 2009.

[97] K. A. Lillycrop, E. S. Phillips, A. A. Jackson, M. A. Hanson, and G. C. Burdge, "Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring," *Journal of Nutrition*, vol. 135, no. 6, pp. 1382–1386, 2005.

[98] K. A. Lillycrop, E. S. Phillips, C. Torrens, M. A. Hanson, A. A. Jackson, and G. C. Burdge, "Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR α promoter of the offspring," *British Journal of Nutrition*, vol. 100, no. 2, pp. 278–282, 2008.

[99] E. Zambrano, P. M. Martinez-Samayoa, C. J. Bautista et al., "Sex differences in transgenerational alterations of growth and metabolism in progeny (F_2) of female offspring (F_1) of rats fed a low protein diet during pregnancy and lactation," *Journal of Physiology*, vol. 566, no. 1, pp. 225–236, 2005.

[100] M. A. Selak, B. T. Storey, I. Peterside, and R. A. Simmons, "Impaired oxidative phosphorylation in skeletal muscle

of intrauterine growth-retarded rats," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 285, no. 1, pp. E130–E137, 2003.

[101] Q. Fu, R. A. McKnight, X. Yu, L. Wang, C. W. Callaway, and R. H. Lane, "Uteroplacental insufficiency induces site-specific changes in histone H3 covalent modifications and affects DNA-histone H3 positioning in day 0 IUGR rat liver," *Physiological Genomics*, vol. 20, pp. 108–116, 2005.

[102] W. Y. Kwong, A. E. Wild, P. Roberts, A. C. Willis, and T. P. Fleming, "Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension," *Development*, vol. 127, no. 19, pp. 4195–4202, 2000.

[103] R. G. Lea, J. E. McCracken, S. S. McIntyre, W. Smith, and J. D. Baird, "Disturbed development of the preimplantation embryo in the insulin-dependent diabetic BB/E rat," *Diabetes*, vol. 45, no. 11, pp. 1463–1470, 1996.

[104] S. Pampfer, I. Vanderheyden, J. E. McCracken, J. Vesela, and R. de Hertogh, "Increased cell death in rat blastocysts exposed to maternal diabetes in utero and to high glucose or tumor necrosis factor-α in vitro," *Development*, vol. 124, no. 23, pp. 4827–4836, 1997.

[105] W. Reik, I. Römer, S. C. Barton, M. A. Surani, S. K. Howlett, and J. Klose, "Adult phenotype in the mouse can be affected by epigenetic in the early embryo," *Development*, vol. 119, no. 3, pp. 933–942, 1993.

[106] W. Dean, L. Bowden, A. Aitchison et al., "Altered imprinted gene methylation and expression in completely ES cell-derived mouse fetuses: association with aberrant phenotypes," *Development*, vol. 125, no. 12, pp. 2273–2282, 1998.

[107] M. S. Patel and M. Srinivasan, "Metabolic programming: causes and consequences," *Journal of Biological Chemistry*, vol. 277, no. 3, pp. 1629–1632, 2002.

[108] B. Z. Stanger, A. J. Tanaka, and D. A. Melton, "Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver," *Nature*, vol. 445, no. 7130, pp. 886–891, 2007.

[109] J. H. Park, D. A. Stoffers, R. D. Nicholls, and R. A. Simmons, "Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1," *Journal of Clinical Investigation*, vol. 118, no. 6, pp. 2316–2324, 2008.

[110] R. N. Kulkarni, U. S. Jhala, J. N. Winnay, S. Krajewski, M. Montminy, and C. R. Kahn, "PDX-1 haploinsufficiency limits the compensatory islet hyperplasia that occurs in response to insulin resistance," *Journal of Clinical Investigation*, vol. 114, no. 6, pp. 828–836, 2004.

[111] S. K. Chakrabarti, J. Francis, S. M. Ziesmann, J. C. Garmey, and R. G. Mirmira, "Covalent histone modifications underlie the developmental regulation of insulin gene transcription in pancreatic β cells," *Journal of Biological Chemistry*, vol. 278, no. 26, pp. 23617–23623, 2003.

[112] J. Francis, S. K. Chakrabarti, J. C. Garmey, and R. G. Mirmira, "PDX-1 links histone H3-Lys-4 methylation to RNA polymerase II elongation during activation of insulin transcription," *Journal of Biological Chemistry*, vol. 280, no. 43, pp. 36244–36253, 2005.

[113] T. G. Deering, T. Ogihara, A. P. Trace, B. Maier, and R. G. Mirmira, "Methyltransferase set7/9 maintains transcription and euchromatin structure at islet-enriched genes," *Diabetes*, vol. 58, no. 1, pp. 185–193, 2009.

[114] A. L. Siebel, A. Z. Fernandez, and A. El-Osta, "Glycemic memory associated epigenetic changes," *Biochemical Pharmacology*, vol. 80, no. 12, pp. 1853–1859, 2010.

[115] J. R. Seckl, "Prenatal glucocorticoids and long-term programming," *European Journal of Endocrinology*, vol. 151, spplement 3, pp. U49–U62, 2004.

[116] B. Blondeau, J. Lesage, P. Czernichow, J. P. Dupouy, and B. Bréant, "Glucocorticoids impair fetal β-cell development in rats," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 281, no. 3, pp. E592–E599, 2001.

[117] B. Bréant, E. Gesina, and B. Blondeau, "Nutrition, glucocorticoids and pancreas development," *Hormone Research*, vol. 65, supplement 3, pp. 98–104, 2006.

[118] A. de Vries, M. C. Holmes, A. Heijnis et al., "Prenatal dexamethasone exposure induces changes in nonhuman primate offspring cardiometabolic and hypothalamic-pituitary-adrenal axis function," *Journal of Clinical Investigation*, vol. 117, no. 4, pp. 1058–1067, 2007.

[119] E. Gesina, F. Tronche, P. Herrera et al., "Dissecting the role of glucocorticoids on pancreas development," *Diabetes*, vol. 53, no. 9, pp. 2322–2329, 2004.

[120] R. A. Simmons, I. Suponitsky-Kroyter, and M. A. Selak, "Progressive accumulation of mitochondrial DNA mutations and decline in mitochondrial function lead to β-cell failure," *Journal of Biological Chemistry*, vol. 280, no. 31, pp. 28785–28791, 2005.

[121] I. E. Peterside, M. A. Selak, and R. A. Simmons, "Impaired oxidative phosphorylation in hepatic mitochondria in growth-retarded rats," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 285, no. 6, pp. E1258–E1266, 2003.

[122] S. Sen and R. A. Simmons, "Maternal antioxidant supplementation prevents adiposity in the offspring of western diet-fed rats," *Diabetes*, vol. 59, no. 12, pp. 3058–3065, 2010.

[123] J. H. Chen, C. N. Hales, and S. E. Ozanne, "DNA damage, cellular senescence and organismal ageing: causal or correlative?" *Nucleic Acids Research*, vol. 35, no. 22, pp. 7417–7428, 2007.

[124] B. J. Jennings, S. E. Ozanne, M. W. Dorling, and C. N. Hales, "Early growth determines longevity in male rats and may be related to telomere shortening in the kidney," *FEBS Letters*, vol. 448, no. 1, pp. 4–8, 1999.

[125] J. L. Tarry-Adkins, J. H. Chen, N. S. Smith, R. H. Jones, H. Cherif, and S. E. Ozanne, "Poor maternal nutrition followed by accelerated postnatal growth leads to telomere shortening and increased markers of cell senescence in rat islets," *FASEB Journal*, vol. 23, no. 5, pp. 1521–1528, 2009.

[126] J. Petrik, B. Reusens, E. Arany et al., "A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II," *Endocrinology*, vol. 140, no. 10, pp. 4861–4873, 1999.

[127] D. Gauguier, P. Froguel, V. Parent et al., "Chromosomal mapping of genetic loci associated with non-insulin dependent diabetes in the GK rat," *Nature Genetics*, vol. 12, no. 1, pp. 38–43, 1996.

[128] D. C. Benyshek, C. S. Johnston, and J. F. Martin, "Glucose metabolism is altered in the adequately-nourished grand-offspring (F3 generation) of rats malnourished during gestation and perinatal life," *Diabetologia*, vol. 49, no. 5, pp. 1117–1119, 2006.

[129] A. J. Drake, B. R. Walker, and J. R. Seckl, "Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 288, no. 1, pp. R34–R38, 2005.

[130] S. E. Ozanne and M. Constancia, "Mechanisms of disease: the developmental origins of disease and the role of the epigenotype," *Nature Clinical Practice Endocrinology and Metabolism*, vol. 3, no. 7, pp. 539–546, 2007.

[131] S. E. Pinney and R. A. Simmons, "Epigenetic mechanisms in the development of type 2 diabetes," *Trends in Endocrinology and Metabolism*, vol. 21, no. 4, pp. 223–229, 2009.

[132] A. J. Drake and L. Liu, "Intergenerational transmission of programmed effects: public health consequences," *Trends in Endocrinology and Metabolism*, vol. 21, no. 4, pp. 206–213, 2010.

[133] R. A. Waterland and K. B. Michels, "Epigenetic epidemiology of the developmental origins hypothesis," *Annual Review of Nutrition*, vol. 27, pp. 363–388, 2007.

[134] P. D. Gluckman, M. A. Hanson, and A. S. Beedle, "Non-genomic transgenerational inheritance of disease risk," *BioEssays*, vol. 29, no. 2, pp. 145–154, 2007.

[135] N. Raychaudhuri, S. Raychaudhuri, M. Thamotharan, and S. U. Devaskar, "Histone code modifications repress glucose transporter 4 expression in the intrauterine growth-restricted offspring," *Journal of Biological Chemistry*, vol. 283, no. 20, pp. 13611–13626, 2008.

[136] S. Chong, N. Vickaryous, A. Ashe et al., "Modifiers of epigenetic reprogramming show paternal effects in the mouse," *Nature Genetics*, vol. 39, no. 5, pp. 614–622, 2007.

[137] A. S. Doherty, M. R. Mann, K. D. Tremblay, M. S. Bartolomei, and R. M. Schultz, "Differential effects of culture on imprinted H19 expression in the preimplantation mouse embryo," *Biology of Reproduction*, vol. 62, no. 6, pp. 1526–1535, 2000.

[138] C. A. Cooney, A. A. Dave, and G. L. Wolff, "Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring," *Journal of Nutrition*, vol. 132, no. 8, pp. 2393S–2400S, 2002.

[139] I. Bogdarina, S. Welham, P. J. King, S. P. Burns, and A. J. Clark, "Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension," *Circulation Research*, vol. 100, no. 4, pp. 520–526, 2007.

[140] B. T. Heijmans, E. W. Tobi, A. D. Stein et al., "Persistent epigenetic differences associated with prenatal exposure to famine in humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 44, pp. 17046–17049, 2008.

[141] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030," *Diabetes Care*, vol. 27, no. 5, pp. 1047–1053, 2004.

[142] World Health Organisation, "Obesity: preventing and managing the global epidemic. Report of a WHO consultation," WHO Technical Report Series, World Health Organisation, Geneva, Switzerland, 2000.

[143] M. G. Kanagalingam, N. G. Forouhi, I. A. Greer, and N. Sattar, "Changes in booking body mass index over a decade: retrospective analysis from a Glasgow maternity hospital," *British Journal of Obstetrics and Gynaecology*, vol. 112, no. 10, pp. 1431–1433, 2005.

[144] P. M. Catalano, "Obesity and pregnancy—the propagation of a viscous cycle?" *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 8, pp. 3505–3506, 2003.

[145] P. M. Catalano, K. Farrell, A. Thomas et al., "Perinatal risk factors for childhood obesity and metabolic dysregulation," *American Journal of Clinical Nutrition*, vol. 90, no. 5, pp. 1303–1313, 2009.

[146] R. A. Waterland, M. Travisano, K. G. Tahiliani, M. T. Rached, and S. Mirza, "Methyl donor supplementation prevents transgenerational amplification of obesity," *International Journal of Obesity*, vol. 32, no. 9, pp. 1373–1379, 2008.

[147] M. H. Vickers, P. D. Gluckman, A. H. Coveny et al., "Neonatal leptin treatment reverses developmental programming," *Endocrinology*, vol. 146, no. 10, pp. 4211–4216, 2005.

[148] S. J. Kim, C. Nian, and C. H. S. McIntosh, "Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 modulate β-cell chromatin structure," *Journal of Biological Chemistry*, vol. 284, no. 19, pp. 12896–12904, 2009.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 592408, 9 pages
doi:10.1155/2011/592408

Review Article

Maternal Obesity and Developmental Programming of Metabolic Disorders in Offspring: Evidence from Animal Models

M. Li, D. M. Sloboda, and M. H. Vickers

Liggins Institute and the National Research Centre for Growth and Development, University of Auckland, Auckland 1142, New Zealand

Correspondence should be addressed to M. H. Vickers, m.vickers@auckland.ac.nz

Received 1 June 2011; Accepted 22 July 2011

Academic Editor: Susan Ozanne

The incidence of obesity and overweight has reached epidemic proportions in the developed world as well as in those countries transitioning to first world economies, and this represents a major global health problem. Concern is rising over the rapid increases in childhood obesity and metabolic disease that will translate into later adult obesity. Although an obesogenic nutritional environment and increasingly sedentary lifestyle contribute to our risk of developing obesity, a growing body of evidence links early life nutritional adversity to the development of long-term metabolic disorders. In particular, the increasing prevalence of maternal obesity and excess maternal weight gain has been associated with a heightened risk of obesity development in offspring in addition to an increased risk of pregnancy-related complications. The mechanisms that link maternal obesity to obesity in offspring and the level of gene-environment interactions are not well understood, but the early life environment may represent a critical window for which intervention strategies could be developed to curb the current obesity epidemic. This paper will discuss the various animal models of maternal overnutrition and their importance in our understanding of the mechanisms underlying altered obesity risk in offspring.

1. Background

The current epidemic of obesity and related metabolic disorders has been seen as a symptom of affluence with the primary cause relating to the development of an obesogenic environment and ease of access to highly calorific foods and reduced energy expenditure in work and leisure activities [1]. The metabolic syndrome is characterised by the clustering of cardiovascular risk factors including diabetes, obesity, hyperlipidaemia, and hypertension and is likely the result of complex interactions between genes, dietary intake, physical activity, and the environment. Within the cluster of risk traits for the metabolic syndrome, insulin resistance and visceral obesity have been recognized as the most important causal factors [2]. A number of genes have been identified that are associated with obesity and metabolic syndrome in humans [1, 3], but the genetic component of this condition cannot account for the marked increases in the prevalence of obesity and metabolic syndrome in recent years. In this context, the developmental origins of health and disease (DOHaD) hypothesis has highlighted the link between the periconceptual, fetal, and early infant phases of life and subsequent development of adult obesity and the metabolic syndrome [4–6].

The mechanisms underpinning the developmental programming framework and the role of genetic versus environmental factors remain speculative. One general thesis is that in response to an adverse intrauterine environment the fetus adapts its physiological development to maximize its immediate chances for survival. These adaptations may include resetting metabolic homeostasis set points, endocrine systems, and downregulating of growth, commonly manifest in an altered birth phenotype. More recently the "predictive adaptive response" (PARs) hypothesis proposes that the degree of mismatch between the pre- and postnatal environments is a major determinant of subsequent disease risk [7, 8]. Thus, it is thought that whilst adaptive changes in fetal physiology may be beneficial for short-term survival *in utero,* they may be maladaptive in later life, contributing to adverse health outcomes when offspring are exposed to catch-up growth, diet-induced obesity, and other factors [8, 9].

Animal models have been extensively used to study the basic physiological principles underlying the DOHaD hypothesis and are essential to the search for the mechanistic

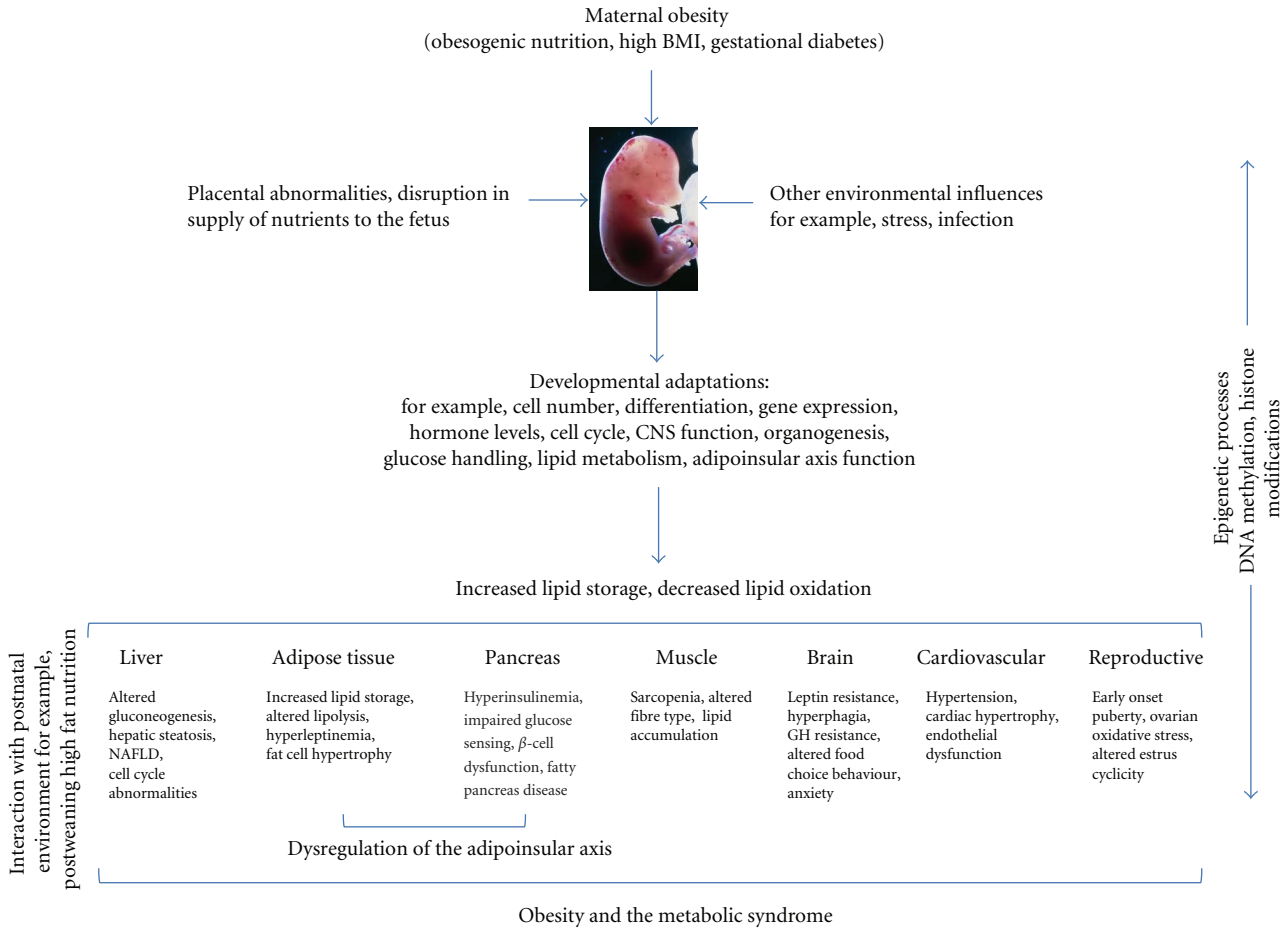


Figure 1: Basic schematic outlining consequences of a maternal obesogenic environment on the health and well-being of offspring. These effects can be modified by the timing and duration of exposure to the obesogenic environment as well as gender and composition of the HF diet (e.g., fat source). Programming effects can be further exacerbated in the presence of a suboptimal postweaning nutritional environment.

links between prenatal and postnatal influences and risk for developing the metabolic syndrome in later life. Epidemiological data suggest that developmental programming occurs within the normal range of birth size [10, 11], but most early experimental work has focused on fetal growth restriction in the assumption that insults impairing fetal growth are likely to be those triggering developmental programming. However, over recent years there has been an increasing focus on developing models of maternal obesity. Obesity in pregnancy and gestational diabetes represent a special problem, not only as a result of their immediate adverse effects on maternal health and pregnancy outcome, but also because of growing evidence for their persistent and deleterious effects on the developing offspring [12]. However, in obese women, it is difficult to discern between genetic and environmental contributions in offspring disease risk. Several obesogenic animal models, primarily performed in the rodent, show a relatively common phenotype of metabolic disorders in offspring, but the magnitude of effects differs with the timing of the nutritional challenge and diet composition [13]. A recent systematic review by Ainge et al. showed that although a maternal HF diet was associated with a real risk of type 2 diabetes and obesity in male offspring, inconsistencies between the studies limited an examination of the *mechanisms* underlying phenotype development [14]. This paper will provide a current summary of animal models of maternal obesity including model species, nature and timing of dietary manipulations, phenotypic outcomes in offspring, possible mechanisms, and the potential role of epigenetics.

2. Animal Models of Maternal Obesity

2.1. Rodent Models. The rodent is the most commonly used model species for investigation of developmental programming via a maternal obesogenic nutritional environment. A maternal cafeteria or high-fat (HF) diet has been shown to induce obesity, insulin and leptin resistance [15–17], hypertension [18–21], fatty pancreas disease [22], hepatic steatosis, and nonalcoholic fatty liver disease in offspring [23–26] (Figure 1). It has also been reported that maternal adiposity, and not dietary fat *per se*, induces hyperleptinemia and insulin resistance in offspring, as well as an increased body weight that persists into adulthood [27]. Even mild maternal overnutrition has been shown to induce increased adiposity, glucose intolerance, and altered brain appetite

regulators in offspring [28]. Our own previous work has shown that a moderate maternal HF diet results in significant obesity and hyperinsulinemia in male and female offspring, independent of the level of preconceptional obesity [29] (Figure 2).

In general, two main approaches have been utilised, a high-fat and/or high-sugar purified diet approach or a "cafeteria diet" designed to mimic a complex western style diet [17, 30, 31]. Both approaches have been extensively utilised over recent years and have provided important insights into disease development, particularly in relation to the development of the metabolic syndrome. There has been some recent debate as to which dietary approach is more closely aligned to the human setting. A purified HF diet normally utilises a modification of a single fat source, for example, lard, in order to induce excess weight gain. Use of these purified "open source" diets has the benefit for targeted mechanistic studies in that manipulation of a single dietary component can be easily undertaken but has the downside that rodents are able to regulate total caloric intake when fed a standard HF diet [32, 33]. A cafeteria diet, a mix of foods typified in the human setting such as highly processed snack food, mimics a more western style diet. However, interpretation of specific macronutrient effects is very difficult due to the widely varied macronutrient sources across the added foods and the dietary interaction across the varied fat, protein, and carbohydrate backgrounds. Further, there is some evidence that specific components utilised in the cafeteria diet may have deleterious effects such as those related to dairy intake in the rodent [34, 35] and oxidative stress [36]. Recent work by Sampey et al. investigated the obesogenic and inflammatory consequences of a cafeteria diet compared to a lard-based 45% (of calories) HF diet in the rodent. Both diets resulted in increased adiposity and hepatosteatosis but cafeteria-fed rats displayed increased inflammation in white fat, brown fat, and liver compared to HF and control groups [37]. Interestingly, the review by Ainge et al. showed that a maternal HF diet did confer an enhanced risk for T2DM and obesity; however, poor glycaemic control across the multiple studies examined appeared to be independent of maternal obesity, birth weight, and level of postweaning diet [14].

2.2. Sheep Models. Sheep models are less studied than the rodent, but there is strong evidence from ovine models that maternal obesity predisposes to altered growth and metabolic sequelae in offspring, data that closely parallels that observed in the small animal models. In a study by Zhang et al., an ovine model of maternal obesity was utilised in which ewes were overfed in order to induce obesity at conception and throughout gestation. At mid-gestation, fetuses from obese ewes were macrosomic, hyperglycemic, and hyperinsulinemic and exhibited markedly increased pancreatic weight and β-cell numbers compared with fetuses of ewes fed to requirements. These data also demonstrated differential impacts of maternal obesity on fetal pancreatic growth and β-cell numbers during early and late gestation. During the first half of gestation there was a marked increase in pancreatic growth, β-cell proliferation, and insulin secretion, followed by a reduction in pancreatic growth and β-cell numbers in late gestation, resulting in reduced circulating insulin at term [38].

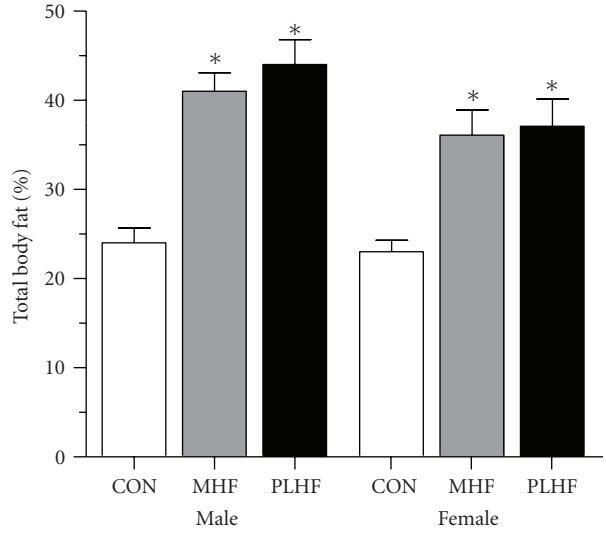


Figure 2: Total body fat mass (%) as quantified by dual energy X-ray absorptiometry (DEXA) in adult (day 150) male and female rat offspring of HF-fed mothers. CON = offspring of control pregnancies, MHF = offspring of mothers fed an HF diet from weaning and throughout pregnancy and lactation, PLHF mothers fed a control diet until conception, and an HF diet throughout pregnancy and lactation. Note that a preconceptional HF diet did not confer an altered risk for obesity development over that of HF exposure during pregnancy and lactation alone. Data are means ± SEM, n = 10-11 per group, $^*P < 0.05$ versus CON. Modified from Howie et al. [29].

Maternal obesity and increased nutrient intake before and during gestation in the ewe is known to result in altered growth, adiposity, and glucose tolerance in adult offspring [39]. As with the rodent studies, different levels of overnutrition and weight gain during pregnancy have differential effects on fetal growth and organ development [40]. Maternal overnutrition in late pregnancy results in an upregulation of PPARγ-activated genes in fetal visceral fat and a subsequent increase in the mass of subcutaneous fat in the postnatal lamb. Exposure to maternal overnutrition during the periconceptional period alone, however, was shown to result in an increase in total body fat mass only in female lambs with a dominant effect on visceral fat depots. Therefore, it was proposed that the early programming of later obesity may result from "two hits", the first occurring as a result of maternal overnutrition during the periconceptional period and the second occurring as a result of increased fetal nutrition in late pregnancy [40].

In contrast to the rodent literature, where maternal obesity has been shown to result in an amplified and prolonged neonatal leptin surge [41], data in the sheep has shown that maternal obesity eliminates the neonatal lamb plasma leptin peak [39]. These differences may be explained via the relative immaturity of the rat at birth compared to the

lamb, with the newborn lamb being born at a more advanced level of maturity equivalent to humans [39].

2.3. Nonhuman Primate. The extensive body of evidence in small animal models and those undertaken in the sheep linking a maternal HF diet to disease risk has been supported by studies, albeit limited, in the nonhuman primate. One of the earliest, in the baboon, showed that overfeeding in the preweaning period permanently increased adiposity in offspring through fat cell hypertrophy, a gender-dependent effect in the females only [42]. Maternal HF diet triggers lipotoxicity in the fetal liver of macaques [43] and predisposes the offspring to develop nonalcoholic fatty liver disease in adulthood. This aligns closely with work in the rodent where a maternal high-fat diet has been shown to lead to "developmental priming" of hepatic steatosis in offspring [24]. Data by Farley and colleagues demonstrated that for normal weight offspring of obese baboons, placental, and fetal phenotypes were consistent with those described for large-for-gestational age human fetuses [44]. Recent work in the macaque by Grayson et al. showed that offspring of mothers fed an HF diet preconceptionally and throughout pregnancy had smaller body weights in the early third trimester but displayed catch-up growth and increased adiposity in the postnatal period—the offspring also developed early-onset excess weight gain independent of postnatal diet [45]. A primary finding of this work was the effect of a maternal HF diet on the offspring's melanocortin system. Third-trimester fetuses from mothers on HF showed increases in proopiomelanocortin mRNA expression, whereas agouti-related protein mRNA and peptide levels were decreased in comparison with control fetuses. In this study, a subgroup of adult HF animals was switched to a control diet during pregnancy (diet reversal). Although at the time of conception the diet reversal animals remained significantly obese and insulin resistant compared to controls, the offspring displayed normal melanocortin levels. These data suggest that chronic consumption of an HF diet during pregnancy, *independent* of maternal obesity and diabetes, can lead to widespread activation of proinflammatory cytokines that may alter the development of the melanocortin system. This aligns with the work in the rat by Howie et al., whereby preconceptional maternal obesity did not impact on obesity in offspring above that induced by an HF diet during pregnancy and lactation alone [29]. It has also recently been shown that chronic consumption of an HF diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring [46].

In the Japanese macaque, consumption of an HF diet, independent of maternal obesity, increased placental inflammatory cytokines and the expression of Toll-like receptor 4 [47]. HF diet consumption also reduced volume blood flow on the fetal side of the placenta and significantly increased the frequency of both placental infarctions and stillbirth. These results suggest that an HF diet, independent of obesity, decreases uterine volume blood flow with maternal obesity and insulin resistance further exacerbating placental dysfunction and resulting in an increased frequency of stillbirth [47]. This aligns with the rodent data whereby a maternal HF diet has been shown to result in reduced fetal and placental junctional zone weights [48].

3. Mechanisms

The mechanisms underpinning maternal obesity and programming of obesity risk in offspring are not well defined. Limited data to date highlight the role of altered leptin production and regulation and changes in the hypothalamic regulation of key genes involved in appetite control and energy balance. There is also evidence of altered skeletal muscle metabolism and maternal HF diet-induced effects on placental structure and function.

3.1. Leptin and the Regulation of Energy Balance. One of the most studied and consistent observations is hyperphagia and altered energy intake [49]. Early data suggested a change in food preference with maternal HF offspring displaying a preference for junk food over chow [50] and more recent studies demonstrate hyperphagia in chow-fed offspring of obese mothers [41, 51]. Programmed resistance to the adipokine leptin is as a prime candidate for the mechanism predisposing towards an altered energy balance. The leptin surge has been well characterised in the rodent; it appears to be neonatal in origin and is associated with an upregulation in leptin mRNA expression in adipose tissue over the same time course [41, 52]. Maternal obesity has been shown to result in an amplified and prolonged leptin surge in neonatal rat offspring [41]. In the rat, the leptin surge is seen as a consequence of elevated maternal serum leptin during the early postnatal period leading to elevated milk leptin concentrations and hyperleptinemia in suckling offspring. However, there are some inconsistencies across studies—milk from HF dams has been shown to have significantly higher fat content compared to controls associated with increased insulin but not leptin concentrations [53]. It must be noted, however, that although the leptin surge in the rodent has been well described, the precise timing and characteristics of the neonatal leptin peak have not been well defined in offspring of either normal or obese mothers in any precocial species. Further studies have described lactational failure and increased neonatal mortality in offspring of HF fed mothers [54]. It has also recently been reported that obese mothers spend significantly more time nursing their young which could manifest as programming changes in the HPA via altered maternal care as described by Meaney and colleagues [55, 56].

3.2. Hypothalamic Reprogramming. Despite the increasing evidence for a neurotropic role of leptin in the rodent, the potential role in humans and the timing of the possible leptin surge is less defined. Kirk et al. have shown that maternal diet-induced obesity permanently influences central processes regulating food intake in offspring via programming of leptin resistance and altered hypothalamic functions involving the arcuate nucleus and paraventricular nucleus. Further, intrauterine and early postnatal overnutrition programmes hypothalamic neurons expressing the appetite stimulator

neuropeptide Y (NPY) and suppressor proopiomelanocortin (POMC) in offspring at weaning [15]. However, the long-term effects of such programming and its interactions with postweaning HF diet consumption remain unclear. Several studies have highlighted alterations in peroxisome proliferator activated receptor (PPAR) gene expression in offspring of obese mothers, which may contribute to the disturbed lipid homeostasis. HF offspring have decreased hepatic PPARγ expression compared with controls and reduced hepatic PPARα expression which negatively correlated with serum triglyceride levels [57].

3.3. Skeletal Muscle and Locomotor Activity. Work by Simar et al. in the adult rat revealed an interaction between maternal obesity and postnatal overnutrition on skeletal muscle metabolism, a postweaning HF diet exerted an additive effect to that of maternal obesity on body weight and skeletal muscle markers of glucose and lipid metabolism but not on plasma glucose and insulin levels, suggesting that maternal obesity and postnatal overnutrition impair skeletal muscle function via different mechanisms [58]. Reduced muscle mass has also been reported in 3- and 6-month-old male and female offspring from obese mice [31] and reduced muscle force in offspring of mothers fed a junk food diet [59]. Work in the sheep matches closely that reported for the rat; lambs born to obese mothers have impaired insulin signalling in muscle compared with control lambs which correlated with increased intramuscular triglycerides and higher expression of fatty acid transporters and PPAR-γ [60].

Although several studies have examined changes in locomotor activity in the setting of maternal undernutrition [61–63], data on energy expenditure and physical activity in models of maternal obesity have yet to be undertaken despite the numerous studies that have observed differences in muscle development in offspring of obese mothers.

3.4. Placental Function. Altered placental function in the setting of maternal obesity has also been the focus of several investigations. Our group and others have reported altered placental structure and function as a result of a maternal HF diet across a range of experimental models. In the pregnant rat, a maternal HF diet has been shown to reduce growth of the fetus and the placental junctional zone, but not placental labyrinth zone growth [48]. In the pregnant sheep, maternal obesity markedly increases placental fatty acid transporter expression and inflammatory signalling pathways and enhances cytokine expression in mid-gestation [57]. Similarly, maternal obesity in the baboon is associated with a maternal inflammatory state and induces structural and functional changes in the placenta [44].

3.5. Interventions. Until relatively recently, developmental programming was seen as an irreversible change in developmental trajectory. Outside of the early taurine reversal work in the setting of the maternal low protein model [64], there is a paucity of data on intervention strategies whether it be nutritional or targeted pharmacologic approaches. It has recently been shown that interventions with leptin, folic acid, and exendin-4 in the early phases of developmental plasticity can ameliorate or reverse some of the effects associated with developmental programming [65–67]. However, these agents were examined in the context of maternal nutritional deprivation and have not been studied in the setting of maternal overnutrition, despite the commonality of offspring phenotypes across the disparate nutritional models. Similarly, exercise has been shown to have beneficial effects in obesity-prone offspring of undernourished mothers [62, 68], but no studies to date have examined exercise interventions in offspring of HF-fed mothers.

There is evidence for a role of diet reversal in ameliorating the effects of maternal obesity on offspring outcome. In the nonhuman primate, diet reversal from an HF to control diet during pregnancy led to normalisation of the melanocortin levels, improvements in fetal hepatic triglycerides, and partial normalization of the expression of gluconeogenic enzymes. These results suggested that simply changing to a normal low-fat diet, specifically during pregnancy, can lower, but not eliminate, the risk for fetal hepatic steatosis [43]. Similar results have been shown in the rat whereby dietary intervention prior to pregnancy reversed metabolic programming in male offspring of obese rats [69].

4. Role of Epigenetics

Epigenetic processes lead to heritable changes in gene function by altering DNA chemistry independent of sequence and may be responsible for tissue-specific gene expression during differentiation. Epigenetic modifications may be one mechanism by which exposure to an altered intrauterine milieu or metabolic perturbation may influence the phenotype of the organism much later in life [70]. However, how the four epigenetic modalities—DNA methylation, non-coding RNA, transcription factors, and histone modifications—contribute to epigenetic memory and how epigenomic changes may mediate the altered control of fetal gene expression as a consequence of maternal obesity are not well characterised.

Experimental data in rodents and recent observations in humans suggest that epigenetic changes in regulatory and growth-related genes play a significant role in mediating the pathophysiological phenotypes derived from developmental programming [71, 72]. Histone modifications in conjunction with DNA methylation regulate chromatin structure and gene expression. However, it is still debated where early life and/or environmental factors can influence the "histone" code in a manner similar to their influence on DNA methylation [73].

Adversity during pregnancy or early neonatal life in experimental programming models results in changes in promoter methylation, therefore, directly or indirectly, affect gene expression in pathways associated with a range of physiologic processes [74]. For example, in the rat, altered promoter methylation and downstream changes in gene expression have been shown for the hepatic glucocorticoid receptor (GR) and PPAR-α [66, 75], influencing carbohydrate and lipid metabolism. The phenotypic effects of epigenetic modifications during development may not manifest until later

in life, especially if they affect genes modulating responses to later environmental challenges, such as dietary challenges with an HF diet. The timing of the developmental windows and the induction of epigenetic changes in key physiologic systems is not well characterised, but it appears to extend from the periconceptional period [76] into postnatal life [77, 78]. Many of the genes regulated by epigenetic change do not appear to be classically imprinted (expressed according to the parental origin of the allele), although some imprinted genes may show altered expression after perturbations during early development, such as if blastocyst culture *in vitro* is prolonged [79].

It has been shown that the promoter in the leptin gene is subject to epigenetic programming, and leptin gene expression can be modulated by DNA methylation [80–82]. Recent studies report that impaired glucose tolerance during pregnancy is associated with adaptations in leptin gene DNA methylation although the functional significance of these changes is not yet clear [83]. Yokomori et al. demonstrated that methylation of specific CpG sites and a methylation-sensitive protein could contribute to changes in leptin gene expression during adipocyte differentiation in 3T3-L1 cells [84]. In addition, differential DNA methylation was observed in promoters of genes involved in glucose metabolism including GLUT4 [85] and uncoupling protein (UCP)-2 [86], both major contributors to the development of T2DM.

Developmental epigenetics is believed to establish "adaptive phenotypes" to meet the demands of the later-life environment [73, 87]. Implicit in this concept is an important process of causality on the cellular level, regulating growth and tissue differentiation and involving chemical changes to the DNA or associated proteins. Once the mechanistic basis of the disease is understood, epigenetic processes are potentially reversible and intervention and strategies aimed at reversal could be devised and implemented. A recent study suggested that a substantial component of metabolic disease risk has a prenatal developmental basis and that perinatal epigenetic analysis may have utility in identifying individual vulnerability to later obesity and metabolic disease [88]. In this study, they reported a link between gene promoter methylation of retinoid x-receptor alpha (RXRA) in umbilical cord tissue and later risk of childhood adiposity.

5. Paternal Transmission

There is now evidence supporting a role for paternal transmission of disease risk across generations. Ng et al. recently reported that a paternal high-fat diet can program β-cell "dysfunction" in rat F1 female offspring. Paternal HF diet altered the expression of 642 pancreatic islet genes in adult female offspring including functional gene clusters related to cation and ATP binding, cytoskeleton, and intracellular transport. Broader pathway analysis demonstrated involvement of calcium-, MAPK-, and Wnt-signalling pathways, apoptosis, and cell cycle regulation. Hypomethylation of the Il13ra2 gene, which showed the highest fold difference in expression, was demonstrated. This work provided the first evidence in mammals of nongenetic, intergenerational transmission of metabolic sequelae of an HFD from father to offspring [89]. Yazbek et al. also provided evidence for paternal transgenerational genetic effects on body weight and food intake. Utilising the obesity-resistant 6C2d congenic strain, which carries the Obrq2aA/J allele on an otherwise C57BL/6J background, obesity-resistant and hypophagic phenotypes were transmitted through the paternal lineage but not the maternal lineage with equal strength for at least two generations [90]. Of note, a recent study has shown that a maternal HF diet has effects on third-generation female body size via the paternal lineage [91] which supports a stable germline-based transgenerational mode of inheritance. The extent of the contribution of obese fathers on offspring phenotype development is now an increasing area of research, particularly as regards the role of nongenetic factors in the causal pathway.

6. Summary

Animal studies across a range of species and varied obesogenic diets have provided clear evidence linking maternal obesity and increased risk for obesity in offspring and are invaluable tools in the investigation of mechanisms underpinning this linkage. Given the current obesity epidemic and the increasing number of obese women entering pregnancy, there is an urgent need for interventional strategies that target developmentally programmed obesity. The evidence available on short- and long-term health impact for mother and child currently favours actions directed at controlling prepregnancy weight and preventing obesity in females of reproductive ages [92] although more trials are needed to evaluate the effects of nutritional and behavioural interventions in pregnancy outcomes. Moreover, suggestions that maternal obesity may transfer obesity risk to child through non-Mendelian (e.g., epigenetic) mechanisms require more long-term investigation. Of note, evidence for the programming of obesity and several other features of the metabolic syndrome have been observed under both nutrient restriction (caloric, protein, iron) and overnutrition studies, possibly suggestive of a commonality of mechanism. The perinatal environment provides a potential therapeutic target, and focusing on this specific developmental stage may translate into improved interventional strategies to stem the growing epidemic of obesity. Failure to recognize that maternal diet and maternal obesity play a critical role in developmental programming of adult disease may ultimately accelerate the obesity epidemic through successive generations, independent of further genetic or environmental factors.

Acknowledgments

The authors acknowledge support from the National Research Centre for Growth and Development, the Health Research Council of New Zealand, the Marsden Fund of the Royal Society of New Zealand, and the Foundation for Research Science and Technology.

References

[1] C. G. Bell, A. J. Walley, and P. Froguel, "The genetics of human obesity," *Nature Reviews Genetics*, vol. 6, no. 3, pp. 221–234, 2005.

[2] L. Duvnjak and M. Duvnjak, "The metabolic syndrome—an ongoing story," *Journal of Physiology and Pharmacology*, vol. 60, supplement 7, pp. 19–24, 2009.

[3] K. G. Hofbauer, "Molecular pathways to obesity," *International Journal of Obesity and Related Metabolic Disorders*, vol. 26, supplement 2, pp. S18–S27, 2002.

[4] K. M. Godfrey and D. J. P. Barker, "Fetal nutrition and adult disease," *The American Journal of Clinical Nutrition*, vol. 71, no. 5, pp. 1344S–1352S, 2000.

[5] B. H. Breier, M. H. Vickers, B. A. Ikenasio, K. Y. Chan, and W. P. S. Wong, "Fetal programming of appetite and obesity," *Molecular and Cellular Endocrinology*, vol. 185, no. 1-2, pp. 73–79, 2001.

[6] A. C. Ravelli, J. H. van Der Meulen, C. Osmond, D. J. Barker, and O. P. Bleker, "Obesity at the age of 50 y in men and women exposed to famine prenatally," *The American Journal of Clinical Nutrition*, vol. 70, no. 5, pp. 811–816, 1999.

[7] P. D. Gluckman and M. A. Hanson, "Developmental origins of disease paradigm: a mechanistic and evolutionary perspective," *Pediatric Research*, vol. 56, no. 3, pp. 311–317, 2004.

[8] P. D. Gluckman, M. A. Hanson, A. S. Beedle, and H. G. Spencer, "Predictive adaptive responses in perspective," *Trends in Endocrinology and Metabolism*, vol. 19, no. 4, pp. 109–110, 2008.

[9] P. D. Gluckman and M. A. Hanson, "Living with the past: evolution, development, and patterns of disease," *Science*, vol. 305, no. 5691, pp. 1733–1736, 2004.

[10] D. J. Barker, "Obesity and early life," *Obesity Reviews*, vol. 8, supplement 1, pp. 45–49, 2007.

[11] D. J. P. Barker, "The origins of the developmental origins theory," *Journal of Internal Medicine*, vol. 261, no. 5, pp. 412–417, 2007.

[12] P. W. Nathanielsz, L. Poston, and P. D. Taylor, "In utero exposure to maternal obesity and diabetes: animal models that identify and characterize implications for future health," *Obstetrics and Gynecology Clinics of North America*, vol. 34, no. 2, pp. 201–212, 2007.

[13] J. A. Armitage, L. Lakasing, P. D. Taylor et al., "Developmental programming of aortic and renal structure in offspring of rats fed fat-rich diets in pregnancy," *Journal of Physiology*, vol. 565, no. 1, pp. 171–184, 2005.

[14] H. Ainge, C. Thompson, S. E. Ozanne, and K. B. Rooney, "A systematic review on animal models of maternal high fat feeding and offspring glycaemic control," *International Journal of Obesity*, vol. 35, pp. 325–335, 2010.

[15] M. J. Morris and H. Chen, "Established maternal obesity in the rat reprograms hypothalamic appetite regulators and leptin signaling at birth," *International Journal of Obesity*, vol. 33, no. 1, pp. 115–122, 2009.

[16] P. D. Taylor and L. Poston, "Developmental programming of obesity in mammals," *Experimental Physiology*, vol. 92, no. 2, pp. 287–298, 2007.

[17] S. A. Bayol, B. H. Simbi, and N. C. Stickland, "A maternal cafeteria diet during gestation and lactation promotes adiposity and impairs skeletal muscle development and metabolism in rat offspring at weaning," *Journal of Physiology*, vol. 567, no. 3, pp. 951–961, 2005.

[18] C. Liang, M. E. Oest, and M. R. Prater, "Intrauterine exposure to high saturated fat diet elevates risk of adult-onset chronic diseases in C57BL/6 mice," *Birth Defects Research Part B*, vol. 86, no. 5, pp. 377–384, 2009.

[19] M. M. Elahi, F. R. Cagampang, D. Mukhtar, F. W. Anthony, S. K. Ohri, and M. A. Hanson, "Long-term maternal high-fat feeding from weaning through pregnancy and lactation predisposes offspring to hypertension, raised plasma lipids and fatty liver in mice," *The British Journal of Nutrition*, vol. 102, no. 4, pp. 514–519, 2009.

[20] I. Khan, V. Dekou, M. Hanson, L. Poston, and P. Taylor,"Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring," *Circulation*, vol. 110, no. 9, pp. 1097–1102, 2004.

[21] A. M. Samuelsson, A. Morris, N. Igosheva et al., "Evidence for sympathetic origins of hypertension in juvenile offspring of obese rats," *Hypertension*, vol. 55, no. 1, pp. 76–82, 2010.

[22] J. A. Oben, T. Patel, A. Mouralidarane et al., "Maternal obesity programmes offspring development of non-alcoholic fatty pancreas disease," *Biochemical and Biophysical Research Communications*, vol. 394, no. 1, pp. 24–28, 2010.

[23] S. Bouanane, H. Merzouk, N. B. Benkalfat et al., "Hepatic and very low-density lipoprotein fatty acids in obese offspring of overfed dams," *Metabolism*, vol. 59, no. 12, pp. 1701–1709, 2010.

[24] K. D. Bruce, F. R. Cagampang, M. Argenton et al., "Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression," *Hepatology*, vol. 50, no. 6, pp. 1796–1808, 2009.

[25] B. M. Gregorio, V. Souza-Mello, J. J. Carvalho, C. A. Mandarim-de-Lacerda, and M. B. Aguila, "Maternal high-fat intake predisposes nonalcoholic fatty liver disease in C57BL/6 offspring," *The American Journal of Obstetrics and Gynecology*, vol. 203, no. 5, pp. 495.e1–495.e8, 2010.

[26] J. A. Oben, A. Mouralidarane, A. M. Samuelsson et al., "Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice," *Journal of Hepatology*, vol. 52, no. 6, pp. 913–920, 2010.

[27] C. L. White, M. N. Purpera, and C. D. Morrison, "Maternal obesity is necessary for programming effect of high-fat diet on offspring," *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 296, no. 5, pp. R1464–R1472, 2009.

[28] S. Rajia, H. Chen, and M. J. Morris, "Maternal overnutrition impacts offspring adiposity and brain appetite markers-modulation by postweaning diet," *Journal of Neuroendocrinology*, vol. 22, no. 8, pp. 905–914, 2010.

[29] G. J. Howie, D. M. Sloboda, T. Kamal, and M. H. Vickers, "Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet," *Journal of Physiology*, vol. 587, no. 4, pp. 905–915, 2009.

[30] Z. Y. Ong and B. S. Muhlhausler, "Maternal "junk-food" feeding of rat dams alters food choices and development of the mesolimbic reward pathway in the offspring," *The FASEB Journal*, vol. 25, no. 7, pp. 2167–2179, 2011.

[31] A. M. Samuelsson, P. A. Matthews, M. Argenton et al., "Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming," *Hypertension*, vol. 51, no. 2, pp. 383–392, 2008.

[32] F. Guo and K. L. Jen, "High-fat feeding during pregnancy and lactation affects offspring metabolism in rats," *Physiology and Behavior*, vol. 57, no. 4, pp. 681–686, 1995.

[33] P. D. Taylor, I. Y. Khan, L. Lakasing et al., "Uterine artery function in pregnant rats fed a diet supplemented with animal lard," *Experimental Physiology*, vol. 88, no. 3, pp. 389–398, 2003.

[34] T. S. Nielsen, S. Purup, A. Wärri, R. W. Godschalk, and L. Hilakivi-Clarke, "Effects of maternal exposure to cow's milk high or low in isoflavones on carcinogen-induced mammary tumorigenesis among rat offspring," *Cancer Prevention Research*, vol. 4, no. 5, pp. 694–701, 2011.

[35] H. Zhou, L. Q. Qin, F. L. Tang, D. F. Ma, P. Y. Wang, and Y. Wang, "Effect of milk on the 7,12-dimethylbenz[a]-anthracene-induced mammary tumor model in rat," *Food and Chemical Toxicology*, vol. 45, no. 10, pp. 1868–1872, 2007.

[36] Y. S. Diniz, A. A. Fernandes, K. E. Campos, F. Mani, B. O. Ribas, and E. L. Novelli, "Toxicity of hypercaloric diet and monosodium glutamate: oxidative stress and metabolic shifting in hepatic tissue," *Food and Chemical Toxicology*, vol. 42, no. 2, pp. 313–319, 2004.

[37] B. P. Sampey, A. M. Vanhoose, H. M. Winfield et al., "Cafeteria diet is a robust model of human metabolic syndrome with liver and adipose inflammation: comparison to high-fat diet," *Obesity*, vol. 19, no. 6, pp. 1109–1117, 2011.

[38] L. Zhang, N. M. Long, S. M. Hein, Y. Ma, P. W. Nathanielsz, and S. P. Ford, "Maternal obesity in ewes results in reduced fetal pancreatic beta-cell numbers in late gestation and decreased circulating insulin concentration at term," *Domestic Animal Endocrinology*, vol. 40, no. 1, pp. 30–39, 2011.

[39] N. M. Long, S. P. Ford, and P. W. Nathanielsz, "Maternal obesity eliminates the neonatal lamb plasma leptin peak," *Journal of Physiology*, vol. 589, no. 6, pp. 1455–1462, 2011.

[40] L. A. George, A. B. Uthlaut, N. M. Long et al., "Different levels of overnutrition and weight gain during pregnancy have differential effects on fetal growth and organ development," *Reproductive Biology and Endocrinology*, vol. 8, article 75, 2010.

[41] S. L. Kirk, A. M. Samuelsson, M. Argenton et al., "Maternal obesity induced by diet in rats permanently influences central processes regulating food intake in offspring," *PLoS ONE*, vol. 4, no. 6, Article ID e5870, 2009.

[42] D. S. Lewis, H. A. Bertrand, C. A. McMahan, H. C. McGill Jr., K. D. Carey, and E. J. Masoro, "Preweaning food intake influences the adiposity of young adult baboons," *Journal of Clinical Investigation*, vol. 78, no. 4, pp. 899–905, 1986.

[43] C. E. McCurdy, J. M. Bishop, S. M. Williams et al., "Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates," *Journal of Clinical Investigation*, vol. 119, no. 2, pp. 323–335, 2009.

[44] D. Farley, M. E. Tejero, A. G. Comuzzie et al., "Feto-placental adaptations to maternal obesity in the baboon," *Placenta*, vol. 30, no. 9, pp. 752–760, 2009.

[45] B. E. Grayson, P. R. Levasseur, S. M. Williams, M. S. Smith, D. L. Marks, and K. L. Grove, "Changes in melanocortin expression and inflammatory pathways in fetal offspring of nonhuman primates fed a high-fat diet," *Endocrinology*, vol. 151, no. 4, pp. 1622–1632, 2010.

[46] E. L. Sullivan, B. Grayson, D. Takahashi et al., "Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring," *Journal of Neuroscience*, vol. 30, no. 10, pp. 3826–3830, 2010.

[47] A. E. Frias, T. K. Morgan, A. E. Evans et al., "Maternal high-fat diet disturbs uteroplacental hemodynamics and increases the frequency of stillbirth in a nonhuman primate model of excess nutrition," *Endocrinology*, vol. 152, no. 6, pp. 2456–2464, 2011.

[48] P. J. Mark, C. Sisala, K. Connor et al., "A maternal high-fat diet in rat pregnancy reduces growth of the fetus and the placental junctional zone, but not placental labyrinth zone growth," *Journal of the Developmental Origins of Health and Disease*, vol. 2, pp. 63–70, 2011.

[49] K. Rooney and S. E. Ozanne, "Maternal over-nutrition and offspring obesity predisposition: targets for preventative interventions," *International Journal of Obesity*, vol. 35, no. 7, pp. 883–890, 2011.

[50] S. A. Bayol, S. J. Farrington, and N. C. Stickland, "A maternal "junk food" diet in pregnancy and lactation promotes an exacerbated taste for "junk food" and a greater propensity for obesity in rat offspring," *The British Journal of Nutrition*, vol. 98, no. 4, pp. 843–851, 2007.

[51] P. Nivoit, C. Morens, F. A. Van Assche et al., "Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance," *Diabetologia*, vol. 52, no. 6, pp. 1133–1142, 2009.

[52] R. S. Ahima, D. Prabakaran, and J. S. Flier, "Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function," *Journal of Clinical Investigation*, vol. 101, no. 5, pp. 1020–1027, 1998.

[53] R. H. Purcell, B. Sun, L. L. Pass, M. L. Power, T. H. Moran, and K. L. Tamashiro, "Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior," *Physiology and Behavior*, vol. 104, no. 3, pp. 474–479, 2011.

[54] D. J. Flint, M. T. Travers, M. C. Barber, N. Binart, and P. A. Kelly, "Diet-induced obesity impairs mammary development and lactogenesis in murine mammary gland," *The American Journal of Physiology—Endocrinology and Metabolism*, vol. 288, pp. E1179–E1187, 2005.

[55] F. A. Champagne, I. C. G. Weaver, J. Diorio, S. Dymov, M. Szyf, and M. J. Meaney, "Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring," *Endocrinology*, vol. 147, no. 6, pp. 2909–2915, 2006.

[56] M. J. Meaney and M. Szyf, "Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome," *Dialogues in Clinical Neuroscience*, vol. 7, no. 2, pp. 103–123, 2005.

[57] M. J. Zhu, Y. Ma, N. M. Long, M. Du, and S. P. Ford, "Maternal obesity markedly increases placental fatty acid transporter expression and fetal blood triglycerides at midgestation in the ewe," *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 299, no. 5, pp. R1224–R1231, 2010.

[58] D. Simar, H. Chen, K. Lambert, J. Mercier, and M. J. Morris, "Interaction between maternal obesity and post-natal over-nutrition on skeletal muscle metabolism," *Nutrition, Metabolism and Cardiovascular Diseases*. In press.

[59] S. A. Bayol, R. MacHaria, S. J. Farrington, B. H. Simbi, and N. C. Stickland, "Evidence that a maternal "junk food" diet during pregnancy and lactation can reduce muscle force in offspring," *European Journal of Nutrition*, vol. 48, no. 1, pp. 62–65, 2009.

[60] X. Yan, Y. Huang, J. X. Zhao et al., "Maternal obesity-impaired insulin signaling in sheep and induced lipid accumulation and fibrosis in skeletal muscle of offspring," *Biology of Reproduction*, vol. 85, no. 1, pp. 172–178, 2011.

[61] M. H. Vickers, B. H. Breier, D. McCarthy, and P. D. Gluckman, "Sedentary behavior during postnatal life is determined by

the prenatal environment and exacerbated by postnatal hypercaloric nutrition," *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 285, no. 1, pp. R271–R273, 2003.

[62] J. L. Miles, K. Huber, N. M. Thompson, M. Davison, and B. H. Breier, "Moderate daily exercise activates metabolic flexibility to prevent prenatally induced obesity," *Endocrinology*, vol. 150, no. 1, pp. 179–186, 2009.

[63] L. Bellinger, D. V. Sculley, and S. C. Langley-Evans, "Exposure to undernutrition in fetal life determines fat distribution, locomotor activity and food intake in ageing rats," *International Journal of Obesity*, vol. 30, no. 5, pp. 729–738, 2006.

[64] B. Reusens, T. Sparre, L. Kalbe et al., "The intrauterine metabolic environment modulates the gene expression pattern in fetal rat islets: prevention by maternal taurine supplementation," *Diabetologia*, vol. 51, no. 5, pp. 836–845, 2008.

[65] D. A. Stoffers, B. M. Desai, D. D. DeLeon, and R. A. Simmons, "Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat," *Diabetes*, vol. 52, no. 3, pp. 734–740, 2003.

[66] K. A. Lillycrop, E. S. Phillips, A. A. Jackson, M. A. Hanson, and G. C. Burdge, "Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring," *Journal of Nutrition*, vol. 135, no. 6, pp. 1382–1386, 2005.

[67] M. H. Vickers, P. D. Gluckman, A. H. Coveny et al., "Neonatal leptin treatment reverses developmental programming," *Endocrinology*, vol. 146, no. 10, pp. 4211–4216, 2005.

[68] J. L. Miles, J. Landon, M. Davison et al., "Prenatally undernourished rats show increased preference for wheel running v. lever pressing for food in a choice task," *The British Journal of Nutrition*, vol. 101, no. 6, pp. 902–908, 2009.

[69] E. Zambrano, P. M. Martínez-Samayoa, G. L. Rodríguez-González, and P. W. Nathanielsz, "Dietary intervention prior to pregnancy reverses metabolic programming in male offspring of obese rats," *Journal of Physiology*, vol. 588, no. 10, pp. 1791–1799, 2010.

[70] R. Simmons, "Epigenetics and maternal nutrition: nature v. nurture," *Proceedings of the Nutrition Society*, vol. 70, pp. 73–81, 2011.

[71] C. Gicquel, A. El-Osta, and Y. Le Bouc, "Epigenetic regulation and fetal programming," *Best Practice and Research in Clinical Endocrinology and Metabolism*, vol. 22, no. 1, pp. 1–16, 2008.

[72] M. Szyf, "Epigenetics, DNA methylation, and chromatin modifying drugs," *Annual Review of Pharmacology and Toxicology*, vol. 49, pp. 243–263, 2009.

[73] W. Y. Tang and S. M. Ho, "Epigenetic reprogramming and imprinting in origins of disease," *Reviews in Endocrine and Metabolic Disorders*, vol. 8, no. 2, pp. 173–182, 2007.

[74] R. L. Jirtle and M. K. Skinner, "Environmental epigenomics and disease susceptibility," *Nature Reviews Genetics*, vol. 8, no. 4, pp. 253–262, 2007.

[75] K. A. Lillycrop, J. L. Slater-Jefferies, M. A. Hanson, K. M. Godfrey, A. A. Jackson, and G. C. Burdge, "Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications," *The British Journal of Nutrition*, vol. 97, no. 6, pp. 1064–1073, 2007.

[76] K. D. Sinclair, C. Allegrucci, R. Singh et al., "DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 49, pp. 19351–19356, 2007.

[77] I. C. Weaver, J. Diorio, J. R. Seckl, M. Szyf, and M. J. Meaney, "Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites," *Annals of the New York Academy of Sciences*, vol. 1024, pp. 182–212, 2004.

[78] I. C. Weaver, N. Cervoni, F. A. Champagne et al., "Epigenetic programming by maternal behavior," *Nature Neuroscience*, vol. 7, no. 8, pp. 847–854, 2004.

[79] A. S. Doherty, M. R. Mann, K. D. Tremblay, M. S. Bartolomei, and R. M. Schultz, "Differential effects of culture on imprinted H19 expression in the preimplantation mouse embryo," *Biology of Reproduction*, vol. 62, no. 6, pp. 1526–1535, 2000.

[80] D. Iliopoulos, K. N. Malizos, and A. Tsezou, "Epigenetic regulation of leptin affects MMP-13 expression in osteoarthritic chondrocytes: possible molecular target for osteoarthritis therapeutic intervention," *Annals of the Rheumatic Diseases*, vol. 66, no. 12, pp. 1616–1621, 2007.

[81] I. Melzner, V. Scott, K. Dorsch et al., "Leptin gene expression in human preadipocytes is switched on by maturation-induced demethylation of distinct CpGs in its proximal promoter," *Journal of Biological Chemistry*, vol. 277, no. 47, pp. 45420–45427, 2002.

[82] R. Stöger, "In vivo methylation patterns of the leptin promoter in human and mouse," *Epigenetics*, vol. 1, no. 4, pp. 155–162, 2006.

[83] L. Bouchard, S. Thibault, S. P. Guay et al., "Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy," *Diabetes Care*, vol. 33, no. 11, pp. 2436–2441, 2010.

[84] N. Yokomori, M. Tawata, and T. Onaya, "DNA demethylation modulates mouse leptin promoter activity during the differentiation of 3T3-L1 cells," *Diabetologia*, vol. 45, no. 1, pp. 140–148, 2002.

[85] N. Yokomori, M. Tawata, and T. Onaya, "DNA demethylation during the differentiation of 3T3-L1 cells affects the expression of the mouse GLUT4 gene," *Diabetes*, vol. 48, no. 4, pp. 685–690, 1999.

[86] M. V. Carretero, L. Torres, U. Latasa et al., "Transformed but not normal hepatocytes express UCP2," *FEBS Letters*, vol. 439, no. 1-2, pp. 55–58, 1998.

[87] S. M. Ho and W. Y. Tang, "Techniques used in studies of epigenome dysregulation due to aberrant DNA methylation: an emphasis on fetal-based adult diseases," *Reproductive Toxicology*, vol. 23, no. 3, pp. 267–282, 2007.

[88] K. M. Godfrey, A. Sheppard, P. D. Gluckman et al., "Epigenetic gene promoter methylation at birth is associated with child's later adiposity," *Diabetes*, vol. 60, no. 5, pp. 1528–1534, 2011.

[89] S. F. Ng, R. C. Lin, D. R. Laybutt, R. Barres, J. A. Owens, and M. J. Morris, "Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring," *Nature*, vol. 467, no. 7318, pp. 963–966, 2010.

[90] S. N. Yazbek, S. H. Spiezio, J. H. Nadeau, and D. A. Buchner, "Ancestral paternal genotype controls body weight and food intake for multiple generations," *Human Molecular Genetics*, vol. 19, no. 21, pp. 4134–4144, 2010.

[91] G. A. Dunn and T. L. Bale, "Maternal high-fat diet effects on third-generation female body size via the paternal lineage," *Endocrinology*, vol. 152, no. 6, pp. 2228–2236, 2011.

[92] L. Poston, L. F. Harthoorn, and E. M. Van Der Beek, "Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement," *Pediatric Research*, vol. 69, pp. 175–180, 2011.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 541308, 9 pages
doi:10.1155/2011/541308

Review Article

Gestational Diabetes Mellitus and Risk of Childhood Overweight and Obesity in Offspring: A Systematic Review

Shin Y. Kim, J. Lucinda England, J. Andrea Sharma, and Terry Njoroge

Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA

Correspondence should be addressed to Shin Y. Kim, skim1@cdc.gov

Received 1 June 2011; Accepted 22 July 2011

Academic Editor: Barbara Alexander

We systematically reviewed research examining the association between gestational diabetes (GDM) and childhood overweight and obesity. We identified studies from three sources: (1) a PubMed search of articles published between January 1990–January 2011, (2) reference lists of publications from the PubMed search, and (3) reference lists of review articles. We included studies that examined GDM separately from pregestational diabetes and childhood overweight or obesity defined as BMI > 85th or 95th percentile. A total of 12 studies were included in the systematic review. Crude odds ratios for the relationship between GDM and childhood overweight or obesity ranged from 0.7 to 6.3; in 8 studies, the associations were not statistically significant. In only 3 studies were results adjusted for any confounders; in the 2 that adjusted for prepregnancy obesity, the GDM and childhood overweight or obesity associations were attenuated and not statistically significant after adjustment. This paper demonstrates inconsistent evidence of an association between GDM and offspring overweight and obesity due to the methodological limitations of existing studies. Recommendations for future research are presented, which address methodological challenges.

1. Introduction

Approximately 4–6% of pregnancies in the United States are complicated by diabetes mellitus (DM), making it one of the most common serious medical complications of pregnancy [1–5]. The majority of cases (>80%) are diagnosed for the first time during pregnancy (gestational DM); the remaining cases are pregestational DM (type 1 or type 2) [2]. Furthermore, the prevalence of diabetes in pregnancy is increasing in the United States, concurrent with the rising prevalence of obesity and type 2 diabetes in the general population; this increase is not explained by changes in the prevalence of other known maternal risk factors, such as advanced maternal age [6–8].

It is commonly stated that intrauterine exposure to maternal diabetes places offspring at increased risk for long-term adverse outcomes including overweight and obesity. In addition, it has been suggested that infants of women with diabetes should be specifically targeted for obesity prevention interventions. This suggestion raises several issues. Maternal obesity is also a risk factor for offspring overweight and obesity, is associated with maternal diabetes, and is a more prevalent condition than either gestational or pregestational DM [9–12]. It is unclear, therefore, whether it would be most effective to target infants of women with diabetes specifically, or all infants of women with prepregnancy obesity. Second, studies commonly cited as providing support for a causal association between maternal gestational DM and offspring overweight and obesity, including those conducted among Pima Indian women, have design limitations including combining pregestational and gestational DM into one exposure group, examination of exposed individuals only without a nondiabetic control group, and failure to control for important potential confounders [13–15].

In this study, we systematically reviewed studies examining the association between gestational DM and childhood overweight and obesity. We focused on gestational DM because it is the most prevalent form of diabetes in pregnancy. We summarized findings and addressed methodological limitations of previously published studies. We did not calculate a combined single estimate of the findings due to the heterogeneity of methodology and rigor among

the studies. Finally, we provided recommendations regarding approaches for future studies.

2. Materials and Methods

2.1. Search Process. We used recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines to identify studies for possible inclusion in this analysis [16]. We first searched PubMed records for the period January 1990–January 2011 using the following search terms for childhood overweight/obesity: (Pregn*) AND (GDM OR gestational diabetes OR diabetes OR glucose) AND (Overweight or obes* or BMI or body mass index or weight gain) AND (child* OR adolescen* OR offspring OR long term OR fetal program* OR imprint*). From this search, the full text was retrieved for papers in which the abstracts mentioned a relationship between maternal gestational DM and childhood overweight and obesity. Studies that did not have full text in English were translated for review.

Next, we manually reviewed the reference lists of the publications retrieved and obtained the entire text of publications that potentially could be included in the systematic review. Finally, we searched the reference lists of review articles on gestational DM and childhood overweight and obesity published in the last five years from January 2006 to January 2011 for additional potential publications. We did not attempt to locate any unpublished studies.

Studies that were considered potentially eligible were then reviewed for inclusion in the analysis based on the following criteria.

(1) Data were reported from a cohort with a nondiabetic exposure group or from a case-control study, and not from a case series.

(2) Cases of gestational DM were not combined with cases of pregestational DM. We did not exclude studies based on criteria for defining gestational DM.

(3) An association was reported (negative, positive, or null) for childhood (ages 2–18 years) overweight and/or obesity using a BMI-for-age-and-sex of >85 or >95th percentile. We did not exclude studies based on the authors' reference population for child growth. However, we did exclude studies that examined BMI only as a continuous variable.

(4) The manuscript was written in English or in a language that could be translated with resources available at CDC.

(5) For studies with offspring outcome assessment at multiple ages, findings from data for longest duration of followup were used. When multiple articles from the same study population met the study criteria, we included only the publication with the most recent data available.

2.2. Data Abstraction. All articles were read and reviewed by two authors (S. Y. Kim and T. Njoroge). The authors abstracted the design, setting, location, and time period; the number and characteristics of study participants; the gestational DM diagnosis criteria; the source(s) for childhood obesity (e.g., medical records and clinical databases), and the statistical methods.

2.3. Statistical Methods. For each study, we constructed separate two-by-two tables to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) of gestational DM and each childhood weight outcome analyzed by the study's authors. If a study presented only prevalence estimates, we contacted the author to request the actual sample size for the percentages. We also presented the adjusted odds ratios when available.

3. Results

Childhood Obesity. We identified 1362 potentially relevant studies by searching PubMed; of these, 144 abstracts reported a finding on the relationship between maternal gestational DM and childhood obesity and the full texts of these articles were retrieved for detailed examination (Figure 1). We also reviewed the reference lists of all 144 studies, and identified an additional 48 studies for possible inclusion. After review of these 192 articles, 140 were excluded, either because they did not report the results of a cohort or case-control study or because they clearly did not address an association between maternal gestational DM and childhood obesity; thus, 52 studies were considered further for inclusion. Of these, 37 studies were excluded because gestational and pregestational DM were combined, there was no nondiabetic control group, or BMI was not presented as 85th or 95th percentile or it was presented only as a continuous variable. An additional 3 studies were excluded because later papers reported results on the same study population. A total of 12 studies met the inclusion criteria [17–28].

Six of the studies were conducted in the United States, and one each was conducted in Germany, Brazil, the United Kingdom, Hong Kong, Finland, or Poland (Table 1). We translated one study and contacted three authors. No studies were excluded because of lack of language translation resources. Sources of information on maternal gestational DM diagnosis included maternal self-report, clinical records, or blood glucose measurements. Information used to determine childhood obesity was obtained from parental report, anthropometric measurements obtained as part of a study protocol, hospital records, or clinical databases.

The crude odds ratios for the relationship between gestational DM and childhood overweight or obesity ranged from 0.7 to 6.3 (Figure 2(a)). When the studies were ordered from offspring overweight to obesity, the magnitude of the association did not increase with increasing levels of offspring BMI. If we exclude the lower and upper values, the OR ranges from 1.0 to 2.5. Eight of the twelve studies had significant findings in the crude analysis. In the three of the twelve studies (two of which were among the eight with a significant finding), the authors adjusted for potential confounders when examining the association between gestational DM and childhood obesity compared to a nondiabetic

Table 1: Studies included in review of maternal gestational diabetes mellitus (GDM) and childhood obesity.

Author, year (population)	Study description (name, years, design)	Number in analysis (cohort)	Child age in years at outcome	GDM diagnosis criteria	Outcome	Number and percent of overweight/obese children among women with and without GDM		Multivariable adjustments (GDM versus no GDM)
						GDM	No GDM	
Boerschmann et al., 2010 (Germany)	German GDM and BABYDIAB study, 1989–2000, prospective	222	11	2 of 3 elevated oral glucose tolerance test of 75 g glucose load	BMI ≥ 90th percentile[d]	23/74 (31.1)	23/148 (15.5)	No
Boney et al., 2005 (USA)	Longitudinal cohort study, years not available, prospective	109 (179)	11	Clinical diagnosis from medical records	BMI > 85th percentile[b]	16/58 (27.6)	14/51 (27.5)	No
Buzinaro et al., 2008 (Brazil)	Hospital cohort, 1988–199, prospective	73	10	2 hr clinical measure twice a day in third trimester	BMI > 85th percentile[a]	12/23 (52.2)	4/27 (14.8)	No
					BMI > 95th percentile[a]	1/23 (4.3)	0/27 (0)	
Gillman et al., 2003 (USA)	Nurses Health Study II, 1996, retrospective	14.881 (16.550)	9–14	Maternal self-report from interview/questionnaire	BMI 85th–95th percentile[b]	72/465 (15.5)	1917/14,416 (13.3)	Yes
					BMI > 95th percentile[b]	45/465 (9.7)	958/14,416 (6.6)	
Hillier et al., 2007 (USA)	Kaiser Permanente Hawaii and Northwest, 1995–2000, prospective	7.782 (9.439)	5–7	3 h 100 g oral glucose tolerance test	Carpenter and Coustan:			Yes
					BMI > 85th percentile[b]	60/173 (34.7)	1,788/7,609 (23.5)	
					BMI > 95th percentile[b]	35/173 (20.2)	928/7,609 (12.2)	
					National Diabetes Data Group:			
					BMI > 85th percentile[b]	103/370 (27.8)	1,788/7,609 (23.5)	
					BMI > 95th percentile[b]	64/370 (17.3)	928/7,609 (12.2)	
Lawlor et al., 2010 (United Kingdom)	The Avon Longitudinal Study of Parents and Children (ALSPAC), 1991–1992, prospective	6.584 (10.591)	9–11	Clinical diagnosis from medical records	BMI > 85th percentile[c]	12/40 (30.0)	1481/6544 (22.6)	Yes
Malee et al., 2002 (USA)	Diabetes in Pregnancy Program at the Women and Infants Hospital, 1991–1993, Prospective	64 (262)	9	2 abnormal 100 g glucose tolerance test	BMI ≥ 85th percentile[d]	11/33 (33.3)	8/31 (25.8)	No

Table 1: Continued.

Author, year (population)	Study description (name, years, design)	Number in analysis (cohort)	Child age in years at outcome	GDM diagnosis criteria	Outcome	Number and percent of overweight/obese children among women with and without GDM		Multivariable adjustments (GDM versus no GDM)
Pirkola et al., 2010 (Finland)	Northern Finland 1986 birth cohort, 1985–1986, prospective	745 (4.168)	16	One abnormal value from a 2 hour, 75 g oral glucose tolerance test	BMI > 85th percentile[c]	18/84 (21.4)	113/661 (17.1)	No
Tam et al., 2009 (Hong Kong)	GDM cohort of women at the Prince of Wales Hospital, 1992–1994, prospective	164 (1032)	7–10	75 g oral glucose tolerance test	BMI ≥ 85th percentile[d]	19/63 (30.2)	26/101 (25.5)	No
Whitaker et al., 1998 (USA)	GDM cohort of women from an HMO in Washington state, 1985–1986, prospective	315 (524)	5–10	3 h 100 g oral glucose tolerance test	BMI ≥ 85th percentile[d]	11/58 (19.0)	62/257 (24.1)	No
Wright et al., 2009 (USA)	Project Viva, 1999–2002, prospective	1086 (1.579)	3	Nonfasting oral glucose challenge test	BMI ≥ 95th percentile[b]	7/51 (13.7)	91/1035 (8.8)	No
Wroblewska-Seniuk et al., 2009 (Poland)	Cohort from the Clinical Hospital of Obstetrics and Gynecology in Poznan, Poland, years not available retrospective	185	4–9	Oral glucose tolerance test between 24th and 28th week of gestation	BMI > 95th percentile[d]	9/34 (26.5)	17/108 (15.7)	No
					BMI 85th–95th percentile[d]	3/34 (8.8)	8/108 (7.4)	

BMI classification reference: [a]WHO International Classification, [b]CDC growth charts, [c]International Obesity Task Force, and [d]Other.

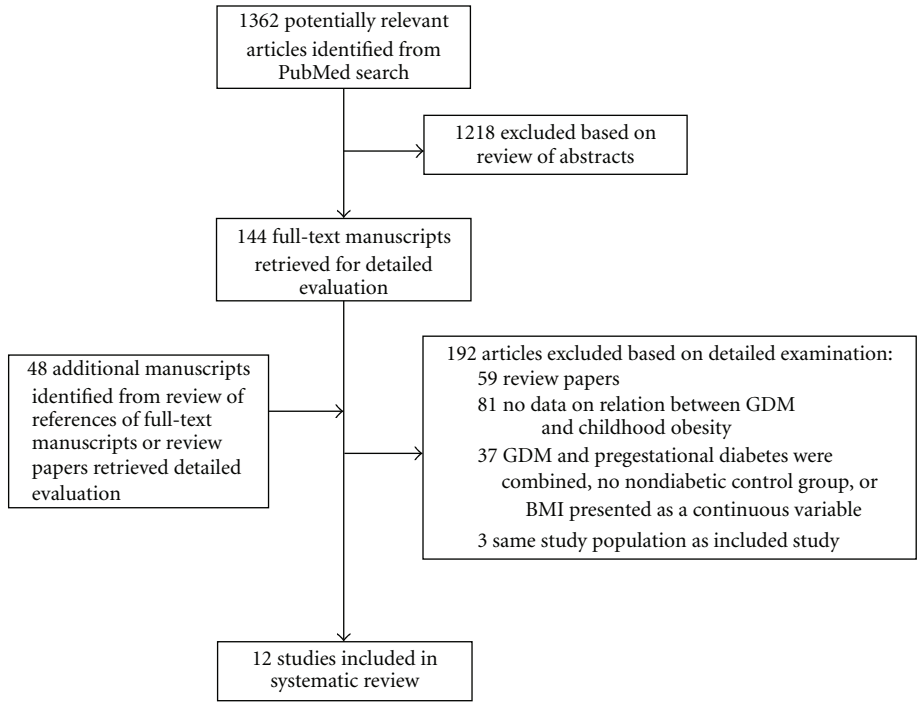


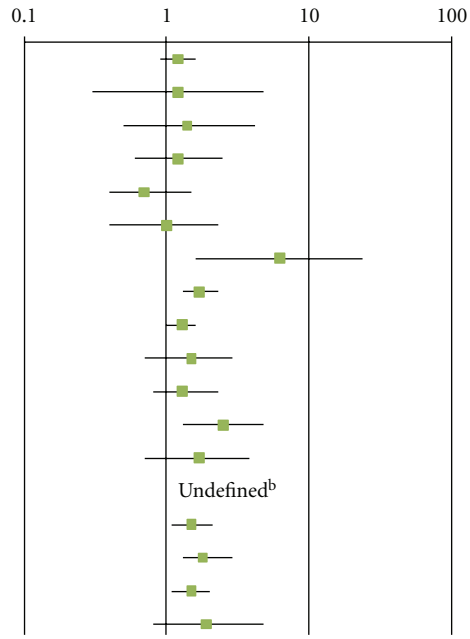
Figure 1: Flow diagram showing the number of studies included in and excluded from the systematic review for childhood obesity.

control group (Figure 2(b)). In the first of the three studies, Gillman and colleagues reported a crude odds ratio (OR) of 1.2 (0.9–1.5) and 1.4 (1.1–2.0) for adolescent weight at 85th–95th percentile and >95th percentile, respectively at age 9–14 years old among the offspring of mothers with gestational DM versus no diabetes [19]. These estimates did not change after adjustment for level of child's physical activity, hours per week watching television, and energy intake. However, adjustment for maternal prepregnancy BMI attenuated the associations for both weight at 85th–95th percentile (AOR = 1.0, 95% CI 0.7–1.3) and at >95th percentile (AOR = 1.2, 95% CI 0.8–1.7), and results were no longer significant. In the second study, Lawlor and colleagues reported a crude OR of 1.5 (0.8, 2.9) for weight >85th percentile at age 9–11 years among offspring of mothers with gestational DM, but this positive finding was reversed after adjustment for prepregnancy BMI (AOR = 0.62, 95% CI 0.3, 1.23) [26]. However, the finding was not significant either before or after the adjustment. In the third study, by Hillier and colleagues, the authors compared treated and nontreated women with gestational DM each to women with no diabetes [20]. They did not adjust for prepregnancy BMI but did adjust for maternal age, parity, gestational weight gain, ethnicity, macrosomia, and sex of child. They reported an adjusted OR of 1.9 (1.3, 2.8) for child's weight >85th percentile and 1.8 (1.1, 2.9) for child's weight >95th percentile at age 5–7 years among offspring of mothers likely not treated for gestational DM (those who met criteria for gestational DM using Carpenter and Coustan criteria only and did not meet the National Diabetes Data Group (NDDG) criteria) compared to offspring of women with no diabetes. They found no significant associations between gestational diabetes and childhood weight >85th percentile (adjusted OR = 1.3 (0.8, 1.9) or for child's weight >95th percentile (adjusted OR = 1.38 (0.8, 2.3)) in women likely treated for gestational DM (those who met criteria for gestational DM using the NDDG criteria). In addition, the authors observed a dose-response relationship between maternal glucose concentration in quartiles among women with no diabetes and risk of childhood overweight and obesity, suggesting that elevated maternal blood glucose does affect risk of overweight and obesity in offspring, and that this risk may be reduced with treatment of gestational DM during pregnancy.

In one of the 12 studies, Boerschmann and colleagues did not adjust for any confounders; however, the authors did present results stratified by maternal BMI among offspring of women with gestational DM. They found that among offspring of women with gestational DM, there was an increase in offspring BMI percentile ≥90 as maternal BMI increased. This increase further supports the strength of maternal BMI [27]. None of the 12 studies included information on genetic factors.

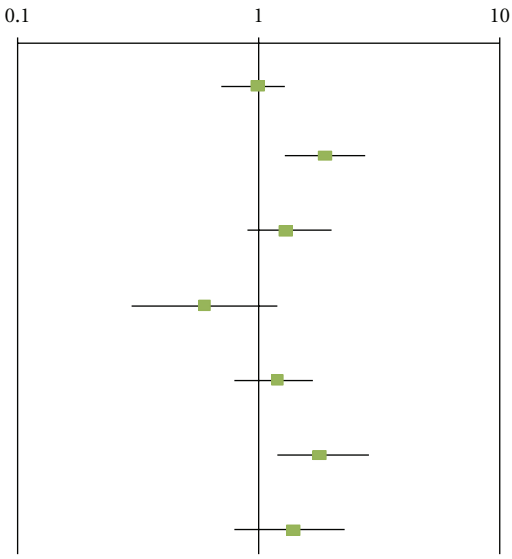
4. Discussion

To our knowledge, ours is the first study to systematically review all published case-control and cohort studies specifically examining the association between maternal gestational DM and the prevalence of offspring overweight and obesity. We excluded many studies from our review because of methodological limitations, including the use of an exposure group combining pregestational and gestational DM, and the lack of a nondiabetic control group. We found that



Author (year)	*N*	Offspring BMI percentile
Gillman et al., (2003)	14,881	85–95
Wroblewska-Seniuk et al., (2009)	185	85–95
Malee et al., (2002)	64	≥85
Tam et al., (2009)	164	≥85
Whitaker et al., (1998)	315	≥85
Boney et al., (2005)	109	>85
Buzinaro et al., (2008)	73	>85
Hillier et al., (C and C; 2007)[a]	7,782	>85
Hillier et al., (NDDG; 2007)[a]	7,782	>85
Lawlor et al., (2010)	6,584	>85
Pirkola et al., (2010)	745	> 85
Boerschmann et al., (2010)	222	≥90
Wright et al., (2009)	1,086	≥95
Buzinaro et al., (2008)[b]	73	>95
Gillman et al., (2003)	14,881	>95
Hillier et al., (C and C; 2007)[a]	7,782	>95
Hillier et al., (NDDG; 2007)[a]	7,782	>95
Wroblewska-Seniuk et al., (2009)	185	>95

(a)



Author (year)	*N*	Offspring BMI percentile
Gillman et al., (2003)[a]	14,881	85–95
Hillier et al., (C and C; 2007)[b,d]	7,782	>85
Hillier et al., (NDDG; 2007)[b,d]	7,782	>85
Lawlor et al., (2010)[c]	6,584	>85
Gillman et al., (2003)[a]	14,881	>95
Hillier et al., (C and C; 2007)[b,d]	7,782	>95
Hillier et al., (NDDG; 2007)[b,d]	7,782	>95

(b)

Figure 2: (a) Association of GDM and childhood overweight or obesity, unadjusted odds ratio, and 95% confidence interval. [a]At the time this analysis was conducted, Kaiser Permanente used the NDDG criteria to diagnose and treat GDM. However, in the analysis, they calculated GDM using both criteria. Therefore, those meeting the NDDG criteria in this analysis were likely treated with diet or diet/insulin, but those meeting only the Carter and Coustan criteria were likely to not be treated. [b]Undefined because odds ratio could not be calculated with a zero cell. (b) Association of GDM and childhood overweight or obesity compared to a nondiabetic control group among studies that adjusted for any confounders, adjusted odds ratios, and 95% confidence intervals. [a]Adjusted for maternal BMI and child's age, gender, Tanner stage, TV watching, physical activity, energy intake, birth weight, breastfeeding duration, birth order, and mom's household income, mother's smoking, dietary restraint, weight cycling, weight concerns, and mother's current BMI. [b]Adjusted for maternal age, parity, weight gain during pregnancy, ethnicity, macrosomia at birth, and sex of child. [c]Adjusted for maternal prepregnancy BMI and sex, age at outcome, height, height squared, maternal age, social class, parity, smoking during pregnancy, mode of delivery, and maternal prepregnancy BMI. [d]At the time this analysis was conducted, Kaiser Permanente used the NDDG criteria to diagnose and treat GDM. However, in the analysis, they calculated GDM using both criteria. Therefore, those meeting the NDDG criteria in this analysis were likely treated with diet or diet/insulin, but those meeting only the Carter and Coustan criteria were likely to not be treated.

studies of the effects of maternal gestational DM on offspring overweight and obesity have yielded inconclusive results, which is consistent with a recent review examining maternal diabetes and offspring BMI z-scores, where they found the association between maternal diabetes and offspring BMI to be no longer significant after adjustment for prepregnancy BMI [29].

5. Fetal Exposure to Maternal Hyperglycemia

Women with preexisting diabetes have a substantially increased risk of pregnancy complications including fetal loss, perinatal mortality, and of delivering an infant with congenital anomalies [30]. Although the mechanisms underlying these associations are not completely understood, it has been shown that tight glycemic control in early pregnancy reduces the prevalence of such pregnancy complications [31]. In contrast to women with pregestational DM who are hyperglycemic throughout pregnancy, women with gestational DM typically develop hyperglycemia in the second or third trimester of pregnancy, and pregnancy complications associated with gestational DM are not as severe [32, 33]. Therefore, we cannot assume that pregestational DM and gestational DM have the same effects on fetal development and long-term offspring outcome, and it is important to study associations between these two conditions and offspring outcomes separately.

In addition to timing of exposure, it is important to consider differences in diagnostic cutpoints for gestational DM. Depending on the cutpoints, it may result in the inclusion of women with milder disease in the gestational DM exposed group, which could attenuate the association between gestational DM and offspring overweight and obesity. Therefore, the severity of disease would be important to consider when examining offspring overweight and obesity.

6. Confounders

6.1. Maternal Prepregnancy Obesity. Studying the relationships between pregestational and gestational DM and risk of overweight and obesity in the offspring is complicated by difficulties in fully controlling for potential confounders, including maternal obesity, genetic factors, and maternal and infant lifestyle. In our review, we found that while many authors reported positive associations between gestational DM and childhood obesity in crude analysis, their results were not adjusted for important potential confounders, most notably maternal obesity. In the three studies that included adjusted analysis, the associations were attenuated after adjustment for confounders. Furthermore, results were adjusted for maternal obesity in only two studies; in both, associations between gestational DM and childhood overweight or obesity were not significant after adjustment.

Maternal obesity is an important risk factor for gestational DM; women who are overweight, obese, or severely obese before pregnancy are two-, four-, and eight-times more likely to develop gestational DM compared with normal-weight women [11]. Infants born to overweight and obese mothers are more likely to be macrosomic, even in the absence of gestational diabetes [34]. In a recent study by Catalano et al., the authors found that prepregnancy obesity was significantly associated with offspring being in the highest BMI tertile and for having metabolic dysregulation at age 6–11 years [35]. They also found that prepregnancy obesity was the strongest perinatal predictor of high BMI in childhood, stronger than either maternal glucose homeostasis or weight gain during pregnancy. Although this study was not included in our review because the outcomes were not defined as overweight or obesity, the results provide additional support that gestational DM cannot be evaluated as an independent risk factor for childhood overweight and obesity without accounting for potential confounding from maternal obesity. This concept is further supported by a follow-up study of offspring of women who participated in the Hyperglycemia and Adverse Pregnancy Outcome Study in Belfast, Northern Ireland. The authors found that at age two the overall correlations between maternal glucose during pregnancy and BMI z-score were weak and that birth weight and maternal BMI remained independent predictors of BMI z-score after adjustment [36].

6.2. Other Potential Confounders. Other potentially important confounders in the association between gestational DM and offspring overweight and obesity include common social, environmental, and genetic factors shared by both the mothers and the offspring. Poor dietary habits and a sedentary lifestyle in the mother may contribute to increased prepregnancy weight and weight gain during pregnancy, and may increase the risk of poor diet and sedentary behavior for the offspring [10]. However, only one of the studies in our review examined the association between physical activity and nutrition and childhood overweight and obesity [19]. Genetic influence is also important to consider. However, it is difficult to fully control for genetics outside of sibling studies, and none of the studies in our review included genetic factors as potential confounders. To our knowledge, no studies examining associations between gestational DM and offspring obesity have taken all of potentially important confounders, including maternal obesity, gestational weight gain, and maternal and infant lifestyle and genetic factors into account.

7. Treatment of Gestational DM

If treatment of gestational DM reduces risk of overweight or obesity in offspring, it may be difficult to consistently detect an association in observational studies. Women with gestational DM are typically instructed to monitor blood sugar and adjust their dietary habits, which may improve long-term offspring outcomes. In only one study did the authors examine treated and nontreated women with gestational DM [20]. They reported significant associations with childhood overweight and with obesity in the nontreated group but not in the treated group. Further evidence that treatment of gestational DM may improve offspring outcome is found in studies of women with high blood glucose concentration,

but not sufficiently high for a diagnosis of gestational DM thus not treated. For example, Deierlein et al. found that fetal exposure to maternal glucose concentration in the high-normal range was associated with the development of overweight and obesity in the offspring at age three years, independent of maternal prepregnancy BMI [37].

8. Future Studies

As previously discussed, most existing observational studies cannot be used to definitively quantify the independent contribution of gestational diabetes to offspring overweight and obesity risk because of unmeasured confounding and other methodological limitations. We recommend the following for future studies.

(1) Observational studies should analyze women with pregestational and gestational DM separately, and if possible include documentation of timing of fetal exposure to elevated maternal glucose levels.

(2) Observational studies should include documentation of lifestyle and other environmental factors present during infancy and childhood.

(3) All studies should address relevant confounders, including maternal prepregnancy BMI. One possible approach would be to make use of databases with linked siblings so outcomes between siblings with discordant exposure to gestational DM could be compared, providing a mechanism to control for shared genetic and lifestyle factors.

(4) When possible, randomized trials for the treatment for mild gestational DM should include long-term followup of offspring assess the effects of maternal interventions during pregnancy on infant and child outcomes [38]. If it can be confirmed that treatment of gestational DM is associated with a reduced risk of overweight or obesity in offspring, it will provide further evidence that there is a causal relationship and that an effective prevention intervention exists.

9. Limitations

This study has some limitations. First, we did not include unpublished studies, therefore our results may be affected by publication bias. In addition, we may have missed studies that were not listed in PubMed or referenced in other published studies or reviews. Finally, these studies are not all directly comparable due to discrepancies in the study population, methodology, gestational DM diagnostic criteria, BMI reference population, and ages. However, the present study is the first to systematically review all published case-control and cohort studies examining the association between maternal gestational DM and the prevalence of offspring overweight and obesity.

10. Conclusions

In conclusion, this review demonstrates that studies of associations between maternal gestational DM on offspring overweight and obesity have yielded inconclusive results. Because maternal obesity is a more prevalent condition than gestational DM and is strongly associated with offspring obesity, we need a better understanding of the relative contributions of maternal obesity and gestational DM to risk before designating infants of women with GDM specifically as targets for obesity prevention efforts. Interventions addressing prepregnancy obesity may have a greater public health impact on childhood overweight and obesity than those targeting offspring of women with gestational DM. A stronger body of evidence is needed to better understand the potential associations between maternal gestational DM and offspring outcomes.

Disclosure

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Acknowledgment

The authors would like to thank Connie Bish and Susan Chu for their feedback and contributions at the inception of this paper.

References

[1] F. Cunningham, N. Gant, K. Leveno, L. Gilstrap, J. Hauth, and K. Wenstrom, *Williams Obstetrics*, McGrow-Hill, New York, NY, USA, 21st edition, 2001.

[2] S. S. Albrecht, E. V. Kuklina, P. Bansil et al., "Diabetes trends among delivery hospitalizations in the U.S., 1994–2004," *Diabetes Care*, vol. 33, no. 4, pp. 768–773, 2010.

[3] D. Getahun, C. Nath, C. V. Ananth, M. R. Chavez, and J. C. Smulian, "Gestational diabetes in the United States: temporal trends 1989 through 2004," *American Journal of Obstetrics and Gynecology*, vol. 198, no. 5, pp. 525.e1–525.e5, 2008.

[4] S. Y. Chu, K. Abe, L. R. Hall, S. Y. Kim, T. Njoroge, and C. Qin, "Gestational diabetes mellitus: all Asians are not alike," *Preventive Medicine*, vol. 49, no. 2-3, pp. 265–268, 2009.

[5] S. Y. Kim, L. England, H. G. Wilson, C. Bish, G. A. Satten, and P. Dietz, "Percentage of gestational diabetes mellitus attributable to overweight and obesity," *American Journal of Public Health*, vol. 100, no. 6, pp. 1047–1052, 2010.

[6] A. H. Mokdad, E. S. Ford, B. A. Bowman et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.

[7] S. Y. Kim, P. M. Dietz, L. England, B. Morrow, and W. M. Callaghan, "Trends in pre-pregnancy obesity in nine states, 1993–2003," *Obesity*, vol. 15, no. 4, pp. 986–993, 2007.

[8] D. Dabelea, J. K. Snell-Bergeon, C. L. Hartsfield, K. J. Bischoff, R. F. Hamman, and R. S. McDuffie, "Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM screening program," *Diabetes Care*, vol. 28, no. 3, pp. 579–584, 2005.

[9] V. Svensson, J. A. Jacobsson, R. Fredriksson et al., "Associations between severity of obesity in childhood and adolescence, obesity onset and parental BMI: a longitudinal cohort study," *International Journal of Obesity*, vol. 35, pp. 46–52, 2011.

[10] V. Burke, L. J. Beilin, and D. Dunbar, "Family lifestyle and parental body mass index as predictors of body mass index in Australian children: a longitudinal study," *International Journal of Obesity*, vol. 25, no. 2, pp. 147–157, 2001.

[11] S. Y. Chu, W. M. Callaghan, S. Y. Kim et al., "Maternal obesity and risk of gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 8, pp. 2070–2076, 2007.

[12] S. Y. Chu, S. Y. Kim, and C. L. Bish, "Prepregnancy obesity prevalence in the United States, 2004-2005," *Maternal and Child Health Journal*, vol. 13, no. 5, pp. 614–620, 2009.

[13] D. Dabelea, "The predisposition to obesity and diabetes in offspring of diabetic mothers," *Diabetes Care*, vol. 30, no. 2, pp. S169–S174, 2007.

[14] B. L. Silverman, L. Landsberg, and B. E. Metzger, "Fetal hyperinsulinism in offspring of diabetic mothers. Association with the subsequent development of childhood obesity," *Annals of the New York Academy of Sciences*, vol. 699, pp. 36–45, 1993.

[15] B. E. Metzger, "Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring," *Clinical Obstetrics and Gynecology*, vol. 50, no. 4, pp. 972–979, 2007.

[16] D. F. Stroup, J. A. Berlin, S. C. Morton et al., "Meta-analysis of observational studies in epidemiology: a proposal for reporting," *Journal of the American Medical Association*, vol. 283, no. 15, pp. 2008–2012, 2000.

[17] C. M. Boney, A. Verma, R. Tucker, and B. R. Vohr, "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus," *Pediatrics*, vol. 115, no. 3, pp. e290–e296, 2005.

[18] E. F. Buzinaro, C. B. Berchieri, A. L. M. Haddad, C. R. Padovani, and W. De Paula Pimenta, "Overweight in adolescent offspring of women with hyperglycemia during pregnancy," *Arquivos Brasileiros de Endocrinologia e Metabologia*, vol. 52, no. 1, pp. 85–92, 2008.

[19] M. W. Gillman, S. Rifas-Shiman, C. S. Berkey, A. E. Field, and G. A. Colditz, "Maternal gestational diabetes, birth weight, and adolescent obesity," *Pediatrics*, vol. 111, no. 3, pp. e221–e226, 2003.

[20] T. A. Hillier, K. L. Pedula, M. M. Schmidt, J. A. Mullen, M. A. Charles, and D. J. Pettitt, "Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia," *Diabetes Care*, vol. 30, no. 9, pp. 2287–2292, 2007.

[21] M. P. Malee, A. Verma, G. Messerlian, R. Tucker, and B. R. Vohr, "Association between maternal and child leptin levels 9 years after pregnancy complicated by gestational diabetes," *Hormone and Metabolic Research*, vol. 34, no. 4, pp. 212–216, 2002.

[22] R. C. Whitaker, M. S. Pepe, K. D. Seidel, J. A. Wright, and R. H. Knopp, "Gestational diabetes and the risk of offspring obesity," *Pediatrics*, vol. 101, no. 2, p. E9, 1998.

[23] W. H. Tam, R. C. W. Ma, X. Yang et al., "Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero," *Pediatrics*, vol. 122, no. 6, pp. 1229–1234, 2008.

[24] C. S. Wright, S. L. Rifas-Shiman, J. W. Rich-Edwards, E. M. Taveras, M. W. Gillman, and E. Oken, "Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure," *American Journal of Hypertension*, vol. 22, no. 2, pp. 215–220, 2009.

[25] K. Wroblewska-Seniuk, E. Wender-Ozegowska, and J. Szczapa, "Long-term effects of diabetes during pregnancy on the offspring," *Pediatric Diabetes*, vol. 10, no. 7, pp. 432–440, 2009.

[26] D. A. Lawlor, A. Fraser, R. S. Lindsay et al., "Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort," *Diabetologia*, vol. 53, no. 1, pp. 89–97, 2010.

[27] H. Boerschmann, M. Pflüger, L. Henneberger, A. G. Ziegler, and S. Hummel, "Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus," *Diabetes Care*, vol. 33, no. 8, pp. 1845–1849, 2010.

[28] J. Pirkola, A. Pouta, A. Bloigu et al., "Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus," *Diabetes Care*, vol. 33, no. 5, pp. 1115–1121, 2010.

[29] L. H. Philipps, S. Santhakumaran, C. Gale et al., "The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis," *Diabetologia*, vol. 54, no. 8, pp. 1957–1966, 2011.

[30] F. Dunne, P. Brydon, K. Smith, and H. Gee, "Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990–2002," *Diabetic Medicine*, vol. 20, no. 9, pp. 734–738, 2003.

[31] J. L. Kitzmiller, J. M. Block, F. M. Brown et al., "Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care," *Diabetes Care*, vol. 31, no. 5, pp. 1060–1079, 2008.

[32] B. M. Casey, M. J. Lucas, D. D. McIntire, and K. J. Leveno, "Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population," *Obstetrics and Gynecology*, vol. 90, no. 6, pp. 869–873, 1997.

[33] X. Xiong, L. D. Saunders, F. L. Wang, and N. N. Demianczuk, "Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes," *International Journal of Gynecology and Obstetrics*, vol. 75, no. 3, pp. 221–228, 2001.

[34] P. M. Catalano and H. M. Ehrenberg, "The short- and long-term implications of maternal obesity on the mother and her offspring," *BJOG*, vol. 113, no. 10, pp. 1126–1133, 2006.

[35] P. M. Catalano, K. Farrell, A. Thomas et al., "Perinatal risk factors for childhood obesity and metabolic dysregulation," *American Journal of Clinical Nutrition*, vol. 90, no. 5, pp. 1303–1313, 2009.

[36] D. J. Pettitt, S. McKenna, C. McLaughlin, C. C. Patterson, D. R. Hadden, and D. R. McCance, "Maternal glucose at 28 weeks of gestation is not associated with obesity in 2-year-old offspring: the Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) family study," *Diabetes Care*, vol. 33, no. 6, pp. 1219–1223, 2010.

[37] A. L. Deierlein, A. M. Siega-Riz, K. Chantala, and A. H. Herring, "The association between maternal glucose concentration and child BMI at age 3 years," *Diabetes Care*, vol. 34, no. 2, pp. 480–484, 2011.

[38] M. B. Landon, C. Y. Spong, E. Thom et al., "A multicenter, randomized trial of treatment for mild gestational diabetes," *New England Journal of Medicine*, vol. 361, no. 14, pp. 1339–1348, 2009.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 985139, 9 pages
doi:10.1155/2011/985139

Research Article

Maternal Behaviors during Pregnancy Impact Offspring Obesity Risk

Suzanne Phelan,[1] Chantelle Hart,[2] Maureen Phipps,[3] Barbara Abrams,[4] Andrew Schaffner,[5] Angelica Adams,[2] and Rena Wing[2]

[1] *Kinesiology Department, California Polytechnic State University, 1 Grand Avenue, San Luis Obispo, CA 93407-0386, USA*
[2] *Department of Psychiatry and Weight Control and Diabetes Research Center, Warren Alpert Medical School of Brown University and The Miriam Hospital, 197 Richmond Street, Providence, RI 02906, USA*
[3] *Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University and Women and Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905, USA*
[4] *School of Public Health, University of California, Berkeley, 140 Warren Hall, Berkeley, CA 94720, USA*
[5] *Statistics Department, California Polytechnic State University, 1 Grand Avenue, San Luis Obispo, CA 93407, USA*

Correspondence should be addressed to Suzanne Phelan, sphelan@calpoly.edu

Received 15 June 2011; Revised 5 August 2011; Accepted 6 August 2011

Academic Editor: Susan Ozanne

This study investigated the effects of maternal changes during pregnancy in diet, exercise, and psychosocial factors on offspring weight parameters at birth and 6 months. In overweight/obese (OW/OB; $n = 132$) mothers, greater % kcal from sweets early inpregnancy was the strongest, independent predictor of higher weight for age (WFA) (beta = 0.19; $P = 0.004$), higher odds ofmacrosomia (OR = 1.1 (1.0–1.2); $P = 0.004$) andWFA >90th percentile at birth (OR = 1.2 (1.1–1.3); $P = 0.002$) and higher WFA at 6 months (beta = 0.30; $P = 0.002$). In normal weight ($n = 153$) mothers, higher intake of soft drinks was the strongest predictor of higher offspring WFA at birth (beta = 0.16; $P = 0.04$) but not at 6 months. Prenatal physical activity, depressive symptoms, and sleep-related variables did not significantly predict offspring weight outcomes. Mothers' eating behaviors during pregnancy, especially intake of sweets in OW/OB mothers, may have a lasting effect on child weight.

1. Introduction

Risk of obesity is shaped, in large part, by early life events starting during gestation. One powerful early life exposure is maternal obesity during pregnancy. Studies have consistently found that higher maternal weight entering and during pregnancy increases risk for obesity among offspring in childhood, adolescence, and adulthood [1, 2]. While shared genes account for some of the similarity in maternal and offspring weight, evidence suggests that exposure to the uterine environment of an obese woman itself may directly program offspring obesity [3].

Another independent determinant of offspring weight status is gestational weight gain (GWG). Both excessive [4] and inadequate [5] weight gain in the mother during gestation have been shown to lead to overly rapid fetal and infant growth rates and the programming of future risk of childhood overweight and metabolic disease. In the USA excessive GWG remains of predominant concern, as 60% of obese women gain more than recommended. Also, approximately 40% of normal weight women gain more than recommended [6], increasing the risk of obesity in their offspring.

Although maternal obesity and excessive GWG are both the result of energy intake exceeding energy expenditure, few studies have examined the specific influences of maternal dietary and exercise behaviors during pregnancy on offspring obesity risk. Some evidence suggests that maternal prenatal intake of protein and fat [7–9] may be positively associated with birth weight. In animal models, prenatal exposures to overnutrition, high-fat and high-protein diets, "junk" food, and stress have been linked with greater adiposity in offspring

[10–12]. In nonpregnant humans, intake of soft drinks and junk food [13], higher dietary disinhibition [14], and restrictive dieting practices [15] have been positively correlated with overweight in children. However, little research has comprehensively examined the impact of maternal prenatal behaviors and psychosocial variables measured during pregnancy on subsequent offspring weight status at birth and 6 months. This information is critical for the design of future intervention trials targeting obesity prevention in children.

The primary aim of this study was to examine the impact of GWG, maternal eating and exercise behaviors, and psychosocial factors on offspring weight status. We hypothesized that offspring exposed to maternal obesity, excessive GWG, poor prenatal eating habits, less exercise in pregnancy, and greater maternal psychosocial distress during gestation would have higher weight for age (WFA) z-scores at birth and 6 months than nonexposed counterparts.

2. Materials and Methods

2.1. Participants and Procedures. Participants were offspring of women recruited into the Fit for Delivery study, a clinical trial that examined the effects of a lifestyle intervention to reduce excessive GWG in normal weight and overweight/obese women (Clinical Trials no. 01117961) [16]. As reported previously [16], the intervention reduced excessive GWG in normal weight but not overweight/obese women. Normal weight and overweight/obese categories were based on the 1990 IOM cut points [17]: normal weight BMI = 19.8 to 26.0 or overweight/obese BMI 26.1–40.0 [17]. Women were recruited at the time of their first prenatal visit from one of six obstetric offices serving a socioeconomic and ethnically diverse population in Providence, RI from 2006 to 2008. Eligibility criteria included nonsmoking, adults (age >18 years), fluency in English, access to telephone, gestational age between 10 and 16 weeks, singleton pregnancy, no current or history of eating disorders, and without major psychiatric illness (i.e., schizophrenia, bipolar disorder, and panic/anxiety disorder) or major medical problems, including diabetes, stroke, and cancer. Women ($n = 32$) who developed gestational diabetes (GDM) were excluded from analysis a priori, given potential impact of GDM on both offspring and maternal weight gain [18]. All mothers provided written informed consent, and all procedures were conducted in accordance with ethical standards for human experimentation. Mothers were paid $25 for attending the 30-week gestation and 6-month postpartum assessments. The study was approved by the Institutional Review Boards at the Miriam Hospital, in Providence, RI., Women and Infants Hospital of Rhode Island Providence, RI and California Polytechnic State University, in San Luis Obispo, Calif.

2.2. Measures

2.2.1. Background Information. At study entry, participants reported via questionnaire information on maternal race/ethnicity, age, education, parity, employment, marital status, and household income. For descriptive purposes, the race variable was defined as non-Hispanic Caucasian, Latina/Hispanic, African-American, and "other." In other analyses, race was categorized as non-Hispanic Caucasian versus all other groups combined. Income was categorized as > $25,000 per year versus ≤ $25,000. Mothers also reported duration of breastfeeding on postpartum questionnaires.

2.2.2. Maternal Anthropometrics. Maternal pregravid weight was based on self-report at time of study enrollment and was shown to be valid compared with physician documented prepregnancy weight [16]. Height was measured by trained research staff using a stadiometer at study entry and was used with pregravid weight to calculate BMI. Total GWG was computed based on pregravid weight and weight at the last clinic visit prior to delivery. Weight at the last clinic visit was objectively measured using a calibrated digital or balance beam scale by research assistant or clinic staff. Data were collected before the 2009 IOM guidelines were released. Based on the 1990 IOM guidelines [17], we classified GWG as "excessive" in normal weight women whose gains were more than 35 pounds (15.9 kg) and overweight (BMI >26 to 29) women whose gains were above 25 pounds (11.4 kg). Similar to other studies, we combined overweight and obese (BMI 29–40) women in our analysis and, thus, also set an upper weight gain goal of 25 pounds (11.4 kg) for these heaviest women [19].

2.2.3. Infant Anthropometrics. Trained research staff abstracted infant and child weight and length from obstetric and pediatric records. We computed birth weight for gestational age z-scores using US Natality reference data from Oken et al. [20] and defined small for gestational age (SGA) at birth as WFA z-scores <10th percentile and large for gestational age as WFA z-scores >90th percentile. Macrosomia was defined as weight >4000 grams [21]. We computed 6-month WFA and sex-specific z scores with 2000 CDC reference data [22] and defined risk of obesity as WFA z-scores >90th percentile. Other variables abstracted from infant medical records included infant sex and gestational age at birth (calculated from last menstrual period or from second trimester ultrasound if the two estimated differed by >10 days).

2.2.4. Behavioral and Psychosocial Factors during Pregnancy. Self-reported measures of dietary intake and exercise expenditure were obtained by trained assessors at study entry and 30-weeks gestation. The Block Food Frequency questionnaire was used to assess daily caloric intake, calories from sugar-sweetened beverages, and percent intake from fat, protein, carbohydrates, and sweets. This questionnaire has been well validated [23] and validated in pregnancy [24]. Participants completed the questionnaire in reference to intake over the past month.

Fast food consumption was assessed based on self-report questions used in our previous research [25]. Energy expenditure was measured using the Paffenbarger Physical Activity Questionnaire [26], a measure which estimates weekly energy expenditure from self-reports of stairs climbed, blocks

walked, and other recreational activities performed in the past week. The Edinburgh Postnatal Depression Scale was used to examine levels of depressive symptoms [27]. The Eating Inventory (EI) [28] was used to assess cognitive restraint and disinhibition. Stress was assessed using the short form of the Perceived Stress Scale [29]. Sleep was assessed using the General Sleep Disturbance questionnaire [30].

2.3. Statistics. Both R (version 2.11.1) and SPSS (PASW version 18.0.1) statistical packages were used. Analyses were conducted separately for normal weight and overweight/obese women, given the observed difference in impact of the lifestyle treatment on GWG [16] and effects of maternal prepregnancy weight on offspring weight outcomes [31]. Pearson's product moment correlations were conducted to examine unadjusted associations between WFA z-scores and maternal variables. Multiple regression (for continuous outcomes) and logistic regression (for categorical outcomes) were used to examine predictors of infant macrosomia, and WFA z-scores at birth and 6 months, and changes in WFA z-scores, adjusting for treatment group, infant sex, recruitment clinic, weeks of gestation at delivery, and breastfeeding (in 6-month analyses). Predictors included both baseline and pregnancy changes over time (between entry and 30-weeks gestation). To determine the most robust set of predictors and correlates of infant outcomes, multiple regression analyses were used. To arrive at a final regression model, stepwise analyses were first conducted within predefined categories (i.e., demographic (age, parity, race, marital status, education, prepregnancy BMI), physical activity (calories expended per week in moderate physical activity TV hours per day), macronutrient (% of calories from fat, carbohydrates, protein, sweets, and total calories), dietary components (fast food and sugar-sweetened soft drinks) psychosocial variables (mood, restraint, disinhibition, and stress), and sleep. Variables that were significant or approached significance ($P < 0.10$) within each category in the stepwise analyses were included together in a comprehensive model. Macronutrient (i.e., % kcal from sweets, fat, and protein) and specific dietary components (i.e., fast food or soft drinks) were analyzed in separate models due to their high collinearity. Similarly, as the percentage of calories from fat and carbohydrates was highly correlated ($r = -.90$; $P = .0001$), only the percentage of calories from fat was used in initial modeling. Similar analyses were conducted using logistic regression to examine impact on odds of macrosomia. Prepregnancy BMI was also examined as a categorical predictor (median split within weight groups), but the same results were observed. Exploratory analyses examined whether treatment condition (intervention versus standard care) interacted with dietary variables and physical activity in predicting offspring weight status. After adjustments (infant sex, recruitment clinic, weeks of gestation at delivery, and breastfeeding), no significant interactions were observed in normal weight or overweight/obese mothers (data not shown).

3. Results

3.1. Participant Characteristics. Excluding participants with miscarriages ($n = 6$) and GDM ($n = 32$), 363 mothers (177 overweight/obese and 186 normal weight) completed the baseline assessment, which occurred between 10 and 16 weeks of pregnancy (13 weeks on average). At 30 weeks, 341 (94%; 160 overweight/obese and 181 normal weight) attended the assessment visit. Of these, 78.5% ($n = 285/363$; 132 overweight/obese and 153 normal weight) had pediatrician records at birth and 68.6% ($n = 249/363$; 121 overweight/obese and 128 normal weight) had pediatrician information at 6 months. There were no significant differences in retention or availability of pediatrician records in normal weight versus overweight/obese mothers at all time points. Comparing mothers of children with versus without pediatrician records at 6 months, those with pediatrician records were older (29.0 ± 5.1 versus 27.4 ± 5.5 years; $P = .008$), more likely to be non-Hispanic White (73.8% versus 53.0% $P = .0001$), and more likely to be married (74.6 versus 55.7%; $P = .001$); no significant differences were observed in prepregnancy BMI, education, income, weeks of gestation at delivery, or maternal GWG.

3.2. Maternal BMI and Offspring Weight Parameters. At birth, WFA z-scores were significantly higher for offspring of overweight/obese compared with normal weight mothers (0.42 ± 0.92 versus 0.21 ± 0.76, resp.; $P = .002$). Similarly, a greater proportion of offspring from overweight/obese mothers were classified as macrosomic (>4000 grams; 17.2% versus 4.8%, resp.; $P = 0.0001$) and at >90th percentile at birth (19.6% versus 7.1%; $P = .001$; Table 1). At 6 months, no significant differences in WFA z-scores were observed between offspring of normal weight and overweight/obese mothers. Between birth and 6 months, the percentage of children with WFA >90th percentile declined slightly in overweight/obese mothers (from 19.6% to 17.6%) but increased from 7% to 15% in the offspring of normal weight mothers (Table 1). Subsequent analyses separately examined predictors of offspring weight in normal weight versus overweight/obese mothers.

3.3. Prenatal Predictors of Offspring Weight

3.3.1. Overweight/Obese Mothers. In initial unadjusted analyses, several significant associations between overweight/obese mothers' prenatal behaviors and offspring WFA z-scores were observed (Table 2).

Multiple regression analyses were then conducted to determine the most robust set of predictors of offspring weight parameters after adjustment for treatment group, infant sex, recruitment clinic, weeks of gestation at delivery, and breastfeeding (in 6-month analyses). Examining predictors of birth weight, the strongest predictor of higher WFA z score was consumption of a greater percentage of calories from sweets early in pregnancy (beta = 0.19; $P = 0.004$; Table 3). Similarly, greater consumption of sweets early in pregnancy was significantly related to higher odds of macrosomia (OR = 1.1 (1.0, 1.2); $P = 0.004$) and WFA >90th percentile at

Table 1: Characteristics of study participants and offspring.

	Overweight/obese $N = 132$	Normal weight $N = 153$	P value
Age, years	28.8 ± 5.1	28.2 5.5	0.30
% primiparous	66.7%	85.5	0.0001
% non-Hispanic White	62.7%	71.5	0.09
% married	68.9%	68.3	0.91
% >high school education	84.7%	86.6	0.67
% income < $25,000/year	23.7	19.0	0.27
% community clinic	28.4%	25.1	0.54
Prepregnancy BMI, kg/m^2	30.5 ± 5.3	22.3 ± 1.8	.0001
% gain above 1990 IOM	63.8%	46.2	0.001
Infant at birth			
Weeks of gestation at birth	38.6 ± 2.5	38.7 1.9	0.14
% male	50.9%	52.4	0.83
WFA birth	0.42 ± 0.92	0.21 ± 0.76	0.02
% macrosomic (>4000 grams) at birth	17.2%	4.8	0.0001
% >90th percentile at birth	19.6%	7.1	0.001
% <10th percentile at birth	3.6%	2.2	0.53
Infant at 6 months			
WFA 6 mo	0.38 ± 1.1 $N = 121$	0.34 ± 1.0 $N = 128$	0.74
% >90th percentile at 6 months	17.6%	36.8	0.14
% <10th percentile at 6 months	7.6%	2.4	0.14
% mostly breastfeeding over first 6 months	28.2%	36.8	0.47

IOM: 1990 Institute of Medicine Guidelines;
WFA birth: weight for gestational age z-scores with Oken et al. [20] reference data;
WFA 6 mo: weight for age, sex-specific z-scores with 2000 Centers for Disease Control reference data.

birth (OR = 1.2 (1.1, 1.3); $P = 0.002$). Each 1% increase in percentage of calories consumed from sweets early in pregnancy increased the odds of macrosomia by 10% and WFA >90th percentile by 20%.

At 6 months, the strongest predictors of higher WFA z-scores were greater percentage of calories from sweets early in pregnancy (beta = 0.30; $t = 3.2$; $P = 0.002$) and also greater increases in percentage of calories from protein during pregnancy beta = 0.20; Table 3). Higher percentage of calories from protein early in pregnancy (OR = 0.38 (0.19, 0.78); $P = 0.04$) was also a significant predictor of reduced odds of WFA >90th percentile at 6 months.

We examined GWG as an independent predictor and potential mediator of effects of maternal prenatal behaviors on offspring weight outcomes (Table 3). Children of overweight/obese mothers who were exposed to excessive GWG ($n = 84$) had an approximate 4.0-fold increase in odds (CI (1.0, 15.1); $P = 0.04$) of being macrosomic and had higher WFA z-scores at birth (0.62 ± 0.84 versus 0.05 ± 0.95; $P = 0.002$) compared with children exposed to adequate GWG. Also, at 6 months, children exposed to excessive GWG had near significant ($P = .06$) higher odds of WFA z score >90th percentile compared with children exposed to adequate weight gain (OR = 6.2 (0.94, 41.1), but no significant association was seen on WFA z-scores (0.45 ± 0.14 versus 0.08 ± 0.18; $P = .11$). When analyzing maternal GWG as a continuous measure, similar results were observed. Total GWG was positively predictive of higher child WFA z score at birth (beta =.41; $t = 4.9$; $P = .0001$) and macrosomia at birth (OR = 1.2 (1.1, 1.3); $P = 0.001$). At 6 months, no significant effects were seen for GWG on odds of WFA >90th percentile ($P = .11$) or average z-scores ($P = .16$) at 6 months.

Examining GWG as a potential mediator, the effects of maternal prenatal behaviors on offspring weight outcomes were generally attenuated (i.e., P value increases between 0.01 and 0.06 across analyses) but not entirely removed when GWG was included in the models (Table 3).

3.4. Normal Weight Mothers. In initial, unadjusted analyses, few significant correlations were found between prenatal behaviors and WFA z-scores at birth and 6 months in the offspring of normal weight mothers. Only lower maternal fat intake (−0.22; $P = 0.01$) and trend for higher carbohydrate intake (0.16; $P = 0.06$) early in pregnancy were correlated with higher WFA z-scores at 6 months.

In final, multiple regression analyses that included adjustments for confounding variables, the strongest predictor of higher WFA z score at birth was greater consumption of soft drinks early in pregnancy (beta = 0.16; $P = 0.04$; Table 4).

Table 2: Significant, unadjusted correlations between prenatal variables and WFA *z*-scores in offspring of overweight/obese mothers.

Maternal variables	Offspring WFA *z* scores at birth	Offspring WFA *z*-scores at 6 months
Early in pregnancy		
% kcal from protein	ns	−0.31, $P = 0.001$
% kcal sweets	0.19, $P = 0.01$	0.36, $P = 0.0001$
Dietary restraint	ns	−0.22, $P = 0.02$
Disinhibition	0.17, $P = 0.03$	ns
Perceived stress	0.18, $P = 0.02$	0.18, $P = 0.05$
Fast food consumption	ns	0.21, $P = 0.03$
During pregnancy		
Increases in dietary restraint	−0.17, $P = 0.004$	ns
Increases in stress	ns	−0.21, $P = 0.03$
Increases in % kcal from carbohydrates	0.18, $P = 0.03$	ns
Increases in % kcal from fat	−0.22, $P = .007$	ns
Increases in % kcal from protein	ns	0.23, $P = .01$

Ns: non-significant, $P \geq .05$;
WFA: weight for age.

Table 3: Final regression models predicting weight for age *z*-scores in offspring of overweight/obese mothers at birth ($N = 132$) and 6 months ($N = 121$).

	B	CI for B	Beta	*P* value*	*P* value GWG**
Final model predicting weight for age *z*-scores at birth					
Prepregnancy BMI	0.005	−0.02, 0.03	0.03	0.73	0.03
Multiparity	0.20	−0.11, 0.50	0.10	0.21	0.13
% kcal from sweets early in preg	0.02	0.003, 0.04	0.19	0.004	0.06
Perceived stress early in preg	0.04	−0.02, 0.09	010	0.18	0.16
Final model predicting weight for age *z*-scores at 6 months					
Prepregnancy BMI	0.009	−0.03, 0.05	0.044	0.639	0.42
Non-Hispanic White (ref: others)	0.12	−0.49, 0.72	0.047	0.706	0.74
% kcal from sweets early in pregnancy Increases in % kcal from protein in preg	0.04	0.02, 0.06	0.296	0.002	0.006
Restraint early in pregnancy	−0.04	−0.09, 0.01	−0.144	0.140	0.12
Increases in perceived stress	0.06	−0.02, 0.13	0.146	0.124	0.19

GWG: gestational weight gain; preg: pregnancy;
BMI: body mass index.
*Adjusted for infant sex, treatment group, recruitment site, weeks of gestation at delivery; 6-month analyses also adjusted for breastfeeding.
**Adjusted for infant sex, treatment group, recruitment site, weeks of gestation at delivery, and total maternal gestational weight gain; 6-month analyses also adjusted for breastfeeding.
Overall omnibus test at birth: $F = 3.0$; $P = 0.004$ (with GWG: $F = 5.6$; $P = 0.0001$); at 6 months: $F = 4.1$; $P = .0001$ (with GWG: $F = 3.9$; $P = .0001$).

The omnibus tests of model coefficients predicting macrosomia and WFA >90th percentile at birth were insignificant and few cases of each were observed.

At 6 months, higher percentage of calories from fat early in pregnancy was a significant predictor of lower WFA z-scores (Table 4; beta = −0.35; $P = 0.001$) and reduced odds of WFA >90th percentile (OR = 0.81 (0.70, 0.94); $P = .007$). Similar, but in the inverse direction, results were observed in models where percentage of calories from carbohydrates (instead of fat) was included (B = 0.04 (0.01, 0.06); beta = 0.27; $P = .006$ for WFA *z* and OR = 1.1 (1.1, 1.3); $P = 0.005$ for WFA >90th percentile). Decreases in perceived stress during pregnancy were also independently related to higher odds of WFA >90th percentile (OR = 1.5 (1.1, 2.0); $P = .01$) but did not independently predict WFA *z*-scores at 6 months.

We also examined GWG as an independent predictor and potential mediator of effects of maternal prenatal behaviors on weight outcomes (Table 4). Children of normal weight mothers who were exposed to excessive GWG ($n = 71$) had higher WFA *z*-scores at birth (0.42 ± 0.75 versus 0.03 ± 0.73; $P = 0.002$) compared with children exposed to adequate GWG, but no significant effects were seen on odds of macrosomia or WFA *z* score >90th percentile. At 6 months, children of normal weight mothers exposed to excessive GWG had significantly ($P = 0.03$) higher odds of WFA *z* score >90th percentile compared with children

Table 4: Final regression models predicting weight for age z-scores in offspring of normal weight mothers at birth ($N = 153$) and 6 months ($N = 128$).

	B	CI for B	Beta	P value*	P value GWG**
Final model predicting weight for age z-scores at birth					
Prepregnancy BMI	0.02	−0.04, 0.09	0.06	0.43	0.69
Multiparity	0.33	0.02, 0.63	0.15	0.004	0.04
Non-Hispanic White (others: ref)	0.35	0.68, 0.009	0.21	0.05	0.07
Daily calories from soft drinks	0.002	0.0001, 0.004	0.16	0.04	0.10
Final model predicting weight for age z-scores at 6 months					
Prepregnancy BMI	0.04	−0.05, 0.13	0.08	0.34	0.31
Multiparity	0.62	0.01, 1.2	0.18	0.05	0.04
% kcal from fat early in preg	−0.06	−0.09, −0.03	−0.35	0.0001	0.001
% kcal from sweets early in preg	−0.02	−0.04, 0.003	−0.15	0.10	0.14

GWG: gestational weight gain; preg: pregnancy; BMI: body mass index.
*Adjusted for infant sex, treatment group, recruitment site, weeks of gestation at delivery; 6-month analyses also adjusted for breastfeeding.
**Adjusted for infant sex, treatment group, recruitment site, weeks of gestation at delivery, and total maternal gestational weight gain; 6-month analyses also adjusted for breastfeeding.
Overall omnibus test at birth: $F = 3.4$; $P = 0.001$ (with GWG: $F = 3.6$; $P = 0.0001$); at 6 months: $F = 3.6$; $P = .001$ (with GWG: $F = 3.3$; $P = 0.001$).

exposed to adequate weight gain (OR = 4.0 (1.2, 13.6)), but no significant association was seen on WFA z-scores at 6 months (0.27 ± 0.83 versus 0.39 ± 1.1; $P = .28$). When analyzing maternal GWG as a continuous measure, no significant effects were observed. Examining GWG as a potential mediator, the effects of maternal prenatal behaviors on offspring weight outcomes were generally attenuated (Table 4).

4. Discussion

This is one of the few studies to prospectively and simultaneously examine the impact of dietary, physical activity, and psychosocial parameters during pregnancy on the offspring weight status of overweight/obese and normal weight mothers. In obese mothers, we found that higher intake of sweets early in pregnancy was related to higher offspring weight status at birth and 6 months. In normal weight mothers, higher intake of soft drinks was the strongest predictor of higher offspring weight status at birth but was not a significant predictor of weight at 6 months. No prior studies have specifically examined impacts of maternal intake of sweets or soft drinks in pregnancy on offspring weight parameters. Our findings are consistent with some studies in nonpregnant adults and children showing a connection between higher intake of sweets and soft drinks and increased weight status [32], but conflicting results have been reported in association with GWG [33]. Overall, the current study extends existing work by suggesting that exposure to foods or drinks high in sugar content early in gestation may predispose offspring to higher weight status early in infancy, independent of maternal GWG.

In obese mothers, lower protein intake early in pregnancy and increased protein intakes over the course of the pregnancy were independently related to higher offspring weight at 6 months. Studies of protein intake in pregnancy have indicated that higher maternal protein intake was positively associated with birth weight [8, 9], but there are notable exceptions [34, 35] and most studies assessed diet later in gestation. By contrast, in normal weight mothers, lower fat intake (and higher carbohydrate intake) early in pregnancy was a significant predictor of higher offspring weight at 6 months. Inverse associations between fat intake early in pregnancy and offspring weight have been reported previously [36], but not consistently [37]. Nutritional effects on the fetus and mother may vary with prepregnancy body weight, trimester of exposure during pregnancy, and overall balance of macronutrients [8, 38]. Although a recent pilot randomized trial [39] found no significant impact of a low glycemic index diet on the offspring weight of overweight/obese mothers, future, larger randomized trials and research with more frequent assessments of diet in pregnancy are needed to untangle the relationship between weight status, time in pregnancy of nutrient exposures, and offspring weight outcomes.

Surprisingly, physical activity and television viewing were not significantly related to offspring weight outcomes in normal weight or overweight/obese mothers. Low levels of physical activity and sedentary lifestyle are known contributing factors to obesity and weight gain in the general population [40]. Also, increasing physical activity during pregnancy has been related to lower GWG in some [41] but not all [42] observational studies. Few clinical trial intervention studies have specifically measured changes in physical activity during pregnancy, but available evidence suggests little to no effect on maternal GWG [16, 43]. Other research has found that a reduction in physical activity by bed rest was associated with an increase in infant birth weight [44]. Overall, findings from the current study support a stronger role for maternal intake than expenditure in predicting offspring weight outcomes, but additional studies with objective measures of physical activity (e.g., accelerometry) are clearly needed.

Also, few maternal psychosocial predictors of offspring weight status were observed within both overweight/obese

and normal weight mothers. Increases in stress were related to lower offspring weight status in normal weight mothers (adjusted analyses) and overweight/obese mothers (unadjusted analyses), which is consistent with earlier research on stress in relation to inadequate GWG [45] and long-term offspring health [46]. Overall, however, the current study's findings suggest that dietary variables may exert more of an effect than maternal psychosocial variables on offspring weight outcomes.

Infants of overweight/obese mothers had higher WFA *z*-scores at birth than nonexposed counterparts, but the postnatal weight trajectories were different. The offspring of overweight mothers were larger at birth but, by 6-months, did not significantly differ from those of normal weight mothers. In fact the percentage of infants of normal weight mothers with WFA *z*-scores >90th percentile doubled between birth and 6-months. We found no significant prenatal predictors of change in WFA *z*-scores between birth and 6 months. Birth weight is an independent predictor of the development of obesity; however, increases in weight during the first 3–6 months of life are also influential on long-term increased risk of obesity [47, 48]. Future research is needed to determine whether differences in postnatal feeding behaviors might explain differential growth rates in offspring of normal weight and overweight/obese mothers.

Excessive GWG was related to offspring weight but more strongly at birth than at 6 months and was not significantly related to changes in WFA *z*-scores. The association between GWG and offspring overweight may decrease as children grow older [49, 50]. Similarly, maternal prenatal behaviors may differentially impact birth and 6 months offspring weights (e.g., protein impacting 6 month but not birth weight in the current study). Interestingly, adjustment for GWG attenuated but generally did not completely remove the impact of dietary variables on offspring weight, particularly at 6 months. This suggests that dietary exposures may impact offspring weight status above and beyond the potential influence of excessive GWG. Future research with more frequent assessments of offspring weight and, potentially, analysis of growth velocities [51] might better inform how and when nutrient exposures in pregnancy impact growth.

This study is one of the first to prospectively examine impacts of prenatal diet, physical activity, and psychosocial exposures on offspring weight outcomes in a diverse sample. The study was able to adjust for several important confounds, including length of gestation and infant sex; however, the sample size was moderate, and only 69% of the offspring (mostly non-Hispanic White) had data available at 6 months. The sample was diverse but self-selected and free of diseases that might contraindicate participation in a lifestyle intervention study; thus, findings may not generalize to the population at large. A self-report, food frequency questionnaire was used, which is useful in ranking nutrient intakes of individual subjects but can be subject to bias, particularly in obese individuals [52]. The study lacked a valid measurement of infant height. Although prepregnancy weight was self-reported, our research has found that women in this study were quite accurate in recalling prepregnancy weight [16]. This study's focus was on predictors of large for gestational age at birth and 6 months, but future research is needed to examine predictors of small for gestational age, which may also predispose offspring to increased fat mass and incidence of metabolic syndrome as children and adults [53]. Also, excessive GWG was classified based on the 1990 IOM GWG guidelines; our data were collected before the newly revised 2009 IOM GWG guidelines were released. Nonetheless, analyses using the 2009 criteria confirmed the current study's findings (data not shown).

5. Conclusions

Findings from the current study indicate that excessive GWG and mothers' eating behaviors during pregnancy, especially intake of sweets in overweight/obese mothers, may influence offspring weight status early in infancy. More research with larger sample sizes and frequent assessments of diet is needed to inform the impact of timing of nutrient exposures on offspring weight status. Also, future adequately powered randomized clinical trials are needed to determine whether modifying maternal prenatal behaviors and GWG can prevent offspring obesity. Identifying modifiable, prenatal causes of childhood obesity will inform future interventions targeting pregnancy as a "teachable moment" for primary and secondary obesity prevention.

Acknowledgments

This research was supported by National Institutes of Health grant DK071667; the NIH was not involved in the design and conduct of the study, collection, management, analysis, and interpretation of the data, or preparation, review, or approval of the paper.

References

[1] R. C. Whitaker, "Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy," *Pediatrics*, vol. 114, no. 1, pp. e29–36, 2004.

[2] C. Li, M. I. Goran, H. Kaur, N. Nollen, and J. S. Ahluwalia, "Developmental trajectories of overweight during childhood: role of early life factors," *Obesity*, vol. 15, no. 3, pp. 760–771, 2007.

[3] E. Oken, "Maternal and child obesity: the causal link," *Obstetrics and Gynecology Clinics of North America*, vol. 36, no. 2, pp. 361–377, 2009.

[4] A. M. Stuebe, M. R. Forman, and K. B. Michels, "Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter," *International Journal of Obesity*, vol. 33, no. 7, pp. 743–752, 2009.

[5] C. le Clair, T. Abbi, H. Sandhu, and P. S. Tappia, "Impact of maternal undernutrition on diabetes and cardiovascular disease risk in adult offspring," *Canadian Journal of Physiology and Pharmacology*, vol. 87, no. 3, pp. 161–179, 2009.

[6] S. Y. Chu, W. M. Callaghan, C. L. Bish, and D. d'Angelo, "Gestational weight gain by body mass index among US women delivering live births, 2004-2005: fueling future obesity," *American Journal of Obstetrics and Gynecology*, vol. 200, no. 3, pp. 271.e1–271.e7, 2009.

[7] E. Petridou, M. Stoikidou, M. Diamantopoulou, E. Mera, N. Dessypris, and D. Trichopoulos, "Diet during pregnancy in relation to birthweight in healthy singletons," *Child Care Health and Development*, vol. 24, no. 3, pp. 229–242, 1998.

[8] V. M. Moore and M. J. Davies, "Diet during pregnancy, neonatal outcomes and later health," *Reproduction, Fertility and Development*, vol. 17, no. 3, pp. 341–348, 2005.

[9] M. S. Kramer, "Balanced protein/energy supplementation in pregnancy," *Cochrane Database of Systematic Reviews*, no. 2, p. CD000032, 2000.

[10] I. Y. Khan, V. Dekou, G. Douglas et al., "A high-fat diet during rat pregnancy or suckling induces cardiovascular dysfunction in adult offspring," *American Journal of Physiology*, vol. 288, no. 1, pp. R127–R133, 2005.

[11] M. Daenzer, S. Ortmann, S. Klaus, and C. C. Metges, "Prenatal high protein exposure decreases energy expenditure and increases adiposity in young rats," *Journal of Nutrition*, vol. 132, no. 2, pp. 142–144, 2002.

[12] S. A. Bayol, S. J. Farrington, and N. C. Stickland, "A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring," *British Journal of Nutrition*, vol. 98, no. 4, pp. 843–851, 2007.

[13] R. R. Lau, M. J. Quadrel, and K. A. Hartman, "Development and change of young adults' preventive health beliefs and behavior: influence from parents and peers," *Journal of Health and Social Behavior*, vol. 31, no. 3, pp. 240–259, 1990.

[14] T. M. Cutting, J. O. Fisher, K. Grimm-Thomas, and L. L. Birch, "Like mother, like daughter: familial patterns of overweight are mediated by mothers' dietary disinhibition," *American Journal of Clinical Nutrition*, vol. 69, no. 4, pp. 608–613, 1999.

[15] S. L. Johnson and L. L. Birch, "Parents' and children's adiposity and eating style," *Pediatrics*, vol. 94, no. 5, pp. 653–661, 1994.

[16] S. Phelan, M. G. Phipps, B. Abrams, F. Darroch, A. Schaffner, and R. R. Wing, "Randomized trial of a behavioral intervention to prevent excessive gestational weight gain: the Fit for delivery study," *American Journal of Clinical Nutrition*, vol. 93, no. 4, pp. 772–779, 2011.

[17] Institute of Medicine (U.S.). Subcommittee on Nutritional Status and Weight Gain during Pregnancy., Institute of Medicine (U.S.). Subcommittee on Dietary Intake and Nutrient Supplements during Pregnancy, *Nutrition During Pregnancy : Part I, Weight Gain : Part II, Nutrient Supplements*, National Academy Press, Washington, DC, USA, 1990.

[18] D. J. Pettitt, K. A. Aleck, H. R. Baird, M. J. Carraher, P. H. Bennett, and W. C. Knowler, "Congenital susceptibility to NIDDM. Role of intrauterine environment," *Diabetes*, vol. 37, no. 5, pp. 622–628, 1988.

[19] P. Brawarsky, N. E. Stotland, R. A. Jackson et al., "Pre-pregnancy and pregnancy-related factors and the risk of excessive or inadequate gestational weight gain," *International Journal of Gynecology and Obstetrics*, vol. 91, no. 2, pp. 125–131, 2005.

[20] E. Oken, K. P. Kleinman, J. Rich-Edwards, and M. W. Gillman, "A nearly continuous measure of birth weight for gestational age using a United States national reference," *BMC Pediatrics*, vol. 3, no. 6, 2003.

[21] S. L. Boulet, G. R. Alexander, H. M. Salihu, and M. Pass, "Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk," *American Journal of Obstetrics and Gynecology*, vol. 188, no. 5, pp. 1372–1378, 2003.

[22] C. L. Ogden, R. J. Kuczmarski, K. M. Flegal et al., "Centers for disease control and prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version," *Pediatrics*, vol. 109, no. 1, pp. 45–60, 2002.

[23] G. Block, A. M. Hartman, and D. Naughton, "A reduced dietary questionnaire: development and validation," *Epidemiology*, vol. 1, no. 1, pp. 58–64, 1990.

[24] *WIC Dietary Assessment Validation Study. Final Report*, Freeman, San Francisco, Calif, USA, 1994.

[25] S. Phelan, H. Wyatt, S. Nassery et al., "Three-year weight change in successful weight losers who lost weight on a low-carbohydrate diet," *Obesity*, vol. 15, no. 10, pp. 2470–2477, 2007.

[26] S. N. Blair, P. H. Haskell, R. S. Paffenbarger, K. M. Vranizan, J. W. Farquhar, and P. D. Wood, "Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments," *American Journal of Epidemiology*, vol. 122, no. 5, pp. 794–804, 1985.

[27] J. L. Cox, J. M. Holden, and R. Sagovsky, "Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale," *British Journal of Psychiatry*, vol. 150, pp. 782–786, 1987.

[28] A. J. Stunkard and S. Messick, "The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger," *Journal of Psychosomatic Research*, vol. 29, no. 1, pp. 71–83, 1985.

[29] S. Cohen, T. Kamarck, and R. Mermelstein, "A global measure of perceived stress," *Journal of Health and Social Behavior*, vol. 24, no. 4, pp. 385–396, 1983.

[30] K. A. Lee and J. F. de Joseph, "Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women," *Birth*, vol. 19, no. 4, pp. 208–213, 1992.

[31] T. Rankinen, A. Zuberi, Y. C. Chagnon et al., "The human obesity gene map: the 2005 update," *Obesity*, vol. 14, no. 4, pp. 529–644, 2006.

[32] K. Nissinen, V. Mikkila, S. Mannisto et al., "Sweets and sugar-sweetened soft drink intake in childhood in relation to adult BMI and overweight. The cardiovascular risk in young finns study," *Public Health Nutrition*, vol. 12, no. 11, pp. 2018–2026, 2009.

[33] A. M. Stuebe, E. Oken, and M. W. Gillman, "Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain," *American Journal of Obstetrics and Gynecology*, vol. 201, no. 1, pp. 58.e1–58.e8, 2009.

[34] F. Mathews, P. Yudkin, and A. Neil, "Influence of maternal nutrition on outcome of pregnancy: prospective cohort study," *British Medical Journal*, vol. 319, no. 7206, pp. 339–343, 1999.

[35] D. Rush, Z. Stein, and M. Susser, "Diet in pregnancy: a randomized controlled trial of nutritional supplements," *Birth Defects*, vol. 16, no. 3, pp. 1–197, 1980.

[36] K. Godfrey, S. Robinson, D. J. Barker, C. Osmond, and V. Cox, "Maternal nutrition in early and late pregnancy in relation to placental and fetal growth," *British Medical Journal*, vol. 312, no. 7028, pp. 410–414, 1996.

[37] M. M. Weigel, W. M. Narvaez, A. Lopez, C. Felix, and P. Lopez, "Prenatal diet, nutrient intake and pregnancy outcome in urban Ecuadorian primiparas," *Archivos Latinoamericanos de Nutricion*, vol. 41, no. 1, pp. 21–37, 1991.

[38] J. Langhoff-Roos, G. Lindmark, and M. Gebre-Medhin, "Maternal fat stores and fat accretion during pregnancy in relation to infant birthweight," *British Journal of Obstetrics and Gynaecology*, vol. 94, no. 12, pp. 1170–1177, 1987.

[39] E. T. Rhodes, D. B. Pawlak, T. C. Takoudes et al., "Effects of a low-glycemic load diet in overweight and obese pregnant women: a pilot randomized controlled trial," *American Journal of Clinical Nutrition*, vol. 92, no. 6, pp. 1306–1315, 2010.

[40] J. O. Hill and E. L. Melanson, "Overview of the determinants of overweight and obesity: current evidence and research issues," *Medicine and Science in Sports and Exercise*, vol. 31, no. 11, pp. S515–S521, 1999.

[41] C. M. Olson and M. S. Strawderman, "Modifiable behavioral factors in a biopsychosocial model predict inadequate and excessive gestational weight gain," *Journal of the American Dietetic Association*, vol. 103, no. 1, pp. 48–54, 2003.

[42] J. Langhoff-Roos, G. Lindmark, E. Kylberg, and M. Gebre-Medhin, "Energy intake and physical activity during pregnancy in relation to maternal fat accretion and infant birthweight," *British Journal of Obstetrics and Gynaecology*, vol. 94, no. 12, pp. 1178–1185, 1987.

[43] B. A. Polley, R. R. Wing, and C. J. Sims, "Randomized controlled trial to prevent excessive weight gain in pregnant women," *International Journal of Obesity*, vol. 26, no. 11, pp. 1494–1502, 2002.

[44] A. Briend, "Maternal physical activity, birth weight and perinatal mortality," *Medical Hypotheses*, vol. 6, no. 11, pp. 1157–1170, 1980.

[45] J. B. Webb, A. M. Siega-Riz, and N. Dole, "Psychosocial determinants of adequacy of gestational weight gain," *Obesity*, vol. 17, no. 2, pp. 300–309, 2009.

[46] F. Lussana, R. C. Painter, M. C. Ocke, H. R. Buller, P. M. Bossuyt, and T. J. Roseboom, "Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile," *American Journal of Clinical Nutrition*, vol. 88, no. 6, pp. 1648–1652, 2008.

[47] E. M. Taveras, S. L. Rifas-Shiman, M. B. Belfort, K. P. Kleinman, E. Oken, and M. W. Gillman, "Weight status in the first 6 months of life and obesity at 3 years of age," *Pediatrics*, vol. 123, no. 4, pp. 1177–1183, 2009.

[48] S. Chomtho, J. C. Wells, J. E. Williams, P. S. Davies, A. Lucas, and M. S. Fewtrell, "Infant growth and later body composition: evidence from the 4-component model," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1776–1784, 2008.

[49] B. H. Wrotniak, J. Shults, S. Butts, and N. Stettler, "Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1818–1824, 2008.

[50] E. Oken, E. M. Taveras, K. P. Kleinman, J. W. Rich-Edwards, and M. W. Gillman, "Gestational weight gain and child adiposity at age 3 years," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 4, pp. 322.e1–322.e8, 2007.

[51] J. Botton, B. Heude, J. Maccario et al., "Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1760–1768, 2008.

[52] L. Lissner, "Measuring food intake in studies of obesity," *Public Health Nutrition*, vol. 5, no. 6, pp. 889–892, 2002.

[53] L. Ibáñez, K. Ong, D. B. Dunger, and F. de Zegher, "Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 6, pp. 2153–2158, 2006.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 596060, 19 pages
doi:10.1155/2011/596060

Review Article

Intergenerational Cycle of Obesity and Diabetes: How Can We Reduce the Burdens of These Conditions on the Health of Future Generations?

Marie-Claude Battista, Marie-France Hivert, Karine Duval, and Jean-Patrice Baillargeon

Division of Endocrinology, Department of Medicine, University of Sherbrooke, Sherbrooke, QC, Canada J1H 5N4

Correspondence should be addressed to Jean-Patrice Baillargeon, jp.baillargeon@usherbrooke.ca

Received 16 June 2011; Revised 5 September 2011; Accepted 6 September 2011

Academic Editor: Barbara Alexander

Prepregnancy overweight or obesity and excessive gestational weight gain have been associated with increased risk of maternal and neonatal complications. Moreover, offspring from obese women are more likely to develop obesity, diabetes mellitus, and car diovascular diseases in their lifetime. Gestational diabetes mellitus (GDM) is one of the most common complications associated with obesity and appears to have a direct impact on the future metabolic health of the child. Fetal programming of metabolic function induced by obesity and GDM may have intergenerational effect and thus perpetuate the epidemic of cardiometabolic conditions. The present paper thus aims at discussing the impact of maternal obesity and GDM on the developmental programming of obesity and metabolic disorders in the offspring. The main interventions designed to reduce maternal obesity and GDM and their ability to break the vicious circle that perpetuates the transmission of obesity and metabolic conditions to the next generations are also addressed.

1. Introduction

Obesity is a major public health problem that was identified as an epidemic by the World Health Organization [1]. The US Centers for Disease Control and Prevention estimates that 34% of adults 20 years of age and over are obese (body mass index (BMI) above 30 kg/m^2), in addition to another 34% who are classified as overweight (BMI 25–30 kg/m^2) for a total of over two-thirds of Americans with inappropriately high body weight. Women are thus more likely to enter pregnancy overweight or obese nowadays. In fact, among a sample of 75.000 delivering women recruited all over USA, 20% were obese [2]. Moreover, offspring from obese women is more likely to develop obesity, diabetes mellitus, and cardio vascular diseases in their lifetime, often at a younger age [3]. This paper will thus focus on maternal obesity and gestational diabetes mellitus (GDM) as determinants for the developmental programming of obesity and metabolic disorders in the offspring. We are also presenting the main interventions tested to reduce those two important maternal burdens and how they can break the vicious circle that perpetuates the transmission of obesity and metabolic conditions to the next generations.

2. Gestational Weight and Metabolic Complications

2.1. Appropriate Gestational Weight Gain. Due in part to con cerns about the increasing prevalence of obesity in reproduc tive-age women, the Institute of Medicine (IOM; which is a nonprofit American organization serving as adviser to the nation to improve health http://www.iom.edu/About-IOM .aspx) recently released new guidelines (Table 1) for gestational weight gain to better reflect the growing body of evidence in favour of lowering weight gain recommendations for overweight and obese pregnant women [4]. In comparison to the previous 1990 guidelines, 1 out of 6 women were differently classified using the new 2009 guidelines, that is, fewer pregnant women were classified as underweight,

Table 1: Recommendation given by the Institute of Medicine in 2009 for appropriate gestational weight gain based on preconception body mass index (BMI).

Preconception BMI (kg/m^2)	Total weight gain during pregnancy	Weight gain during 2nd and 3rd trimesters (per week)
<18.5	28–40 lbs/13–18 kg	1.0–1.3 lbs/0.5-0.6 kg
18.5–24.9	25–35 lbs/11–16 kg	0.8–1.0 lbs/0.4-0.5 kg
25.0–29.9	15–25 lbs/7–11 kg	0.5–0.7 lbs/0.2-0.3 kg
≥30.0	11–20 lbs/5–9 kg	0.4–0.6 lbs/0.2-0.3 kg

Adapted from [4].

normal weight, or obese, and more as overweight [5]. Moreover, 17.1% of appropriate gainers based on 1990 recommendations would now be classified as overgainers [5]. As some people were worried by these severe guidelines, Einerson et al. showed, in a retrospective study, that the new recommended weight gain thresholds were safe for both the mothers and the developing child [6]. In fact, those new weight gain thresholds were clinically effective in reducing caesarean and pregnancy-induced hypertension, and no increase in the proportion of low-birth weight infants was recorded in 691 participants as compared to the proportion observed in obese women with appropriate weight gain based on 1990 recommendations [6].

However, according to these new guidelines, Weisman et al. reported from a population-based cohort study that 40% of normal weight women exceeded the IOM recommendations, while excess weight gain was observable in 63% and 62% of overweight and obese women, respectively, [7]. The same group also showed that prepregnancy overweight women were 3 times more likely to exceed the recommended weight gain than normal-weight women [7]. In a recent observational study including 144 30-week pregnant women, 33% of participants reported an excessive gestational weight gain [8]. Factors associated with excess weight gain included prepregnancy overweight as well as low physical activity and high-food intake during pregnancy, as reported by the participants. On the other hand, some factors seem to be associated with lower risk of excess weight gain such as menarche occurring at an older age and increased hours of sleep [8]. In summary, these results suggest that pregnant women frequently exceed the recommended gestational weight gain, but it may be feasible to optimize weight loss by promoting physical activity and healthy eating among women of reproductive age.

2.2. Obesity-Associated Obstetrical and Neonatal Complications. Prepregnancy overweight or obesity and excessive pregnancy weight gain both have been independently associated with increased risk of complications. Indeed, several studies demonstrated the association between increased maternal BMI and higher risks of obstetric and neonatal complications [9]. Obese women are at increased risk of complications over the whole spectrum of peripregnancy period: antepartum, intrapartum, intraoperative, postoperative, and postpartum (for review, see [10, 11]). Briefly, at the maternal level, obesity increases the risk of menstrual disorders [12], infertility [13], miscarriage [14], pregnancy-induced hypertension and preeclampsia [15], GDM [16], induction of labour and caesarean section [17], and haemorrhage, infection, and venous thromboembolism. At the level of the newborn, maternal obesity is also associated with many complications: macrosomia (defined as a birth weight >4.000 g), shoulder dystocia [18], fetal distress, and perinatal morbidity/mortality (for review, see [10]). Still birth [19] and birth defects such as hydrocephaly, omphalocele, heart, and neural tube defects [20, 21] are among the disastrous neonatal outcomes that have been associated to maternal obesity (identified as the top modifiable risk factor). In a large population-based retrospective cohort study [22] including singleton macrosomic live births infants, it was demonstrated that the overall risk of obstetrical complications was increased almost 3-fold in obese (BMI $\geq$ 30 kg/m^2) as compared to nonobese mothers (BMI < 30 kg/m^2) (17% versus 6%). Macrosomic neonates born from obese mothers were at increased risk of birth injury, hyaline membrane disease, meconium aspiration syndrome, and more required assisted ventilation. Project Viva study [23] analysed data from 2.012 recruited mother-child pairs in order to determine the level of gestational weight gain which was associated with the lowest predicted prevalence of adverse obstetrical and neonatal outcomes. They showed that the mean total gestational weight gain was 15.6 kg. The lowest predicted outcome prevalence occurred with a weight gain of 11.2 kg for women with prepregnancy BMI in the normal range, with a weight loss of 1.2 kg for overweight women, and with a weight loss of 7.6 kg for obese participants.

Weight gain between each pregnancy (or not returning to prepregnancy body weight) is also associated with increased adverse health issues. Indeed, a large population-based Swedish cohort study including women who had 2 consecutive live-birth pregnancies robustly showed that in comparison to women whose prepregnancy BMI did not change much between both pregnancies (−1 to 0.9 BMI points), mothers who gained more than 3 units of BMI between pregnancies increased by 30% to 110% their adjusted estimated risks of important complications (odds ratio of 1.78 for preeclampsia, 1.76 for gestational hypertension, 2.09 for GDM, 1.32 for caesarean delivery, 1.63 for stillbirth, and 1.87 for large-for-gestational-age birth). These risks were associated with the amount of weight change between pregnancies, and this association was also noted in women who had a healthy prepregnancy BMI for both pregnancies [24]. This example underscores the point that women do not necessarily need to be in transition from a normal BMI to overweight or obese-BMI, but those relatively small increases in BMI were associated with adverse outcomes. Collectively, these data emphasize the importance of adequate gestational weight gain in pregnant obese women, as recently recommended by the Institute of Medicine, in order to avoid maternal and neonatal complications.

3. Gestational Diabetes Mellitus (GDM)

3.1. Definition and Diagnosis. According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [25], GDM is defined as an impaired glucose tolerance that is first recognized during pregnancy, and it occurs in approximately 7% of pregnancies in the USA. Based on a meta-analysis, GDM incidence varies from 1.3% to 19.9% depending on screening and diagnostic guidelines that are followed and the study populations [26]. In 2010, new recommendations brought up by the IADPSG were approved to diagnose GDM [27]. This guideline suggests to screen with a 75 g oral glucose tolerance test (OGTT) without prior glucose challenge and to diagnose GDM if the fasting plasma glucose is $\geq$5.1 mmol/L and/or the 1-hour postload plasma glucose is $\geq$10.0 mmol/L and/or the 2-hour postload plasma glucose is $\geq$8.5 mmol/L.

3.2. Pathophysiology of Gestational Diabetes. Normal pregnancy is characterized by an insulin-resistant state in order to fulfill the increasing metabolic demand ordered by the developing foetus. The physiologic result of insulin resistance is thus an increase in insulin secretion by the pancreatic β-cells in order to compensate for reduced insulin action. However, women who fail to do so will progressively develop GDM [28]. In GDM, insulin resistance and the relative insulin deficiency due to pancreatic β-cell dysfunction are the primary metabolic changes. As gluconeogenesis increases, as a result of hepatic insulin resistance, and relative insulin deficiency is exacerbated, hyperglycemia becomes more severe. However, many questions still remain in order to adequately understand the mechanisms by which GDM takes place. It is not in the scope of this paper to discuss the pathophysiology of GDM, but mechanisms presently under investigation include the role of genetic factors, glucose transport activity, adipokines defects, and adipose tissue dysregulation (for review, see [29]).

3.3. Relationship between Gestational Diabetes and Maternal Obesity. Importantly, overweight and obese women are more insulin resistant than their lean counterparts and also more prone to β-cell dysfunction [30], which is mainly due to adipose tissue dysregulation and largely influenced by ethnicity and age [31]. For these reasons, obesity is an important determinant of the long-term risk of developing type 2 diabetes in genetically predisposed individuals. Consequently, overweight or obese women begin their pregnancy with insulin resistance and increased predisposition for β-cell dysfunction, which could result in GDM with the pregnancy-related progression of insulin resistance. An excess of weight gain during pregnancy would further worsen these phenomena and increase the risk of GDM as well, even in women with normal prepregnancy weight.

GDM is thus one of the most common obstetrical complications associated with obesity. The Project Viva study explored the relationship of trimester-specific rate of weight gain with impaired glucose tolerance during pregnancy [32]. In this study, the authors showed that the median rate of weight gain during early pregnancy (less than 13 weeks) was of 0.22 kg/week, while it was of 0.50 kg/week during midpregnancy. Accordingly, they showed that women who gained more than 0.22 kg/week during early pregnancy increased by 40% their odds of developing impaired glucose tolerance even if they gained more than 0.50 kg/week during midpregnancy. Moreover, women who were high gainers during early and midpregnancy doubled their odds for impaired glucose tolerance diagnosed during 2nd trimester [32]. By analyzing data from 7 states using the Pregnancy Risk Assessment Monitoring System (PRAMS), Kim et al. showed that the proportion of GDM that was attributable to overweight, obesity and extreme obesity was, respectively, of 15.4%, 9.7%, and 21.1% [33]. The overall population-attributable fraction for overweight/obesity, after subtracting women with normal weight, was 46.2%. However, it was recently shown in 36.597 Canadian women, that the increased incidence of glucose disorders during pregnancy was not explained by higher maternal prepregnancy adiposity [34]. These contradictory results between studies may be explained by different population ethnic background and patterns of gestational weight gain, which are important factors to consider in the interpretation of studies on GDM.

3.4. Gestational Diabetes-Associated Neonatal Complications. Excessive fetal growth is probably the most frequent and important outcome of GDM. It was long known that the nutritional status of the mother and accordingly her glycemic control may directly be in relation with her infant growth. This concept was based on studies reporting that macrosomia occurs as a result of fetal insulin hypersecretion in response to the mother rise of glycemia [35]. On the other hand, it was shown in pregnant rats that maternal hypoglycemia generates intrauterine growth restriction of the offspring, which was accompanied by fetal hypoglycemia and hypoinsulinemia [36]. Accordingly, while the mother glucose can diffuse through the placental barrier [37], maternal insulin cannot [38]. So, in situation of mother hyperglycemia, the foetus is consequently exposed to important quantities of glucose. In order to regulate its own glucose homeostasis, the foetus increases its insulin secretion, which is an important growth factor in the developing foetus. The foetus is thus more exposed to insulin leading to excessive growth and later programming of metabolic functions [39]. Additionally to macrosomia, many of the perinatal complications that have been associated with obesity are also known to be associated with GDM [40]. These include increased risks for preeclampsia, caesarean, stillbirth, spontaneous abortion and congenital malformations.

The question thus arising is whether the increased risk of adverse perinatal outcome in obese women is related to obesity *per se* or the increased risk of developing GDM. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study attempted to address such question. This trial enrolled more than 23.000 mothers and baby pairs. This study showed a strong linear association between fasting and post-challenge glucose and the incidence of macrosomia and neonatal adiposity [41]. They also clearly showed that the impact

of hyperglycaemia on the foetus was present at a much lower glucose concentration than previously thought [42]. This study thus suggests that complications may arise even with gestational glucose levels below the thresholds of GDM. Furthermore, a retrospective study of 413 women with GDM or impaired glucose tolerance found that fetal macrosomia was not associated with maternal glucose values, except fasting glucose levels between 32 and 35 weeks of pregnancy, while maternal obesity was a strong risk factor for macrosomia throughout these pregnancies [43]. On the other hand, a recent study suggested that pre-GDM was a stronger predictor of increase in birth defect prevalence than maternal obesity in their study population [44]. So the question of whether adverse perinatal outcomes in obese pregnant women are due to GDM (clinical or subclinical) is still unanswered and remains an open field for research.

4. Fetal Programming of Adult Diseases

In addition to the previously cited neonatal complication induced by maternal obesity and GDM, offspring born from these women are more likely to develop health problems later in life. In fact, in the early 1990, David Barker published a paper in the British Medical Journal entitled "*The fetal and infants origin of adult disease. The womb may be more important than the home*" [45]. This concept of fetal programming or developmental plasticity states that an insult or stress, occurring during period of maximal growth and development of an organ, overcome normal physiological processes. In such situation, the organ needs to adapt to its new environment, which then conducts to adaptation/reprogramming of functions of this organ [46]. In his 1990 paper, Barker was visionary as he stated that "research should be redirected towards the intrauterine environment rather than the environment in later childhood-housing, family income, diet, and other influences" [45].

Of the first studies that were conducted to support the concept of fetal programming, maternal nutrition, either deficient or excessive, during pregnancy was pinpoint to have various and often deleterious effects on the offspring. Of the most critical and cited examples are the Dutch Famine and some studies conducted in Pima Indians. During World War II, food supply and calories intake were dramatically restricted in the Netherlands. This dark period was called the Dutch Hunger Winter. Consequently, foetuses that were exposed to this famine during mid- to late pregnancies had small placentas, were born small-for-gestational age when compared to those foetuses exposed in the early phase of pregnancy. As these foetuses became adults, the proportion of individuals suffering from glucose intolerance and insulin resistance was greater among those whose fetal insult occurred during mid- to late pregnancy. However, atherogenic lipid profile, increased BMI and raised cardiovascular risk were greater among those who were exposed during early pregnancy [47].

Pima Indians are a recognized population for increased prevalence of obesity and type 2 diabetes particularly since their nutritional income was greatly modified by a typical Westernized diet in the past few decades [48]. In comparison to infants born from mothers who developed diabetes after pregnancy, those born from women who had diabetes before pregnancy were more prone to obesity, had higher blood glucose and glycated haemoglobin levels, lower C-HDL concentration and were more likely to develop diabetes during their childhood [49, 50]. These results suggests that the period when the fetal insult occur is very determinant in the reprogramming of functions and that either a poor or a too rich maternal nutrition can lead to a U-shaped association for risk of future adult diseases, with both low and high birth weight being associated with risk of adverse health consequences.

5. Long-Term Health Effect of Gestational Obesity on the Offspring

5.1. Clinical Studies. Major factors associated with fetal adiposity are maternal prepregnancy BMI and weight gain dur ing pregnancy [51]. Many studies have reported that mother prepregnancy BMI and gestational weight gain were positively associated with offspring BMI at birth as well as during infancy, childhood and early adulthood [52–56]. A recent retrospective study of 8.400 children in the US found that children born from obese mothers were twice as likely to be obese at 24 months of age [57]. It was shown that at time of birth, infants born from obese women had increased adiposity, homeostasis model assessment of insulin resistance (HOMA-IR, a fasting index estimating insulin resistance), cord blood leptin and interleukin-6 (IL-6) concentra tions. Moreover, fetal adiposity and mother prepregnancy BMI were both highly correlated with fetal HOMA-IR [58].

In a recent prospective cohort of 146.894 offspring from 136.050 families, Lawlor and colleagues explored whether and how maternal weight gain is associated with increased offspring BMI at 18 years old. They showed that maternal weight was positively associated to young adult adiposity. They also provided evidences that offspring adiposity later in life was mostly explained by familial characteristics in those born to normal weight mothers, but mainly influenced by intrauterine mechanisms in overweight and obese mothers [59]. Moreover, as caesarean is one important adverse outcome associated with maternal obesity, it was shown that offspring born by caesarean were more likely to suffer from obesity at age 23–25 years in comparison to those born vaginally, even after appropriate adjustments (15% versus 10%) [60]. In the longitudinal 1986 Northern Finland Birth Cohort study including 4.168 participants, Pirkola et al. found that infants born from overweight and GDM mothers had a 40% and 26% higher prevalence for being either overweight or having abdominal obesity at the age of 16 years. This risk was also present in the subgroup of infants born to overweight mothers who were free of GDM during pregnancy [61]. This significant impact of maternal obesity on child obesity at a later age, independent of maternal glycemic status, was confirmed in other studies [62]. This led us to speculate that maternal obesity, either directly or through its associated complications, is a risk factor for increased

adiposity and reprogramming of metabolic functions in the offspring at birth as well as the perpetuation of this increased adiposity into adulthood.

5.2. Potential Mechanisms for the Long-Term Impacts of Gestational Obesity on the Offspring

5.2.1. Metabolic and Hormonal Theories. In order to better understand the fetal programming of increased fat mass observed in human epidemiological studies, animal model of maternal obesity was developed. Although not yet well understood, few mechanisms of action for such long-lasting effect in offspring were proposed. The most common animal model is the one using a high-fat diet either during gestation alone or in combination to lactation period. However, one question that can be addressed for the validity of this model in term of similarity with real obesity observed in women is whether maternal obesity acts as a programming agent *per se* or whether other aspects of the obesity-inducing diet drive the fetal responses. To answer this question, Spraque-Dawley rats where fed an obesogenic liquid diet by intragastric cannulation to induce obesity in those dams [63]. At mating period, dams were transferred to a control diet and thereafter offered back their obesogenic diet. In order to specifically target the intrauterine life as an obesogenic environment, after birth, pups born from obese animals were cross-fostered to lean dams at birth. In comparison with those born from lean dams, the offspring of obese dams exhibited increased adiposity and insulin resistance until postnatal day 130. This study therefore strongly suggests an independent effect of maternal obesity, specifically during the fetal period, on risk of obesity in the offspring. In line with this study, Bayol et al. showed in 10-week-old rats born to mothers fed a westernized high-fat diet throughout the course of gestation and lactation an exacerbated preference for palatable foods, at the expense of protein-rich foods, that was accompanied by increased body weight and fat mass when compared to control offspring [64]. In these rats, exacerbated adiposity was accompanied by elevated insulin, glucose, triglycerides and cholesterol plasma concentrations. Furthermore, a group of offspring from mothers fed the westernized diet during pregnancy and lactation were switched to a balanced chow diet after weaning. In comparison to offspring born from dams who were never exposed to prenatal junk food diet, exposed offspring exhibited a relative increase in perirenal fat pad mass (a visceral fat depot) and adipocyte hypertrophy, which is believed to reflect reduced ability for adipogenesis and hyperplasia, as well as modulation of genes involved in glucose and insulin regulation and in adipose tissue functions [65]. These studies demonstrate that an obesogenic maternal diet during pregnancy and lactation may directly contribute to the development of total body adiposity, adipose tissue dysfunction, central fat accumulation and metabolic disease later in life.

Obesity, insulin resistance, glucose intolerance and metabolic syndrome were also shown after culling pups to smaller litter size during lactation (F0 generation) [66]. Generational transmission of these pathological states, except for obesity, was observed in the aging offspring born from rats of the F0 generation even though they were not themselves exposed to overnutrition (F1 generation). In the second generation of offspring (F2 generation), fasting hyperglycemia and glucose intolerance were still apparent by 4 months of age [66]. In mouse as in nonhuman primates, in addition to impairing adiposity, maternal high-fat diet induces in the offspring an increase in gluconeogenic enzyme expression [67] or a reduction in liver insulin signalling and activation of JNK and IKK beta [68]. These studies thus provide a mechanism of action for the fatty liver and insulin resistance observed in those offspring. In line with the previous observations, offspring born to dams fed a fat-rich diet throughout gestation and lactation had a dysfunctional adipose tissue as characterized by impaired adipokines production (leptin, adiponectin) and enzymatic function (lipoprotein lipase and hormone-sensitive lipase). These defaults were worsened when the offspring were themselves fed the fat-rich diet after weaning [69]. Thus, *in utero* exposure to maternal obesity and unhealthy diet pattern *per se* can program multiple aspects of energy-balance regulation in the offspring that may be the leading cause of perpetuated adult metabolic diseases.

5.2.2. The Epigenetic Matter. One possible mechanism by which obesity and metabolic disturbances can occur in offspring is related to epigenetic modifications of genes which may be induced by the *in utero* environment and result in gene expression without altering DNA sequences. Epigenetic changes are defined as the transmission of DNA or RNA activity without modifying the nucleotide sequence. Epigenetic misprogramming during development by maternal nutrition or by obesity-related metabolic milieu is now widely thought to have a persistent effect on the developmental plasticity of the foetus leading to obesity-related diseases in children [70]. Studies suggest that maternal obesity, via a pro-inflammatory milieu, insulin resistance, or other hormonal factors, causes epigenetic programming of the foetus [3, 71] which predisposes to the development of obesity and type 2 diabetes mellitus early in life, thus perpetuating the vicious circle of obesity.

Recently, Plagemann and colleagues reported that neonatal overfeeding by culling pups to smaller litters size during lactation resulted in early weight gain, obesity, hyperleptinemia, hyperglycemia, increased insulin to glucose ratio and increased insulin receptor promoter (IRP) methylation in the hypothalamus [72]. Moreover, by performing longitudinal analysis of the data, blood glucose was positively associated to IRP methylation ($r = 0.52$; $P = 0.04$), independently of group (overfed or control). These data are in accordance with the observation that one mechanism by which glucose intolerance could occur in rat offspring exposed to high fat diet may be through increased hepatic gluconeogenesis and histone modification of the offspring liver Pkc1 gene which encodes the phosphoenolpyruvate carboxykinase 1 enzyme [73]. These data thus suggest that obese women carry a "milieu" that can potentially impair the developing child epigenomic-associated metabolic status and then lead to adulthood diseases.

5.2.3. The Placental Effect. Another possible mechanism by which maternal nutrition can impact on the offspring may be through placental effects. Recently, a prospective observational study using a nonhuman primate model gave important insight into the consequences of high-fat diet-induced maternal obesity. In comparison to control mothers and independently of their BMI status, those mothers receiving the high-fat diet had a reduction in uterine blood flow and increase placental inflammation. Furthermore, mothers on the high-fat diet who developed obesity and displayed signs of hyperinsulinemia demonstrated a further decrease in their placental blood flow on the fetal side, thus favouring placental ischemia and stillbirth [74]. Moreover, when female C57BL/6 mice were fed a high-fat diet for 1 month prior to conception and throughout gestation, in addition to developing obesity and insulin resistance, their placentas lacked trophoblast cells and showed increased signs of oxidative stress, as compared to controls [75].

In human pregnancies complicated by obesity, higher placental pro-inflammatory cytokines and higher circulating IL-6 were measured [76]. Accordingly, it was recently demonstrated that exposition of human primary trophoblastic cell culture to IL-6 stimulated fatty acid accumulation. The authors also showed that irrespective of BMI, maternal 3rd-trimester circulating IL-6 levels negatively correlates with placental lipoprotein lipase enzyme activity thereby decreasing fatty acid uptake by the placenta. However, these last results were not replicated in culture conditions [77]. Moreover, fetal adiposity was positively correlated to maternal IL-6 [78], and adult offspring born to IL-6-deficient dams were heavier, had increased adiposity, decreased insulin sensitivity and leptin concentration [79]. IL-6-deficient mice presented reduced leptin concentration in their milk and wild type cross-fostered to IL-6-deficient mice had increased weight and adipocyte size and showed altered hypothalamic gene expression. It can thus be speculated that placental inflammation generated by maternal obesity can contribute to the metabolic disturbance observed in the offspring. Collectively, these data associates maternal obesity to fetal programming of metabolic disease by impaired placental function.

6. Long-Term Health Effect of Gestational Diabetes on the Offspring

6.1. Clinical Studies. In addition to maternal obesity, prepregnancy diabetes or GDM has been associated with increased risk in the offspring of developing later in life obesity, insulin resistance, and type 2 diabetes [80, 81]. In a large prospective analysis including mother-infant pairs who were enrolled in the National Collaborative Perinatal Project, infants born from GDM mothers were more likely to have elevated birth weight and presented a higher BMI Z-score at 7 years of age [82]. In order to further deepen the mechanism by which GDM induces adiposity in children, a study tested 41 children born from mothers with GDM, 41 children born from diabetic fathers (and mother with normal glucose tolerance), and 548 children born from parents with both normal glucose tolerance (control) [83, 84]. In comparison to control newborns, those exposed to maternal diabetes were bigger while those born to diabetic fathers were lighter. Following up the children at 5 years of age, daughters of diabetic mothers developed larger subscapular and triceps skinfold thicknesses and displayed higher insulin concentrations during the oral glucose tolerance test (OGTT), which was accompanied by higher insulin increment. These daughters were also more prone to develop impaired glucose tolerance in comparison to control children (18.3% versus 1.7%). At 5 years of age, children of diabetic fathers had similar anthropometric data to controls, but daughters had an increased prevalence of impaired glucose tolerance (10.5% versus 1.7%). This data lead the authors to speculate that in children born to diabetic father, glucose intolerance in later life may be programmed by low birth weight. However, since daughters of diabetic mothers were characterized both by increased adiposity and lower insulin sensitivity, which was not the case for daughters of diabetic fathers, these findings pinpoint to the direct influence of the intrauterine milieu on fetal programming of later disease.

Regarding maternal glucose tolerance during pregnancy, as determined by the 2nd-trimester OGTT, it was found that the higher the maternal plasma glucose was increased dur ing the test, the higher the cord plasma glucose to insulin ratio was decreased in comparison to cord blood of foetuses born to normoglycemic mothers, but with pro-insulin-to-insulin ratio maintained stable [85]. These results suggest that maternal diabetes affect fetal insulin sensibility rather than β-cell function and that this may lead to altered metabolic function in the children later in life. Accordingly, in a cohort of 21 children aged between 5 and 10 years, Bush and colleagues showed that 2nd-trimester glycemic level 1 hour after a 50 g oral glucose load was inversely correlated with insulin sensitivity assessment during a liquid meal tolerance test in the children, but positively associated with static β-cell response and this was independently of adiposity [86]. Taken together, these studies suggest that at a young age, children who were exposed to high glucose concentrations during their fetal life develop metabolic dysfunctions with time. Studies using gold standard techniques for metabolic assessment and larger cohort are needed to really conclude on the specific effects of high maternal glucose on the reprogramming of fetal functions.

6.2. Potential Mechanisms for the Long-Term Impacts of Gestational Diabetes on the Offspring. Animal studies were also conducted in order to pinpoint the influence of GDM on the transgenerational transmission of obesity and diabetes. In fact, already in the early 90s', studies performed in rodents showed that maternal hyperglycemia leads to overweight, impaired glucose tolerance, hyperinsulinemia and insulin resistance in the offspring later in life [87, 88]. Such metabolic consequences persisted through the F1 and F2 generations [87–89]. In mice, it was recently reported that these defects were perpetuated to the next generations through maternal and/or paternal lineages imprinted genes

[90, 91]. Moreover, Bouchard and colleagues recently demonstrated, in placentas of mothers experiencing glucose intolerance during pregnancy, an inverse relationship between maternal plasma glucose concentration 2 hours after an OGTT and placental fetal side leptin DNA methylation. Increased placental leptin DNA methylation was also associated to lower cord blood leptin mRNA [92]. These results thus indicate that, as shown for maternal obesity, gestational hyperglycemia induces during fetal life an epigenetic mode of inheritance for the transmission of adulthood obesity and associated metabolic disturbances.

7. Interventional Studies Aimed at Reducing the Impact of Maternal Obesity and/or Gestational Diabetes on the Offspring

The question next arising is whether maternal weight loss (before or during pregnancy) can reverse or at least reduce the potential burden of obesity on the offspring. Or more generally, in those mothers who are overweight or obese and/or develop GDM, how can we reduce the risk of transgenerational transmission of obesity and diabetes to the developing child?

In a population of glucose-intolerant subjects, the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS) demonstrated the effectiveness of an intensive program of lifestyle modification, which was accompanied by modest weight loss, in order to prevent almost 60% of new cases of type 2 diabetes mellitus [93, 94]. Moreover, the American Dietetic Association [95], the American Society for Nutrition [95], and the British Fertility Society [96] have all recommended that overweight/obese women should be provided with assistance to lose weight prior to conception and maintain a healthy lifestyle to prevent excess weight gain during pregnancy. Furthermore, a recent review of the literature proposed that improved weight management by adequate nutritional diet may be successful in preventing GDM in pregnant women [97].

7.1. Lessons from Bariatric Surgery. Consistent with the importance for weight loss, most bariatric surgery has shown some beneficial [98, 99] effects on pregnancy outcomes in obese mothers and their neonates even though it was not the case in some other studies (as reviewed in [100]). Of note, bariatric surgery is also likely to affect patients' eating habits that contribute to improve obstetrical and neonatal complications in addition to weight loss. One lesson that we learned from bariatric surgery is that children born to mothers after weight loss due to bariatric surgery had a reduction in macrosomic prevalence in comparison to the siblings born before surgery, without difference in prevalence of low birth weight [101]. In the children born from a pregnancy occurring after the mother underwent bariatric surgery, their risk of developing obesity into adulthood was greatly reduced [101]. Moreover, in a retrospective study, it was shown that in women who delivered after a bariatric surgery, the incidence of GDM and caesarean was less than in pregnancies that occurred before surgery [102]. These data thus imply that maternal weight loss and improvement of metabolic state before pregnancy improve obstetrical and neonatal complications, as well as adulthood-programmed disease in the offspring.

7.2. Lifestyle Management and Weight Control before or during Pregnancy. In the next section, we will present clinical (summarized in Table 2) and animal (summarized in Table 3) studies that have examined the main interventions tested to reduce the impact of maternal obesity and gestational diabetes and how they can break the vicious circle that perpetuates the transmission of obesity and metabolic conditions to the next generations.

7.2.1. Clinical Studies. Regarding lifestyle management during pregnancy, few studies assessing the role of a dietitan intervention alone have been published. A randomized controlled trial undertaken in Belgium enrolled 122 obese pregnant women in 3 groups receiving either nutritional advice from a brochure; the brochure and lifestyle education by a dietitian; or no intervention [103]. By assessing dietitian intervention using food log book or questionnaires, the authors found that while their intervention positively impacted on nutritional habits of participants, it did not result in any improvement of obstetrical or neonatal outcomes. On the other hand, Wolff et al. showed that when obese pregnant women were assisting to frequent nutritional consultation with a specialized dietitian (ten 1-hour sessions during pregnancy), they gained less gestational weight and reduced their fasting insulin, glucose and leptin concentrations, thus suggesting improved metabolic control [104]. However, as in the previous paper, similar obstetrical and neonatal complications between intervention and control women were observed. These studies thus suggest that in order to achieve more optimal weight gain during pregnancy with a nutritional approach alone, it seems important that the participant benefits from individualized professional advices.

The results of studies assessing the benefits of exercise alone either before and/or during pregnancy are worth mentioning. In a small cohort of obese pregnant women, Callaway and colleagues showed that even though an increase in energy expenditure of 900 kcal/week was achieved by 28 weeks of gestation with an individualized exercise program, HOMA-IR and GDM outcomes were not different in comparison to the group receiving usual care, and the authors concluded that the efficiency of their intervention was not convincing [105]. Nevertheless, they showed that by 28 weeks, fasting glucose was significantly reduced and that by 36 weeks, fasting insulin was significantly reduced by 28% in mothers of the intervention group, thus suggesting that these metabolic gains still may show some benefits on a longer-term basis in their children. Clapp et al. also found that in women physically active before pregnancy, those who sustained intensive activity throughout pregnancy gain less gestational weight than those who stopped physical activity at the beginning of pregnancy [106]. Moreover, they showed beneficial effects on the newborns such as reduced birth weight, ponderal index, percent body fat and fat mass.

Table 2: Most important human clinical interventions trials performed in pregnant mothers to reduce or improve maternal, neonatal, and child outcomes.

Study	Population	Study design	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcomes
Guelinckx et al. 2010*Am J Clin Nutr* [103]	$n = 122$, nondiabetic obese (BMI > 29) pregnant (<15 weeks) women	Randomized controlled trial	*Passive group*: brochure on general advices at 1st prenatal visit *Active group*: brochure + 3 group sessions with dietitian during pregnancy on nutrition and physical activity *Control group*: routine care	*Gestational weight gain*: similar *GDM incidence*: N/A *Intervention impact*: in active group, improved nutritional habits during pregnancy and compared to other groups; similar physical activity	*Intervention impact*: similar	*Intervention impact*: similar birth weight	N/A
Wolff et al., 2008 *Int J Obes* [104]	$n = 50$, nondiabetic obese (BMI = 35) pregnant (<15 weeks) women	Randomized controlled trial	*Intervention group*: ten individual sessions with dietitian during pregnancy to improve gestational weight gain with energy intake restriction *Control group*: routine care	*Gestational weight gain*: ↓ 6.7 kg versus controls ($P = 0.002$) *GDM incidence*: similar *Intervention impact*: at 27 weeks: ↓insulin, ↓leptin versus controls at 36 weeks: ↓ insulin, ↓ glucose versus controls	*Intervention impact*: similar	*Intervention impact*: similar birth weight, placental weight, head, and abdominal circumference	N/A
Callaway et al., 2010 *Diabetes Care* [105]	$n = 50$, obese (BMI ≥ 30) pregnant women *participants with type 1 diabetes excluded	Randomized controlled trial	*Intervention group*: individual exercise program with energy expenditure (EE) goal of 900 kcal/week from 12-week gestation to delivery *Control group*: routine care	*Gestational weight gain*: N/A *GDM incidence*: in intervention group, 12% ↑ at 12 week ($P = 0.07$) and similar at 28 week ($P = 0.57$) *Intervention impact*: at 28 weeks: ↑ EE ($P = 0.04$), ↓ fasting glucose ($P = 0.03$), at 36 weeks: ↓ fasting insulin ($P = 0.05$)	N/A	N/A	N/A

Table 2: Continued.

Study	Population	Study design	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcomes
Clapp. 1996*J Pediatr* [106]	$n = 40$, recruited before pregnancy, healthy (BMI not mentioned) caucasian women. Offspring aged 5 yrs: $n = 12$ girls and 8 boys in each group	Prospective cohort study	*Active women*: healthy and physically active before and throughout pregnancy. *Control women*: healthy and physically active before and stop at initiation of pregnancy No intervention in children	*Gestational weight gain*: ↓ in active versus control group *GDM incidence*: N/A	N/A	*Intervention impact*: ↓ birth weight, ponderal index, fat mass, body fat %, and abdominal circumference ($P < 0.01$)	*Intervention impact at 5 years of age*: ↓ weight, skinfolds, arm area fat mass ($P < 0.01$), and ponderal index ($P < 0.05$); ↑general intelligence, language skill ($P < 0.01$), and neurodevelop-mental score ($P < 0.05$)
Artal et al., 2007 *Appl Physiol Nutr Metab* [107]	$n = 96$, overweight or obese (BMI > 25) pregnant (<33 weeks) women with GDM (no insulin)	Randomized controlled trial No control group without intervention	*Diet (D) group*: individual counseling on diet and weight gain goal according to BMI *Exercise and diet (ED) group*: same plus individual counseling on moderate exercise All received usual GDM management	*Gestational weight gain*: ↓ in ED versus D group ($P < 0.05$) *GDM incidence*: 1st trimester: similar 2nd trimester: similar in term of prescription related to insulin to maintain glucose.	*Intervention impact*: similar caesarean rates	*Intervention impact*: similar for macrosomia, small for gestational age and birth weight	N/A
Quinlivan et al., 2011*Aust N Z J Obstet Gynaecol* [108]	$n = 124$, overweight or obese (BMI > 25) pregnant women	Randomized controlled trial	*Intervention group*: 4 steps individual approach: (1) continuity of care provider, (2) weighting at each visit, (3) brief dietary intervention by a food technologist, and (4) psychological support *Control group*: routine care	*Gestational weight gain*: ↓ in intervention versus control ($P < 0.001$) *GDM incidence*: ↓ in intervention versus control ($P < 0.04$)	*Intervention impact*: N/A	*Intervention impact*: similar birth weight	N/A
Korpi-Hyovalti et al., 2011 *BMC Public health* [109]	$n = 54$, high risk for GDM pregnant (8–12 weeks) women irrespective of BMI at inclusion	Open multicenter randomized controlled trial	*Intervention group*: individual counseling on nutrition (dietitian) and physical activity (physiotherapist) *Control group*: close followup	*Gestational weight gain*: small ↓ in intervention group ($P = 0.062$) *GDM incidence*: similar	*Intervention impact*: similar	*Intervention impact*: heavier birth weight ($P = 0.047$); similar rates of macrosomia, admissions to NICU and respiratory distress	N/A

Table 2: Continued.

Study	Population	Study design	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcomes
Lindholm et al., 2010 *Acta Obstet Gynecol Scand* [110]	$n = 25$, overweight (BMI 30–35, $n = 11$) or obese (BMI > 35, $n = 14$) pregnant women	Uncontrolled prospective intervention study	Individual counseling with midwife every 2 weeks + 2 group sessions from 1st trimester to delivery on diet and exercise. One initial consultation with dietitian Goal: gestational weight gain ≤ 6 kg	*Gestational weight gain*: 14/25 reached goals; ↓ in prepregnancy BMI > 35 versus 30–35 ($P = 0.001$) *GDM incidence*: as expected	*Intervention impact*: in prepregnancy BMI > 35 versus 30–35: ↑gestational weeks ($P = 0.04$), ↓ caesarean ($P = 0.04$)	*Intervention impact*: fetal growth and birth weight: as expected	N/A
Shirazian et al., 2010 *Am J Perinatol* [111]	$n = 41$, nondiabetic obese (BMI > 30) pregnant women	Prospective study with historical controls	*Intervention group*: individual counseling on healthy diet and exercise, ≥ 5 one-on-one counselling or phone calls + ≥ 1 seminar/trimester x/trimester. Weight gain goal ≤ 15 lbs. *Control group*: routine care	*Gestational weight gain*:1/2 of control ($P = 0.003$) *GDM incidence*: similar	*Intervention impact*: similar	*Intervention impact*: similar birth weight and rates of fetal complications	N/A
Crowther et al., 2005 *N Engl J Med* [112] Gillman et al., 2010 *Diabetes Care* [113]	$n = 1\,000$, mild GDM pregnant women (median BMI = 26) Offspring aged 4-5 yrs: $n = 94$ (intervention group); $n = 105$ (control group)	Multicenter randomized controlled trial ACHOIS study	*Intervention group*: individual dietary and lifestyle counseling, usual GDM care, insulin therapy in 20% of women; from recruitment (24–34 week gestation) to delivery *Control group*: routine care No intervention in children	*Gestational weight gain*: ↓ in intervention versus control ($P = 0.01$) *GDM incidence*: similar *Intervention impact*: ↑postpartum quality of life	*Intervention impact*: ↑ induction of labor ($P < 0.001$), similar caesarean rates	*Intervention impact*: ↓ perinatal complications ($P = 0.01$), ↑ admission to neonatal nursery ($P = 0.01$), ↓ birth weight ($P < 0.001$), ↓ macrosomia (<0.001)	*Intervention impact*: in offspring 4-5 y.o., similar BMI Z-score, and proportion of BMI ≥ 85th percentile
Landon et al., 2009 *N Engl J Med* [114]	$n = 900$, mild GDM pregnant women (median BMI = 30)	Multicenter randomized controlled trial	*Intervention group*: individual nutritional counseling, usual GDM care, insulin therapy (required in 37 women); from recruitment (24–31 weeks) to delivery *Control group*: routine care, insulin therapy (required in 2 women)	*Gestational weight gain*: ↓ in intervention versus control ($P < 0.001$). *GDM incidence*: N/A *Intervention impact*: achievement of maternal glucose targets	*Intervention impact*: ↓ caesarean ($P = 0.01$), shoulder dystocia ($P = 0.02$), preeclampsia, or hypertension ($P = 0.01$)	*Intervention impact*: ↓ birth weight ($P < 0.001$), macrosomia ($P < 0.001$), fat mass ($P = 0.003$); similar perinatal complications, small for gestational age, admissions to NICU, and respiratory distress	N/A

Table 2: Continued.

Study	Population	Study design	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcomes
Garner et al., 1997 *Am J Obstet Gynecol* [115] And Malcolm et al., 2006 *Diabet Med* [116]	$n = 300$, low-risk pregnant (24–32 weeks) women with GDM Offspring aged 7–11 yrs: $n = 46$ (intervention group), $n = 25$ (control group)	Randomized controlled trial	*Intervention group*: individual dietary counseling by dietitian biweekly, usual GDM care, insulin therapy (required in 36 women) *Control group*: not seen by dietitian; recommended to eat unrestrictedly according to Canada food guide; biweekly self-glucose monitoring No intervention in children	*Gestational weight gain*: similar *GDM incidence*: similar OGTT area under the curves *Intervention impact*: at 28–30 weeks: ↑ preprandial glucose levels ($P = 0.001$) at 36–38 weeks: ↓ preprandial ($P = 0.035$) and 1-hour postprandial ($P = 0.009$) glucose levels	*Intervention impact*: similar caesarean rates	*Intervention impact*: similar birth weight, perinatal complications	*Intervention impact*: similar mean fasting glucose, mean fasting insulin, and mean 2 hrs glucose and insulin; 5 children born to mothers from intervention group had AGT
Moses et al., 2006 *Am J Clin Nutr* [117]	$n = 70$, pregnant (12–16 weeks) women *Participants with conditions associated to abnormal glucose metabolism and insulin resistance problem were excluded	Randomized controlled trial No control group without intervention	*Low-glycemic index group*: individual nutritional counseling by dietitian 5 times during pregnancy on recommended nutritional intake plus low-glycemic index diet *High-glycemic index group*: idem except for recommendation of high-glycemic index diet	*Gestational weight gain*: similar *GDM incidence*: similar (only 1 case) *Intervention impact*: in low versus high-glycemic index group: ↓ glycemic index ($P < 0.001$), fasting glucose ($P = 0.034$)Within low-glycemic index group: ↓ fasting glucose ($P = 0.001$)	*Intervention impact*: in low- versus high-glycemic index group: similar caesarean rates	*Intervention impact*: in low- versus high-glycemic index group: ↓birth weight ($P = 0.051$), macrosomia ($P = 0.001$), ponderal index ($P = 0.03$); similar perinatal complications, small for gestational age, admissions to NICU, respiratory distress	N/A

ACHOIS: Australian Carbohydrate Intolerance in Pregnant Women study, AGT: abnormal glucose tolerance, BMI: body mass index, GDM: gestational diabetes mellitus, MET: metabolic equivalent task, NICU: neonatal intensive care unit, N/A: not applicable, OGTT: oral glucose tolerance test.

Table 3: Most important interventions performed in pregnant animals to reduce or improve maternal, neonatal, and offspring outcomes.

Study	Animal model	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcome
Dolinoy et al., 2006 *Environ Health Perspect* [119]	Heterozygous viable yellow agouti (A^{vy}) mice $n = 15$, unsupplemented litters (52 offspring) $n = 12$, genistein supplemented (44 offspring)	Females (8–10 weeks of age) received phytoestrogen-free modified AIN-93G diet or modified AIN-93G diet supplemented with 250 mg/kg of genistein (comparable to human high-soy diet) Diet provided 2 weeks before mating, throughout pregnancy and lactation	N/A	N/A	*Day 21*:similar litter size, wean weight, percent survival, sex ratio; maternal supplementation favored pseudoagouti versus full agouti (yellow coat) phenotype ($P = 0.0005$) + ↑ Agouti gene methylation	Agouti gene methylation highly correlated between day 21 and 150 in offspring whose mothers received supplement At week 60: ↓ weight in pseudoagouti versus full agouti mice ($P = 0.0001$) Pseudoagouti: normal weight versus full agouti (more obese)
Sen et al., 2010 *Diabetes* [120]	Female Sprague-Dawley rats *Diets*: control (C, $n = 10$); control + antioxidant (CAox, $n = 10$); Western (W, $n = 10$), high protein + fat (HP + F, $n = 10$); W + Aox (WAox, $n = 10$)	Female rats received diets from age 4 to 13–15 weeks (end of gestation). Litters culled to 8 pups. Studies performed in male offspring only. At weaning, offered control diet.	*End of gestation*:↑ gestational weight gain in dams offered W and WAox versus C; similar glucose and food consumption;↑ insulin, free-fatty acid (FFA) and leptin in W versus C, but ↓ in WAox versus W	N/A	*Embryos*:in W versus C: ↑oxidative stress, ↓ in WAox *Birth*: similar weight In W versus C: ↑ FFA, insulin and leptin *2 weeks*: in W versus C: ↑ fat mass, FFA, insulin, leptin, proadipogenic, and lipogenic genes expression, but↓ in WAox versus W	*2 months*: in W versus C:↑ total and central fat mass, insulin, leptin, proadipogenic and lipogenic genes expression, but↓ in WAox versus W; ↑ impaired glucose tolerance, but normalized in WAox (similar to C)

Table 3: Continued.

Study	Animal model	Intervention	Maternal outcomes	Gestational or obstetrical outcomes	Neonatal outcomes	Long-term offspring outcome
Zambrano, et al. 2010 *J Physiol* [121]	Female albino Wistar rats $n = 5$; control $n = 5$; obesogenic; $n = 5$ dietary intervention (DINT)	At 3 weeks, females rats received obesogenic (0; $n = 10$) or control (C; $n = 5$) diets At 90 days, O dams were either continued on O diet ($n = 5$) or receiving the C diet (DINT; $n = 5$) One month after, animals were bred and continued prepregnancy diet throughout pregnancy and lactation Litters culled to 10 pups; pup sex ratio 1 : 1	N/A	*90 days*:in O and DINT versus C: ↑weight *Breeding and delivery*: in O versus C: ↑weight, but ↓ in DINT versus O *Weaning*: in O versus C: ↑leptin, but ↓ in DINT versus O	*Birth and weaning*: similar morphometric variable *Weaning*: in O versus C: ↑subcutaneous fat tissue, serum triglycerides, leptin, insulin, but ↓ in DINT versus O; similar glucose despite ↑ insulin (suggesting insulin resistance), but ↓ in DINT versus O	*Postnatal day 120*: in O versus C: ↑serum glucose, insulin, insulin resistance, but similar glucose with ↑ insulin in DINT versus C (suggesting partial recovery of insulin resistance) *Postnatal day 150*: similar body weight In O versus C: ↑ fat and leptin, larger fat cell size In DINT versus C: non-significant ↓ in fat mass and fat cell size

Moreover, these benefits were maintained at 5 years of age as these children had reduced weight, ponderal index and skinfolds as well as presented improved neurodevelopmental skills. A recent paper reviewing prospective, retrospective and cross-sectional studies assessing prepregnancy and early pregnancy physical activity in over 35.000 and 4.400 participants, respectively, suggested that these women were at reduced risk of GDM [118].

Other trials aimed to improve maternal, neonatal and long-term offspring outcomes by lifestyle management. Indeed, it was shown by Artal and colleagues that, in obese women with GDM, the addition of physical activity to improved dietary habits resulted in less gestational gain weight when compared to the effect of diet alone, without compromising neonatal outcomes [107]. Quinlivan and colleagues performed a randomized-controlled trial enrolling overweight or obese Australian pregnant participants allocated to standard care or a 4-step approach consisting of a visit with an interdisciplinary team including: (1) an obstetrician for continuity of maternal care, (2) a food technologist for nutritional habits and for providing food information, (3) a nurse performing weight measurements and (4) a psychologist to evaluate signs of depression and anxiety [108]. This interdisciplinary lifestyle intervention lead to a significant reduction in gestational weight gain (7.0 versus 13.8 kg) and in the incidence of GDM (6 versus 29%), as compared to standard care. In spite of these clinically significant differences in obstetrical outcomes, neonate weights were similar between the 2 groups. Similarly, a group of Finland's pregnant women at risk for GDM, based on the results of an OGTT performed during first trimester, were randomised to the intervention group, consisting of dietary and physical activity counselling, or in the control group [109]. Weight gain was slightly, although not significantly, reduced in the intervention group (11.4 versus 13.9; $P = 0.06$), but no difference was observed between groups regarding glucose tolerance during 2nd trimester. However, although obstetrical and neonatal outcomes were similar between groups, they showed a slight, but significant increase birth weight in the intervention versus close follow-up group. Other studies have shown that lifestyle improvement by nutritional or physical activity behavioural modifications during pregnancy resulted in recommended gestational weight gain or lower gain than with control intervention [110, 111]. Altogether, these trials and others (including review [122] and meta-analysis [123]) suggest that it is feasible to improve weight management and/or the metabolic state of obese or at-risk women during pregnancy, without negative impact on fetal outcomes. However, results are somewhat scarce, controversial and inconsistent regarding the impact on maternal and fetal medical complications, and long-term follow-up studies are lacking in order to determine whether they have long lasting metabolic benefits on the offspring.

The benefits of controlling adequately maternal hyperglycemia during pregnancy are now well established and have influenced international guidelines on the diagnosis and treatment of gestational hyperglycaemic disorders. The Australian Carbohydrate Intolerance in Pregnant Women (ACHOIS) study showed that in women with mild impaired glucose tolerance but treated with dietary advices and if needed, insulin, macrosomia incidence and serious neonatal complications were significantly reduced as compared to the routine care group [112]. However, intervention was associated with higher admission to neonatal care unit and increased rate of labor induction although caesarean rate were similar. This intervention was not associated with any change in BMI in children at 4-5 years of age between groups [113]. In a randomized controlled trial held in the US, Landon and colleagues showed similar results in women with mild gestational diabetes enrolled in the intervention group consisting of a dietary intervention, self-monitoring of blood glucose and, if needed, insulin therapy [114]. In comparison to control group who received usual care, the intervention did not result in improved neonatal complications as in the ACHOIS study, but it resulted in better fetal growth, as shown by reduced incidence of macrosomia, large-for-gestational age as well as fetal fat mass [114]. Unlike the ACHOIS study, this trial found a reduction in preeclampsia, caesarean and shoulder dystocia. Results of the long-term follow-up of the offspring are not yet available. However, in 71 children assessed between 7–11 years of age, Malcolm and colleagues found that interventions in women with gestational diabetes aiming for either minimal or tight glycemic control during pregnancy [115] were equally effective for the prevention of impaired glucose tolerance [116]. However, this conclusion needs to be interpreted with caution because no control group was included and this study was limited by its relatively small sample size.

Since carbohydrates are the main determinant of postprandial blood glucose level [124], intervention trials were assessed or are presently being held to establish the effect of low glycemic index diet during pregnancy on neonatal outcomes [125, 126]. Accordingly, one interventional study conducted in healthy pregnant women proposed that low glycemic index diet reduces the incidence of macrosomia [117]. In pregnancies complicated by GDM, it is generally accepted that a low glycemic index diet is indicated because it was shown to facilitate glucose control without compromising obstetric and fetal outcomes [127, 128]. In a recent systematic review of literature on low glycemic index diet, Louie et al. proposed that until results of larger randomised control trials are available, low glycemic index diet should not be introduced into clinical practice, except for mothers with GDM, because data are not consistent and supported by large cohorts [129].

In brief, these clinical intervention trials showed some benefits in terms of improved gestational weight gain but few provided convincing data for better impact on the neonates. However, limitations include mainly small number of participants (lack of power) and possible publication bias. As it is otherwise satisfactory to observe that these interventions were not detrimental to the fetus, the next question arising is whether they have a long lasting impact on later childhood obesity or metabolic function.

7.2.2. Animal Studies. Although the impact of gestational obesity and diabetes on the offspring is well described, human

trials conducted to determine whether maternal interventions could break down the vicious cycle on future generation are still at their infancy. Therefore, only animal studies can help us to make some inferences for the moment. In fact, the potential beneficial impact of nutritional intervention were reported in the yellow Agouti mice and in rats born to fat-fed mothers. In the yellow Agouti mice, authors showed that *in utero* exposure to the dietary antioxidant genistein, at levels present in human adult populations consuming high-soy diets, reduces obesity by altering the epigenome in those mice [119]. In addition, offspring born from dams fed a fat Westernized diet developed by 2 weeks of age greater adiposity and glucose intolerance than those born from dams fed the control diet [120]. However, offspring born from dams fed the Westernized diet and supplemented with antioxidant normalized their fat mass as well as their leptin, glucose, insulin and non-esterified fatty acid blood concentrations to levels similar to the control group.

Zambrano and colleague showed that giving a normal chow to obese female rats 1 months prior to mating and throughout pregnancy and lactation in comparison to obese rats who were kept on the obesogenic diet throughout entire study period resulted in dams with lower gestational weight gain but in offspring of similar phenotype and weight from birth to 150 days of age [121]. These results are in agreement with the previously reported literature in human where maternal interventions with the aim to reduce gestational weight gain had no effect on the foetuses birth weight. However, by 21 days of age, offspring born to mothers on the intervention arm significantly improved their high fat mass, hypertriglyceridemia, hyperleptinemia, hyperinsulinemia and insulin resistance, in comparison to rats born from untreated obese dams, and almost to the same levels as in rats born from non-obese dams. By 150 days of age, improvements in leptinemia, fat mass and adipocyte cell size were still observable [121].

These results suggest that maternal intervention aimed at reducing gestational weight gain has tremendous long lasting metabolic effects on the offspring, even if fetal and neonatal profile were similar or slightly changed. It is therefore possible to extrapolate that even though interventions in humans did not result in improved newborn phenotype, beneficial effects on the intrauterine milieu may have long lasting effect on adulthood health of the offspring.

8. Conclusion

In summary, obesity is a common and growing condition affecting women health. Accordingly, women are more likely to enter pregnancy being overweight and often exceed the recommended gestational weight gain. As one major weight-associated complication, GDM may lead to profound and long lasting effect in the child. Moreover, even without the development of GDM, gestational maternal weight increases the future risk of cardiometabolic conditions in the offspring. Fetal programming of metabolic function induced by obesity and GDM may have intergenerational effect and thus, perpetuate the burden of such conditions. Mechanisms by which reprogramming of fetal function might occur is directly through maternal metabolic and hormonal effects, epigenetic alterations or impaired placental function. Periconceptional weight loss interventions have demonstrated their ability to reverse the impacts of maternal obesity and GDM on the child and are of great importance for the prevention of future cardiometabolic risks in the offspring, and may thus be the best approach to break the vicious circle of intergenerational propagation of obesity and diabetes. However, the nature and the timing of intervention should be carefully considered because it could also by itself induce organ reprogramming and potential long-term effect on the offspring [130, 131]. In addition, larger cohorts and long-term randomized controlled trials are necessary to provide robust conclusions.

References

[1] "Obesity: preventing and managing the global epidemic," Report of a WHO Consultation 894, 1997.

[2] S. Y. Chu, S. Y. Kim, and C. L. Bish, "Prepregnancy obesity prevalence in the United States, 2004-2005," *Maternal and Child Health Journal*, vol. 13, no. 5, pp. 614–620, 2009.

[3] S. S. Huda, L. E. Brodie, and N. Sattar, "Obesity in pregnancy: prevalence and metabolic consequences," *Seminars in Fetal and Neonatal Medicine*, vol. 15, no. 2, pp. 70–76, 2010.

[4] Institute of Medicine, *Weight Gain During Pregnancy: Reexamining the Guidelines*, The National Academies Press, Washington, DC, USA, 2009.

[5] T. A. M. Simas, X. Liao, A. Garrison, G. M. T. Sullivan, A. E. Howard, and J. R. Hardy, "Impact of updated institute of medicine guidelines on prepregnancy body mass index categorization, gestational weight gain recommendations, and needed counseling," *Journal of Women's Health*, vol. 20, no. 6, pp. 837–844, 2011.

[6] B. D. Einerson, J. K. Huffman, N. B. Istwan, D. J. Rhea, and S. D. Joy, "New gestational weight gain guidelines:an observational study of pregnancy outcomes in obese women," *Obesity*. In press.

[7] C. S. Weisman, M. M. Hillemeier, D. Symons Downs, C. H. Chuang, and A. M. Dyer, "Preconception predictors of weight gain during pregnancy. Prospective findings from the central Pennsylvania women's health study," *Women's Health Issues*, vol. 20, no. 2, pp. 126–132, 2010.

[8] E. Althuizen, M. N. M. Van Poppel, J. C. Seidell, and W. Van Mechelen, "Correlates of absolute and excessive weight gain during pregnancy," *Journal of Women's Health*, vol. 18, no. 10, pp. 1559–1566, 2009.

[9] J. M. Dodd, R. M. Grivell, A.-M. Nguyen, A. Chan, and J. S. Robinson, "Maternal and perinatal health outcomes by body mass index category," *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 51, no. 2, pp. 136–140, 2011.

[10] J. E. Ramsay, I. Greer, and N. Sattar, "ABC of obesity: obesity and reproduction," *British Medical Journal*, vol. 333, no. 7579, pp. 1159–1162, 2006.

[11] R. P. Gunatilake and J. H. Perlow, "Obesity and pregnancy: clinical management of the obese gravida," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 2, pp. 106–119, 2011.

[12] F. A. C. Souza, R. Dias, C. E. Fernandes, F. Pimentel, and D. Dias, "Menstrual irregularity: a possible clinical marker of metabolic dysfunction in women with class III obesity,"

Gynecological Endocrinology, vol. 26, no. 10, pp. 768–772, 2010.

[13] M. Metwally, T. C. Li, and W. L. Ledger, "The impact of obesity on female reproductive function," *Obesity Reviews*, vol. 8, no. 6, pp. 515–523, 2007.

[14] M. J. Turner, C. Fattah, N. O'Connor, N. Farah, M. Kennelly, and B. Stuart, "Body mass index and spontaneous miscarriage," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 151, no. 2, pp. 168–170, 2010.

[15] R. Gaillard, E. A. Steegers, A. Hofman, and V. W. Jaddoe, "Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The Generation R study," *Journal of Hypertension*, vol. 29, no. 5, pp. 937–944, 2011.

[16] D. Simmons, "Diabetes and obesity in pregnancy," *Best Practice and Research*, vol. 25, no. 1, pp. 25–36, 2011.

[17] C. Hamon, S. Fanello, L. Catala, and E. Parot, "Maternal obesity: effects on labor and delivery. "Excluding other diseases that might modify obstetrical management"," *Journal de Gynecologie Obstetrique et Biologie de la Reproduction*, vol. 34, no. 2, pp. 109–114, 2005.

[18] C. M. Jevitt, "Shoulder dystocia: etiology, common risk factors, and management," *Journal of Midwifery and Women's Health*, vol. 50, no. 6, pp. 485–497, 2005.

[19] V. Flenady, L. Koopmans, P. Middleton et al., "Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis," *The Lancet*, vol. 377, no. 9774, pp. 1331–1340, 2011.

[20] M. I. Blomberg and B. Källén, "Maternal obesity and morbid obesity: the risk for birth defects in the offspring," *Birth Defects Research A*, vol. 88, no. 1, pp. 35–40, 2010.

[21] K. J. Stothard, P. W. G. Tennant, R. Bell, and J. Rankin, "Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 301, no. 6, pp. 636–650, 2009.

[22] H. M. Salihu, H. E. Weldeselasse, K. Rao et al., "The impact of obesity on maternal morbidity and feto-infant outcomes among macrosomic infants," *The Journal of Maternal-Fetal and Neonatal Medicine*, vol. 87, no. 9, pp. 641–646, 2011.

[23] E. Oken, K. P. Kleinman, M. B. Belfort, J. K. Hammitt, and M. W. Gillman, "Associations of gestational weight gain with short- and longer-term maternal and child health outcomes," *American Journal of Epidemiology*, vol. 170, no. 2, pp. 173–180, 2009.

[24] E. Villamor and S. Cnattingius, "Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study," *The Lancet*, vol. 368, no. 9542, pp. 1164–1170, 2006.

[25] International Association of Diabetes and Pregnancy Study Groups, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 33, supplement 1, pp. S62–S69, 2010.

[26] S. Y. Chu, W. M. Callaghan, S. Y. Kim et al., "Maternal obesity and risk of gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 8, pp. 2070–2076, 2007.

[27] B. E. Metzger, S. G. Gabbe, B. Persson et al., "International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnanc," *Diabetes Care*, vol. 33, no. 7, pp. 676–682, 2010.

[28] E. A. Reece, G. Leguizamón, and A. Wiznitzer, "Gestational diabetes: the need for a common ground," *The Lancet*, vol. 373, no. 9677, pp. 1789–1797, 2009.

[29] A. Harlev and A. Wiznitzer, "New insights on glucose pathophysiology in gestational diabetes and insulin resistance," *Current Diabetes Reports*, vol. 10, no. 3, pp. 242–247, 2010.

[30] A. Giacca, C. Xiao, A. I. Oprescu, A. C. Carpentier, and G. F. Lewis, "Lipid-induced pancreatic β-cell dysfunction: focus on in vivo studies," *American Journal of Physiology*, vol. 300, no. 2, pp. E255–E262, 2011.

[31] P. C. Chandler-Laney, R. P. Phadke, W. M. Granger et al., "Adiposity and beta-cell function: relationships differ with ethnicity and age," *Obesity*, vol. 18, no. 11, pp. 2086–2092, 2010.

[32] S. J. Herring, E. Oken, S. L. Rifas-Shiman et al., "Weight gain in pregnancy and risk of maternal hyperglycemia," *American Journal of Obstetrics and Gynecology*, vol. 201, no. 1, pp. e61–e67, 2009.

[33] S. Y. Kim, L. England, H. G. Wilson, C. Bish, G. A. Satten, and P. Dietz, "Percentage of gestational diabetes mellitus attributable to overweight and obesity," *American Journal of Public Health*, vol. 100, no. 6, pp. 1047–1052, 2010.

[34] M. H. Davenport, M. K. Campbell, and M. F. Mottola, "Increased incidence of glucose disorders during pregnancy is not explained by pre-pregnancy obesity in London, Canada," *BMC Pregnancy and Childbirth*, vol. 10, p. 85, 2010.

[35] J. Pederson, "Hyperglycemia and hyperinsulinism theory and birthweight," in *The Pregnant Diabetic and Her Newborn: Problems and Management*, pp. 211–220, Williams and Wilkins, Baltimore, Md, USA, 1977.

[36] P. A. Gruppuso, R. Migliori, J. B. Susa, and R. Schwartz, "Chronic maternal hyperinsulinemia and hypoglycemia. A model for experimental intrauterine growth retardation," *Biology of the Neonate*, vol. 40, no. 3-4, pp. 113–120, 1981.

[37] M. U. Baumann, S. Deborde, and N. P. Illsley, "Placental glucose transfer and fetal growth," *Endocrine*, vol. 19, no. 1, pp. 13–22, 2002.

[38] J. M. Keller and J. S. Krohmer, "Insulin transfer in the isolated human placenta," *Obstetrics and Gynecology*, vol. 32, no. 1, pp. 77–80, 1968.

[39] A. Plagemann, "A matter of insulin: developmental programming of body weight regulation," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 21, no. 3, pp. 143–148, 2008.

[40] S. Schneider, B. Hoeft, and N. Freerksen, "Neonatal complications and risk factors among women with gestational diabetes mellitus," *Acta Obstetricia et Gynecologica Scandinavia*. In press.

[41] S. Riskin-Mashiah, G. Younes, A. Damti, and R. Auslender, "First-trimester fasting hyperglycemia and adverse pregnancy outcomes," *Diabetes Care*, vol. 32, no. 9, pp. 1639–1643, 2009.

[42] B. E. Metzger, M. Contreras, D. A. Sacks et al., "Hyperglycemia and adverse pregnancy outcomes," *New England Journal of Medicine*, vol. 358, no. 19, pp. 1991–2002, 2008.

[43] U. M. Schaefer-Graf, R. Heuer, Ö. Kilavuz, A. Pandura, W. Henrich, and K. Vetter, "Maternal obesity not maternal glucose values correlates best with high rates of fetal macrosomia in pregnancies complicated by gestational diabetes," *Journal of Perinatal Medicine*, vol. 30, no. 4, pp. 313–321, 2002.

[44] J. R. Biggio, V. Chapman, C. Neely, S. P. Cliver, and D. J. Rouse, "Fetal anomalies in obese women: the contribution of diabetes," *Obstetrics and Gynecology*, vol. 115, no. 2, pp. 290–296, 2010.

[45] D. J. P. Barker, "The fetal and infant origins of adult disease," *British Medical Journal*, vol. 301, no. 6761, p. 1111, 1990.

[46] D. J. P. Barker, "The long-term outcome of retarded fetal growth," *Clinical Obstetrics and Gynecology*, vol. 40, no. 4, pp. 853–863, 1997.

[47] T. J. Roseboom, J. H. P. Van der Meulen, A. C. J. Ravelli, C. Osmond, D. J. P. Barker, and O. P. Bleker, "Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview," *Molecular and Cellular Endocrinology*, vol. 185, no. 1-2, pp. 93–98, 2001.

[48] R. A. Price, M. A. Charles, D. J. Pettitt, and W. C. Knowler, "Obesity in Pima Indians: large increases among post-World War II birth cohorts," *American Journal of Physical Anthropology*, vol. 92, no. 4, pp. 473–479, 1993.

[49] D. J. Pettitt, R. G. Nelson, M. F. Saad, P. H. Bennett, and W. C. Knowler, "Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy," *Diabetes Care*, vol. 16, no. 1, pp. 310–314, 1993.

[50] J. C. Bunt, P. Antonio Tataranni, and A. D. Salbe, "Intrauterine exposure to diabetes is a determinant of hemoglobin A1c and systolic blood pressure in pima indian children," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 6, pp. 3225–3229, 2005.

[51] S. M. Nelson, P. Matthews, and L. Poston, "Maternal metabolism and obesity: modifiable determinants of pregnancy outcome," *Human Reproduction Update*, vol. 16, no. 3, Article ID dmp050, pp. 255–275, 2009.

[52] A. A. Mamun, M. O'Callaghan, L. Callaway, G. Williams, J. Najman, and D. A. Lawlor, "Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of ageevidence from a birth cohort study," *Circulation*, vol. 119, no. 13, pp. 1720–1727, 2009.

[53] C. R. Gale, M. K. Javaid, S. M. Robinson, C. M. Law, K. M. Godfrey, and C. Cooper, "Maternal size in pregnancy and body composition in children," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 10, pp. 3904–3911, 2007.

[54] I. Koupil and P. Toivanen, "Social and early-life determinants of overweight and obesity in 18-year-old Swedish men," *International Journal of Obesity*, vol. 32, no. 1, pp. 73–81, 2008.

[55] B. L. Rooney, M. A. Mathiason, and C. W. Schauberger, "Predictors of obesity in childhood, adolescence, and adulthood in a birth cohort," *Maternal and Child Health Journal*, vol. 15, no. 8, pp. 1166–1175, 2011.

[56] R. Cooper, E. Hyppönen, D. Berry, and C. Power, "Associations between parental and offspring adiposity up to midlife: the contribution of adult lifestyle factors in the 1958 British Birth Cohort Study," *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 946–953, 2010.

[57] R. C. Whitaker, "Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy," *Pediatrics*, vol. 114, no. 1, pp. e29–36, 2004.

[58] P. M. Catalano, L. Presley, J. Minium, and S. H. D. Mouzon, "Fetuses of obese mothers develop insulin resistance in utero," *Diabetes Care*, vol. 32, no. 6, pp. 1076–1080, 2009.

[59] D. A. Lawlor, P. Lichtenstein, A. Fraser, and N. Långström, "Does maternal weight gain in pregnancy have long-term effects on offspring adiposity? A sibling study in a prospective cohort of 146,894 men from 136,050 families," *American Journal of Clinical Nutrition*, vol. 94, no. 1, pp. 142–148, 2011.

[60] H. A. S. Goldani, H. Bettiol, M. A. Barbieri et al., "Cesarean delivery is associated with an increased risk of obesity in adulthood in a Brazilian birth cohort study," *American Journal of Clinical Nutrition*, vol. 93, no. 6, pp. 1344–1347, 2011.

[61] J. Pirkola, A. Pouta, A. Bloigu et al., "Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus," *Diabetes Care*, vol. 33, no. 5, pp. 1115–1121, 2010.

[62] G. M. Egeland and S. J. Meltzer, "Following in mother's footsteps? Mother-daughter risks for insulin resistance and cardiovascular disease 15 years after gestational diabetes," *Diabetic Medicine*, vol. 27, no. 3, pp. 257–265, 2010.

[63] K. Shankar, A. Harrell, X. Liu, J. M. Gilchrist, M. J. J. Ronis, and T. M. Badger, "Maternal obesity at conception programs obesity in the offspring," *American Journal of Physiology*, vol. 294, no. 2, pp. R528–R538, 2008.

[64] S. A. Bayol, S. J. Farrington, and N. C. Stickland, "A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring," *British Journal of Nutrition*, vol. 98, no. 4, pp. 843–851, 2007.

[65] S. A. Bayol, B. H. Simbi, J. A. Bertrand, and N. C. Stickland, "Offspring from mothers fed a "junk food" diet in pregnancy and lactation exhibit exacerbated adiposity that is more pronounced in females," *Journal of Physiology*, vol. 586, no. 13, pp. 3219–3230, 2008.

[66] T. Pentinat, M. Ramon-Krauel, J. Cebria, R. Diaz, and J. C. Jimenez-Chillaron, "Transgenerational inheritance of glucose intolerance in a mouse model of neonatal overnutrition," *Endocrinology*, vol. 151, no. 12, pp. 5617–5623, 2010.

[67] C. E. McCurdy, J. M. Bishop, S. M. Williams et al., "Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates," *Journal of Clinical Investigation*, vol. 119, no. 2, pp. 323–335, 2009.

[68] N. G. Ashino, K. N. Saito, F. D. Souza et al., "Maternal high-fat feeding through pregnancy and lactation predisposes mouse offspring to molecular insulin resistance and fatty liver," *Journal of Nutritional Biochemistry*. In press.

[69] N. B. Benkalfat, H. Merzouk, S. Bouanane et al., "Altered adipose tissue metabolism in offspring of dietary obese rat dams," *Clinical Science*, vol. 121, no. 1, pp. 19–28, 2011.

[70] K. A. Lillycrop, "Effect of maternal diet on the epigenome: implications for human metabolic disease," *Proceedings of the Nutrition Society*, vol. 70, no. 1, pp. 64–72, 2011.

[71] E. Jarvie, S. Hauguel-de-Mouzon, S. M. Nelson, N. Sattar, P. M. Catalano, and D. J. Freeman, "Lipotoxicity in obese pregnancy and its potential role in adverse pregnancy outcome and obesity in the offspring," *Clinical Science*, vol. 119, no. 3, pp. 123–129, 2010.

[72] A. Plagemann, K. Roepke, T. Harder et al., "Epigenetic malprogramming of the insulin receptor promoter due to developmental overfeeding," *Journal of Perinatal Medicine*, vol. 38, no. 4, pp. 393–400, 2010.

[73] R. S. Strakovsky, X. Zhang, D. Zhou, and Y.-X. Pan, "Gestational high fat diet programs hepatic phosphoenolpyruvate carboxykinase gene expression and histone modification in neonatal offspring rats," *Journal of Physiology*, vol. 589, no. 11, pp. 2707–2717, 2011.

[74] A. E. Frias, T. K. Morgan, A. E. Evans et al., "Maternal high-fat diet disturbs uteroplacental hemodynamics and increases the frequency of stillbirth in a nonhuman primate model of excess nutrition," *Endocrinology*, vol. 152, no. 6, pp. 2456–2464, 2011.

[75] C. Liang, K. DeCourcy, and M. R. Prater, "High-saturated-fat diet induces gestational diabetes and placental vasculopathy in C57BL/6 mice," *Metabolism*, vol. 59, no. 7, pp. 943–950, 2010.

[76] K. A. Roberts, S. C. Riley, R. M. Reynolds et al., "Placental structure and inflammation in pregnancies associated with obesity," *Placenta*, vol. 32, no. 3, pp. 247–254, 2011.

[77] S. Lager, N. Jansson, A. L. Olsson, M. Wennergren, T. Jansson, and T. L. Powell, "Effect of IL-6 and TNF-α on fatty acid uptake in cultured human primary trophoblast cells," *Placenta*, vol. 32, pp. 121–127, 2011.

[78] T. Radaelli, J. Uvena-Celebrezze, J. Minium, L. Huston-Presley, P. Catalano, and S. Hauguel-de Mouzon, "Maternal interleukin-6: marker of fetal growth and adiposity," *Journal of the Society for Gynecologic Investigation*, vol. 13, no. 1, pp. 53–57, 2006.

[79] S. Lager, I. W. Asterholm, E. Schéle et al., "Perinatal lack of maternal IL-6 promotes increased adiposity during adulthood in mice," *Endocrinology*, vol. 152, no. 4, pp. 1336–1346, 2011.

[80] L. Poston, "Intergenerational transmission of insulin resistance and type 2 diabetes," *Progress in Biophysics and Molecular Biology*, vol. 106, no. 1, pp. 315–322, 2011.

[81] A. Burguet, "Long-term outcome in children of mothers with gestational diabetes," *Diabetes & Metabolism*, vol. 36, no. 6 Pt 2, pp. 682–694, 2010.

[82] K. Baptiste-Roberts, W. K. Nicholson, N.-Y. Wang, and F. L. Brancati, "Gestational diabetes and subsequent growth patterns of offspring: the national collaborative perinatal project," *Maternal and Child Health Journal*. In press.

[83] G. V. Krishnaveni, J. C. Hill, S. D. Leary et al., "Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy," *Diabetes Care*, vol. 28, no. 12, pp. 2919–2925, 2005.

[84] G. V. Krishnaveni, J. C. Hill, S. R. Veena et al., "Truncal adiposity is present at birth and in early childhood in south Indian children," *Indian Pediatrics*, vol. 42, no. 6, pp. 527–538, 2005.

[85] Z.-C. Luo, E. Delvin, W. D. Fraser et al., "Maternal glucose tolerance in pregnancy affects fetal insulin sensitivity," *Diabetes Care*, vol. 33, no. 9, pp. 2055–2061, 2010.

[86] N. C. Bush, P. C. Chandler-Laney, D. J. Rouse, W. M. Granger, R. A. Oster, and B. A. Gower, "Higher maternal gestational glucose concentration is associated with lower offspring insulin sensitivity and altered β-cell function," *Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 5, pp. E803–E809, 2011.

[87] L. Aerts, K. Holemans, and F. A. Van Assche, "Maternal diabetes during pregnancy: consequences for the offspring," *Diabetes/Metabolism Reviews*, vol. 6, no. 3, pp. 147–167, 1990.

[88] G. Dorner, A. Plagemann, J. Ruckert et al., "Teratogenetic maternofoetal transmission and prevention of diabetes susceptibility," *Experimental and Clinical Endocrinology*, vol. 91, no. 3, pp. 247–258, 1988.

[89] G. Dorner and A. Plagemann, "Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life," *Hormone and Metabolic Research*, vol. 26, no. 5, pp. 213–221, 1994.

[90] G. A. Dunn and T. L. Bale, "Maternal high-fat diet promotes body length increases and insulin insensitivity in second-generation mice," *Endocrinology*, vol. 150, no. 11, pp. 4999–5009, 2009.

[91] G. A. Dunn and T. L. Bale, "Maternal high-fat diet effects on third-generation female body size via the paternal lineage," *Endocrinology*, vol. 152, no. 6, pp. 2228–2236, 2011.

[92] L. Bouchard, S. Thibault, S.-P. Guay et al., "Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy," *Diabetes Care*, vol. 33, no. 11, pp. 2436–2441, 2010.

[93] J. Tuomilehto, J. Lindström, J. G. Eriksson et al., "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance," *New England Journal of Medicine*, vol. 344, no. 18, pp. 1343–1350, 2001.

[94] W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," *New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.

[95] A. M. Siega-Riz and J. C. King, "Position of the American dietetic association and American society for nutrition: obesity, reproduction, and pregnancy outcomes," *Journal of the American Dietetic Association*, vol. 109, no. 5, pp. 918–927, 2009.

[96] A. H. Balen and R. A. Anderson, "Impact of obesity on female reproductive health: British fertility society, policy and practice guidelines," *Human Fertility*, vol. 10, no. 4, pp. 195–206, 2007.

[97] A. S. Morisset, A. St-Yves, J. Veillette, S. J. Weisnagel, A. Tchernof, and J. Robitaille, "Prevention of gestational diabetes mellitus: a review of studies on weight management," *Diabetes/Metabolism Research and Reviews*, vol. 26, no. 1, pp. 17–25, 2010.

[98] A. Abodeely, G. D. Roye, D. T. Harrington, and W. G. Cioffi, "Pregnancy outcomes after bariatric surgery: maternal, fetal, and infant implications," *Surgery for Obesity and Related Diseases*, vol. 4, no. 3, pp. 464–471, 2008.

[99] M. A. Grundy, S. Woodcock, and S. E. Attwood, "The surgical management of obesity in young women: consideration of the mother's and baby's health before, during, and after pregnancy," *Surgical Endoscopy and Other Interventional Techniques*, vol. 22, no. 10, pp. 2107–2116, 2008.

[100] I. Guelinckx, R. Devlieger, and G. Vansant, "Reproductive outcome after bariatric surgery: a critical review," *Human Reproduction Update*, vol. 15, no. 2, pp. 189–201, 2009.

[101] J. Smith, K. Cianflone, S. Biron et al., "Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 11, pp. 4275–4283, 2009.

[102] A. E. Burke, W. L. Bennett, R. M. Jamshidi et al., "Reduced incidence of gestational diabetes with bariatric surgery," *Journal of the American College of Surgeons*, vol. 211, no. 2, pp. 169–175, 2010.

[103] I. Guelinckx, R. Devlieger, P. Mullie, and G. Vansant, "Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a randomized controlled trial," *American Journal of Clinical Nutrition*, vol. 91, no. 2, pp. 373–380, 2010.

[104] S. Wolff, J. Legarth, K. Vangsgaard, S. Toubro, and A. Astrup, "A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women," *International Journal of Obesity*, vol. 32, no. 3, pp. 495–501, 2008.

[105] L. K. Callaway, P. B. Colditz, N. M. Byrne et al., "Prevention of gestational diabetes: feasibility issues for an exercise intervention in obese pregnant women," *Diabetes Care*, vol. 33, no. 7, pp. 1457–1459, 2010.

[106] J. F. Clapp 3rd, "Morphometric and neurodevelopmental outcome at age five years of the offspring of women who continued to exercise regularly throughout pregnancy," *Journal of Pediatrics*, vol. 129, no. 6, pp. 856–863, 1996.

[107] R. Artal, R. B. Catanzaro, J. A. Gavard, D. J. Mostello, and J. C. Friganza, "A lifestyle intervention of weight-gain restriction: diet and exercise in obese women with gestational diabetes mellitus," *Applied Physiology, Nutrition and Metabolism*, vol. 32, no. 3, pp. 596–601, 2007.

[108] J. A. Quinlivan, L. T. Lam, and J. Fisher, "A randomised trial of a four-step multidisciplinary approach to the antenatal care of obese pregnant women," *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 51, no. 2, pp. 141–146, 2011.

[109] E. A. L. Korpi-Hyövälti, D. E. Laaksonen, U. S. Schwab et al., "Feasibility of a lifestyle intervention in early pregnancy to prevent deterioration of glucose tolerance," *BMC Public Health*, vol. 11, article 179, 2011.

[110] E. S. Lindholm, M. Norman, C. P. Kilander, and D. Altman, "Weight control program for obese pregnant women," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 89, no. 6, pp. 840–843, 2010.

[111] T. Shirazian, S. Monteith, F. Friedman, and A. Rebarber, "Lifestyle modification program decreases pregnancy weight gain in obese women," *American Journal of Perinatology*, vol. 27, no. 5, pp. 411–414, 2010.

[112] C. A. Crowther, J. E. Hiller, J. R. Moss, A. J. McPhee, W. S. Jeffries, and J. S. Robinson, "Effect of treatment of gestational diabetes mellitus on pregnancy outcomes," *New England Journal of Medicine*, vol. 352, no. 24, pp. 2477–2486, 2005.

[113] M. W. Gillman, H. Oakey, P. A. Baghurst, R. E. Volkmer, J. S. Robinson, and C. A. Crowther, "Effect of treatment of gestational diabetes mellitus on obesity in the next generation," *Diabetes Care*, vol. 33, no. 5, pp. 964–968, 2010.

[114] M. B. Landon, C. Y. Spong, E. Thom et al., "A multicenter, randomized trial of treatment for mild gestational diabetes," *New England Journal of Medicine*, vol. 361, no. 14, pp. 1339–1348, 2009.

[115] P. Garner, N. Okun, E. Keely et al., "A randomized controlled trial of strict glycemic control and tertiary level obstetric care versus routine obstetric care in the management of gestational diabetes: a pilot study," *American Journal of Obstetrics and Gynecology*, vol. 177, no. 1, pp. 190–195, 1997.

[116] J. C. Malcolm, M. L. Lawson, I. Gaboury, G. Lough, and E. Keely, "Glucose tolerance of offspring of mother with gestational diabetes mellitus in a low-risk population," *Diabetic Medicine*, vol. 23, no. 5, pp. 565–570, 2006.

[117] R. G. Moses, M. Luebcke, W. S. Davis et al., "Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes," *American Journal of Clinical Nutrition*, vol. 84, no. 4, pp. 807–812, 2006.

[118] D. K. Tobias, C. Zhang, R. M. Van Dam, K. Bowers, and F. B. Hu, "Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis," *Diabetes Care*, vol. 34, no. 1, pp. 223–229, 2011.

[119] D. C. Dolinoy, J. R. Weidman, R. A. Waterland, and R. L. Jirtle, "Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome," *Environmental Health Perspectives*, vol. 114, no. 4, pp. 567–572, 2006.

[120] S. Sen and R. A. Simmons, "Maternal antioxidant supplementation prevents adiposity in the offspring of western diet-fed rats," *Diabetes*, vol. 59, no. 12, pp. 3058–3065, 2010.

[121] E. Zambrano, P. M. Martínez-Samayoa, G. L. Rodríguez-González, and P. W. Nathanielsz, "Dietary intervention prior to pregnancy reverses metabolic programming in male offspring of obese rats," *Journal of Physiology*, vol. 588, no. 10, pp. 1791–1799, 2010.

[122] H. Skouteris, L. Hartley-Clark, M. McCabe et al., "Preventing excessive gestational weight gain: a systematic review of interventions," *Obesity Reviews*, vol. 11, no. 11, pp. 757–768, 2010.

[123] I. Streuling, A. Beyerlein, and R. von Kries, "Can gestational weight gain be modified by increasing physical activity and diet counseling? A meta-analysis of interventional trials," *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 678–687, 2010.

[124] W. C. Bevier and L. Jovanovič, "Weight gain and gestational diabetes mellitus is a sensitive issue," *Diabetes Care*, vol. 31, no. 1, p. e1, 2008.

[125] E. T. Rhodes, D. B. Pawlak, T. C. Takoudes et al., "Effects of a low-glycemic load diet in overweight and obese pregnant women: a pilot randomized controlled trial," *American Journal of Clinical Nutrition*, vol. 92, no. 6, pp. 1306–1315, 2010.

[126] J. Walsh, R. Mahony, M. Foley, and F. Mc Auliffe, "A randomised control trial of low glycaemic index carbohydrate diet versus no dietary intervention in the prevention of recurrence of macrosomia," *BMC Pregnancy and Childbirth*, vol. 10, article 16, 2010.

[127] S. M. Grant, T. M. S. Wolever, D. L. O'Connor, R. Nisenbaum, and R. G. Josse, "Effect of a low glycaemic index diet on blood glucose in women with gestational hyperglycaemia," *Diabetes Research and Clinical Practice*, vol. 91, no. 1, pp. 15–22, 2011.

[128] R. G. Moses, M. Barker, M. Winter, P. Petocz, and J. C. Brand-Miller, "Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial," *Diabetes Care*, vol. 32, no. 6, pp. 996–1000, 2009.

[129] J. C. Louie, J. C. Brand-Miller, and T. P. Markovic, "Glycemic index and pregnancy: a systematic literature review," *Journal of Nutrition and Metabolism*, vol. 2010, Article ID 282464, 8 pages, 2010.

[130] S. Zhang, L. Rattanatray, S. M. MacLaughlin et al., "Periconceptional undernutrition in normal and overweight ewes leads to increased adrenal growth and epigenetic changes in adrenal IGF2/H19 gene in offspring," *FASEB Journal*, vol. 24, no. 8, pp. 2772–2782, 2010.

[131] L. Rattanatray, S. M. MacLaughlin, D. O. Kleemann, S. K. Walker, B. S. Muhlhausler, and I. C. McMillen, "Impact of maternal periconceptional overnutrition on fat mass and expression of adipogenic and lipogenic genes in visceral and subcutaneous fat depots in the postnatal lamb," *Endocrinology*, vol. 151, no. 11, pp. 5195–5205, 2010.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 349286, 18 pages
doi:10.1155/2011/349286

Review Article

Fetoplacental Vascular Endothelial Dysfunction as an Early Phenomenon in the Programming of Human Adult Diseases in Subjects Born from Gestational Diabetes Mellitus or Obesity in Pregnancy

Andrea Leiva,[1] Fabián Pardo,[1] Marco A. Ramírez,[1,2] Marcelo Farías,[1] Paola Casanello,[1] and Luis Sobrevia[1]

[1] *Cellular and Molecular Physiology Laboratory (CMPL) and Perinatology Research Laboratory (PRL), Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Catolica de Chile, P.O. Box 114-D, Santiago, Chile*
[2] *Biomedical Department, Faculty of Health Sciences, Universidad de Antofagasta, Antofagasta, Chile*

Correspondence should be addressed to Luis Sobrevia, sobrevia@me.com

Received 16 June 2011; Revised 11 August 2011; Accepted 7 September 2011

Academic Editor: Susan Ozanne

Gestational diabetes mellitus (GDM) and obesity in pregnancy (OP) are pathological conditions associated with placenta vascular dysfunction coursing with metabolic changes at the fetoplacental microvascular and macrovascular endothelium. These alterations are seen as abnormal expression and activity of the cationic amino acid transporters and endothelial nitric oxide synthase isoform, that is, the "endothelial L-arginine/nitric oxide signalling pathway." Several studies suggest that the endogenous nucleoside adenosine along with insulin, and potentially arginases, are factors involved in GDM-, but much less information regards their role in OP-associated placental vascular alterations. There is convincing evidence that GDM and OP prone placental endothelium to an "altered metabolic state" leading to fetal programming evidenced at birth, a phenomenon associated with future development of chronic diseases. In this paper it is suggested that this pathological state could be considered as a metabolic marker that could predict occurrence of diseases in adulthood, such as cardiovascular disease, obesity, diabetes mellitus (including gestational diabetes), and metabolic syndrome.

1. Introduction

Pregnancy is a physiological state with a complex anatomical and functional interaction between mother and fetus [1]. When this interaction is not a success, the mother, the fetus, or both exhibit functional impairments. Complications of pregnancy are important causes of maternal mortality, where gestational diabetes mellitus (GDM) and obesity of the mother in pregnancy (OP) are major obstetric pathologies. Fetal-maternal interaction could result in metabolic disturbances leading, for example, to placental and endothelial dysfunction [2, 3]. Endothelial dysfunction is defined as an altered capacity of the endothelium to take up and metabolize the cationic amino acid L-arginine, the substrate for nitric oxide (NO) synthesis via NO synthases (NOS) [4, 5]. Interestingly, it is reported that GDM and OP are pathological conditions associated with altered L-arginine transport and NO synthesis (i.e., the "L-arginine/NO signalling pathway"), probably due to altered uptake and metabolism of adenosine [6, 7], an endogenous nucleoside acting as vasodilator in most vascular beds [8, 9]. These pathophysiological characteristics are considered key in the establishment of a "programmed state" of the developing fetus (i.e., "fetal programming"). This concept refers to the impact of abnormal intrauterine conditions on the development of diseases in adulthood and becomes a key mechanism associated with future development of chronic diseases including cardiovascular disease (CVD), diabetes mellitus, and metabolic syndrome (a concept globalizing clinical association of obesity, type II or non-insulin-dependent diabetes mellitus, hypertension, and dyslipidaemia) [10–12]. Interestingly, GDM is a condition that also increases the risk

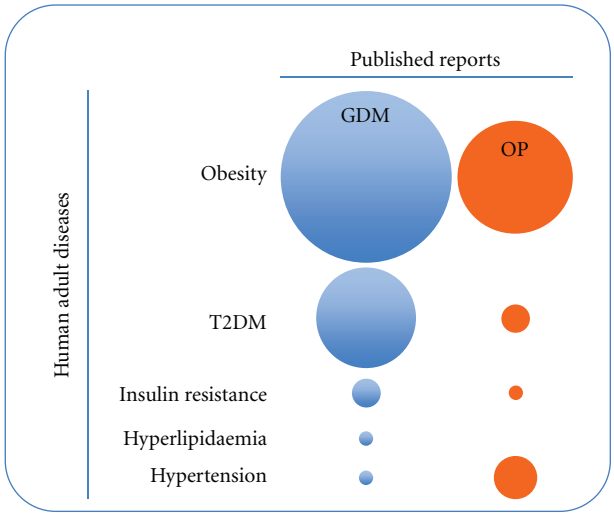


Figure 1: Comparison of published reports addressing a potential association of human adult diseases in subjects from pregnancies coursing with gestational diabetes mellitus or obesity in pregnancy. Gestational diabetes mellitus (GDM, column of light-blue circles) and obesity in pregnancy (OP, column of orange circles) are pathological conditions in human subjects. Different number of reports (*x*-axis, *Published reports*), in this cartoon represented as relative size of corresponding light-blue and orange circles, suggest that GDM and OP are differentially associated with increased incidence of human adult diseases (*y*-axis, *Human adult diseases*), such as obesity, type 2 diabetes mellitus (T2DM), insulin resistance, hyperlipidaemia, or hypertension. Data taken from [13, 77, 78, 81, 84, 92, 190, 195–212].

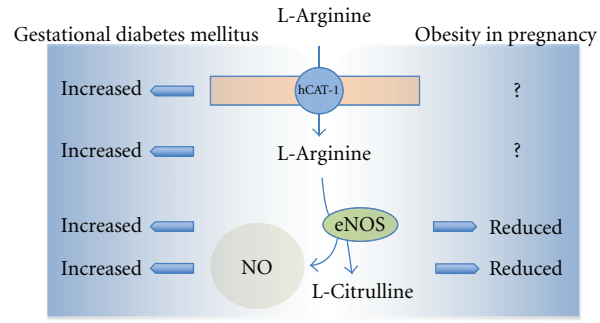


Figure 2: Endothelial L-arginine/NO signalling pathway in gestational diabetes mellitus and obesity in pregnancy. In human endothelial cells L-arginine is taken up via cationic amino acid transporters 1 (hCAT-1) accumulating this amino acid in the intracellular space. L-Arginine is then metabolized by the endothelial nitric oxide synthase (eNOS) into L-citrulline and nitric oxide (NO) as a co-product. Gestational diabetes mellitus is associated with higher expression and activity of hCAT-1 leading to supraphysiological accumulation of L-arginine. This phenomenon results in higher L-arginine metabolism by eNOS due to increased expression and activity of this enzyme leading to overproduction of NO. In endothelial cells from OP there is no information addressing whether this pathological condition alters L-arginine transport and intracellular accumulation, but reduces eNOS expression and activity leading to lower than physiological synthesis of NO.

of obesity in children and adolescents [13], a phenomenon leading to high incidence of type 2 diabetes mellitus (T2DM) [14]. OP is also related to neonatal metabolic compromise, which is already apparent in the offspring at birth, characterized by reduced insulin sensitivity and higher concentrations of inflammatory markers [13]. Surprisingly, few studies have been reported regarding the potential association between GDM and OP as pathological conditions of the mother during pregnancy leading to diseases in the adulthood, the latter most likely programmed during the intrauterine life period (Figure 1). These concepts are discussed in this paper in terms of the fetus-placenta interaction and consequences of GDM and OP leading to fetal vascular disturbances. We also suggest that, based in the discussed observations, our attention should be certainly switched towards a better understanding of the gestational period as a key interventional target in the prevention of adult diseases at the state where fetal programming of adult diseases occurs.

2. Endothelial Dysfunction

Endothelial cells play a crucial role in the regulation of vascular tone through the release of vasoactive substances, including nitric oxide (NO) [4, 5, 15]. In pathological pregnancies, such as GDM [6, 16], intrauterine growth restriction (IUGR) [2], or preeclampsia [17], the synthesis and/or bioavailability of NO are altered leading to changes in blood flow of the human placenta which could result in limiting fetal growth and development [1, 3]. NO is a gas synthesized from the cationic, semiessential amino acid L-arginine in a metabolic reaction leading to equimolar formation of L-citrulline and NO (Figure 2) [5]. This reaction requires the activity of NO synthases (NOS), of which at least three isoforms have been identified, that is, neuronal NOS (nNOS or type I), inducible NOS (iNOS or type II), and endothelial NOS (eNOS or type III) [4, 5, 18]. The NO diffuses from the endothelium to the underlying layer of vascular smooth muscle cells leading to cyclic GMP (cGMP)-dependent vasodilatation [5]. In vessels without innervation, such as the placenta and the distal segment of the umbilical cord [1, 19], vascular tone is regulated by the synthesis and release of vasoconstrictors and vasodilators from the endothelium [3]. The reduced ability of this tissue to stimulate NO-mediated vasodilatation is referred to as endothelial dysfunction [20]. This phenomenon is strongly correlated with cardiovascular disease (CVD) risk factors [21] and with early states of chronic diseases such as hypertension [22], hypercholesterolemia [23], diabetes mellitus [24], hyperhomocysteinaemia [25], and chronic renal [26] and cardiac failure [27]. Interestingly, eNOS expression and activity is highly regulated in human fetoplacental microvascular and macrovascular endothelium, an effect that is differential in these two vascular beds; thus, endothelial dysfunction and perhaps increased risk of appearance of chronic diseases in adulthood will also depends on the type of fetal vascular bed that is altered in diseases of pregnancy [16].

Activity of NOS may depend on the ability of endothelial cells to take up their specific substrate L-arginine via a variety

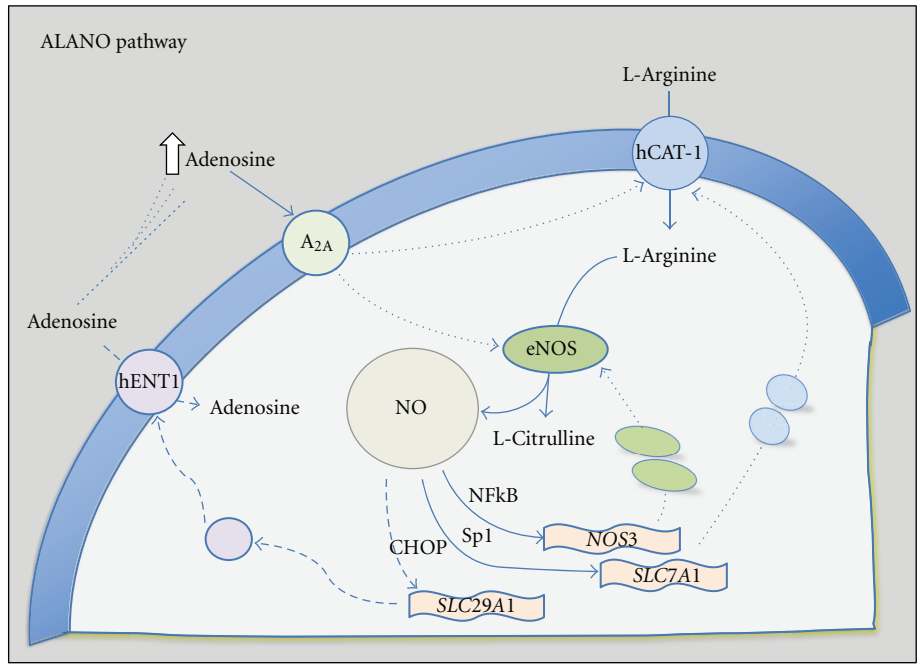


Figure 3: Adenosine/L-arginine/nitric oxide (ALANO) signalling pathway in gestational diabetes mellitus. Human umbilical vein (macrovasculature) and placental microvascular endothelial cells exhibit increased (solid light-blue arrows) L-arginine transport via the cationic amino acid transporters 1 (hCAT-1) but reduced (segmented light-blue arrows) adenosine uptake via the equilibrative nucleoside transporter 1 (hENT1). The latter phenomenon leads to accumulation (white up arrow) of adenosine in the extracellular space, which then stimulates A_{2A} adenosine receptors to activate (dotted light-blue arrows) maximal transport capacity of hCAT-1 and maximal metabolic capacity of endothelial nitric oxide synthase (eNOS) leading to supraphysiological levels of nitric oxide (NO) and L-citrulline. The gas NO activates hC/element-binding protein (CBP) homologous protein 10-C/EBPα transcription factor complex (CHOP) leading to repression of *SLC29A1* gene expression resulting in reduced hENT1 protein synthesis and abundance at the plasma membrane. On the other hand, NO activates the transcription factor-specific protein 1 (Sp1) and nuclear factor κB (NFκB) leading to increase transcription of *SLC7A1* and *NOS3* genes, respectively. This phenomenon results in higher abundance of hCAT-1 and eNOS protein increasing L-arginine transport and NO synthesis. From data in [6, 16, 39, 48, 52, 59].

of membrane transport systems [2, 28–30]. In human endothelial cells, L-arginine is taken up via membrane transport systems grouped as systems y^+, y^+L, $b^{0,+}$, and $B^{0,+}$ [31–33]. System y^+ conforms a family of proteins known as cationic amino acid transporters (CATs) (hereafter referred as "CATs family"), with CAT-1, CAT-2A, CAT-2B, CAT-3, and CAT-4 isoforms [34] whose expression and activity, and the mechanisms modulating these phenomena, have been extensively described [30, 33–35], including in the human placenta [36–38]. Human fetoplacental endothelium takes up adenosine via equilibrative nucleoside transporters (ENTs) [6, 16, 39–41]. Four members of the ENT family of solute carriers (*SLC29A* genes) have been cloned from human tissues, that is, hENT1, hENT2, hENT3 and hENT4 [40, 41]. In primary cultures of human umbilical vein endothelial cells (HUVECs), adenosine transport is mainly (~80%) mediated by hENT1 with the remaining transport (~20%) being mediated by hENT2 [39, 42, 43]. Recent reports show that these proteins are also expressed in human placental microvascular endothelial cells (hPMECs); however, contribution of hENT1 and hENT2 to total adenosine transport in this cell type is similar compared with adenosine transport in HUVEC [17, 44]. hENT3 and hENT4 seem not to play a significant role in endothelium (see [16, 45–47]). Interestingly, adenosine has been suggested as a nucleoside increasing L-arginine/NO signalling pathway in HUVEC [39, 48], hPMEC [17, 49], rat cardiomyocytes in response to the ENTs inhibitor dipyridamole [41], and in skeletal microvascular endothelium in response to hypoxia [50]. This phenomenon has been referred to as endothelial "ALANO" signalling pathway (adenosine/L-arginine/nitric oxide) first characterized in HUVEC from GDM pregnancies [6, 16, 48]. The mechanism involves adenosine activation of A_{2A}-adenosine receptors and increased expression of hCAT-1 and eNOS, via activation of key signalling molecules including mitogen-activated protein kinases of 42 and 44 kDa ($p42/44^{mapk}$) and protein kinase C (PKC) [6, 7, 16, 39, 48]. Thus, a relationship between expression and activity of hCATs and hENTs in HUVEC from GDM has been established (Figure 3) [6, 16, 48, 51, 52].

3. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a syndrome characterized by glucose intolerance leading to maternal hyperglycaemia first recognized during pregnancy [53]. GDM is associated with abnormal foetal development and perinatal complications, such as macrosomia and neonatal

hypoglycaemia [54]. Alterations associated with GDM result from a change in the amount of D-glucose available to the fetus due to alterations in the physiology of the placenta (e.g., increased D-glucose transplacental transport) or by hormone-induced dysfunction (e.g., altered insulin signalling), phenomena that could lead to abnormal growth of the fetus (macrosomia) and perinatal complications [16, 55, 56]. Clinical manifestations of GDM have been attributed mainly to the condition of hyperglycaemia, hyperlipidaemia, hyperinsulinemia, and fetoplacental endothelial dysfunction [54, 55]. Various organs show structural and functional alterations, including endothelial dysfunction of the micro- and macrocirculation in the fetoplacental circulation, in GDM [16, 57]. Increased NO synthesis has also been reported in human placental veins and arteries [58] and in primary cultures of HUVEC [7, 51, 59] isolated from pregnancies with GDM (Table 1). Thus, vascular dysfunction resulting from this syndrome may be a consequence of a functional dissociation between the synthesis of NO and/or its bioavailability to the vascular endothelium and smooth muscle in the human placenta circulation. Even when the GDM-associated endothelial dysfunction regards altered endothelial L-arginine/NO signalling pathway, most studies regarding the mechanisms behind these effects of GDM are not conclusive. However, it is conceivable that these alterations are the result of alterations in multiple, rather than single, metabolic mechanisms including sensitivity of the human fetal endothelium to vasoactive molecules such as adenosine [39, 48] or insulin [7, 47].

3.1. Endothelial Dysfunction in Gestational Diabetes Mellitus

3.1.1. L-Arginine/NO Signalling Pathway. In primary cultures of HUVEC from GDM, synthesis of NO [7, 39, 59], L-arginine transport [39], and its intracellular concentration [16] are increased (Figure 2). GDM-associated increase of L-arginine transport is due to higher maximal velocity (V_{max}) for transport, most likely resulting from higher hCAT-1 expression [39]. Since general activators of PKC increase L-arginine transport and because activation of $p42/44^{mapk}$ is increased in response to NO and PKC, the mechanisms by which L-arginine transport is activated in GDM in HUVEC seem to depend on these intracellular signalling molecules.

PKC and $p42/44^{mapk}$ are also involved in the stimulation of L-arginine transport via hCAT-1 by insulin in HUVEC [30, 33, 47, 60]. This phenomenon seems to result from increased *SLC7A1* (for hCAT-1) promoter transcriptional activity via a mechanism involving the zinc finger promoter-selective transcription-factor-specific protein 1 (Sp1) binding to multiple consensus sequences identified between −177 and −105 bp from the ATG (transcription starting sequence) of this gene [33]. Insulin causes relaxation of human umbilical vein rings in an endothelium- and hCAT-like transport activity-dependent manner [33]. Since this vascular response is found using physiological plasma concentrations of insulin (~0.01–0.1 nM), it is feasible that *SLC7A1* expression and most likely hCAT-1 activity are under tonic regulation by physiological insulinemia in human umbilical veins. Insulin-induced umbilical vein relaxation was lower in vessels from GDM compared with normal pregnancies [7]. This phenomenon could be the result of a less reactive umbilical vein, perhaps due to tonic and basally increased vasodilation due to overrelease and/or accumulation of adenosine at the umbilical vein blood [7]. In addition, it is known that insulin effect in patients with insulin resistance is improved by infusion of adenosine receptor agonists suggesting that insulin biological effects could be facilitated upon adenosine receptor activation [61]. This mechanism is also plausible in the human fetoplacental circulation where activation of adenosine receptors is also, apparently, facilitating insulin-increased L-arginine/NO signalling pathway [47]. Altogether these findings could be crucial for fetal insulin modulation of endothelial-derived NO synthesis in human umbilical vessels from pregnancy diseases associated with hyperinsulinemia, such as GDM, and other states of insulin resistance [6, 7, 16, 30, 47].

3.1.2. Adenosine Transport. HUVEC from GDM also exhibit reduced adenosine transport (Figure 3) [6, 16]. GDM effect on adenosine uptake is proposed to result from a lower hENT1 transport capacity (V_{max}/K_m) due to reduced V_{max} rather than altered intrinsic properties (i.e., unaltered apparent K_m) of this type of nucleoside transporters [7, 51, 59]. Since adenosine uptake efficiency (i.e., adenosine molecules per transporter per cell per second) is unaltered in HUVEC from GDM [62], reduced hENT1 expression could explain this effect of GDM. Alternatively, a lower number of nucleoside-binding sites per endothelial cell (~50%) have been estimated in HUVEC from GDM compared with cells from normal pregnancies [62]. In addition, an apparent recycling of hENT1 from the plasma membrane to perinuclear location has been shown in this cell type [63, 64]. Thus, not only a reduced activity and expression but also hENT1 recycling could be a mechanism involved in GDM altered adenosine transport in human fetal endothelium [16, 65, 66]. It is also known that NO inhibits *SLC29A1* (for hENT1) promoter transcriptional activity in HUVEC from GDM, where a higher NO synthesis due to eNOS activation (phosphorylation of eNOS at Ser^{1177} residue) [39] as well as increased total eNOS expression [59] is reported. The *SLC29A1* promoter region spanning from −2154 to −1810 bp from the ATG contains sequence(s) for inhibitory transcription factor(s) leading to downregulation of this gene expression in HUVEC from GDM [59]. Interestingly, GDM effect requires activation of the NO-dependent repressive transcription factors complex conformed by hC/element-binding protein homologous protein 10 (CHOP)-CCAAT/enhancer-binding protein α (C/EBPα) (hCHOP-C/EBPα) [51]. These regulatory mechanisms of hENT1 expression and/or intracellular localization could be key events to understand the recently reported GDM-increased plasma adenosine concentration (~600 nM) in umbilical vein blood [7] compared with normal pregnancies (~350 nM) [7, 67–69]. Reduced expression and/or activity of hENTs is a phenomenon that could also explain the elevated extracellular adenosine concentration detected in the culture medium of HUVEC from GDM (~900–2,000 nM) [7] compared with normal (~50–500 nM) pregnancies [7, 69].

Table 1: Effect of GDM, obesity, and hypercholesterolaemia on ALANO signalling pathway.

Element	Pregnancy			Nonpregnancy					
	GDM			Obesity			Hypercholesterolemia		
	Cell type	Effect	References	Cell type	Effect	References	Cell type	Effect	References
hENT1 expression	HUVEC	Reduced	[7, 39, 51]						
	hPMEC	Reduced	[16, 44]						
hENT1 activity	HUVEC	Reduced	[7, 39, 51]						
	hPMEC	Reduced	[16, 44]						
hENT2 expression	HUVEC	Unaltered	[16]						
	hPMEC	Reduced	[16, 44]						
hENT2 activity	HUVEC	Unaltered	[16]						
	hPMEC	Reduced	[16, 44]						
Extracellular adenosine	HUVEC	Increased	[7, 48]						
hCATs, expression	HUVEC	Increased	[39]	hP	Reduced	[213]	EAhy926	Increased	[128]
							rAR	Increased	[127]
hCATs, activity	HUVEC	Increased	[39]	hP	Reduced	[213]	EAhy926	Increased	[128]
							rAR	Reduced	[127]
							bAEC	Reduced	[214]
							pAEC	Reduced	[215]
							HUVEC	Unaltered	[216]
							HUVEC	Unaltered	[217]
eNOS expression	HUVEC	Increased	[39, 51]	hVEC	Unaltered	[173]	hSVEC	Reduced	[129]
	hPT	Increased	[218]	mVEC	Increased	[219]	rbAS	Reduced	[131]
				hAd	Increased	[220]	HUVEC	Reduced	[130]
				hHep	Unaltered	[221]			
eNOS activity	HUVEC	Increased	[7, 39, 51]	hVEC	Reduced	[173]	hSVEC	Reduced	[129]
	hVT	Unaltered	[222]	mVEC	Reduced	[219]	rbAR	Reduced	[131]
				mHep	Reduced	[223]	HUVEC	Reduced	[130]
				hP	Unaltered	[213]	pAEC	Reduced	[215]
NO level	HUVEC	Increased	[11]	*	Increased	[221]	hSVEC	Reduced	[129]
Arginase 1				mHep	Increased	[223]			
Arginase 2							hAEC	Increased	[136–138]
							mAEC	Increased	[137, 138]

hENT1: human equilibrative nucleoside transporter 1; hENT2: human equilibrative nucleoside transporter 2; hCATs: human cationic amino acid transporters; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; HUVEC: human umbilical vein endothelial cell; hPMEC: human placental microvascular endothelial cell; hPT: human placental tissue; hVT: human villous tissue; hP: human platelets; hVEC: human vascular endothelial cell; mVEC: mouse vascular endothelial cell; hAd: human adipocyte; hHep: human hepatocyte; mHep: mouse hepatocyte; EAhy 926: human endothelial cell line EAhy 926; rAR: rat aortic ring; bAEC: bovine aortic endothelial cell; pAEC: porcine aortic endothelial cell; hSVEC: human saphenous vein endothelial cell; rbAS: rabbit aortic segment; rbAR: rabbit aortic ring; hAEC: human aortic endothelial cell; mAEC: mouse aortic endothelial cell; *measurement performed in human serum.

Insulin also reduces hENT1-mediated adenosine transport in HUVEC from normal pregnancies but restores GDM-associated reduced hENT1 expression and activity in this cell type [7, 70]. One of the proposed mechanisms accounting for this beneficial effect of insulin on adenosine transport is an activation of A_{2A}-adenosine receptors by extracellular adenosine, which is increased due to reduced hENT1 transport activity in this cell type. In addition, a role for a differential expression of insulin receptor isoforms A (IR-A) and B (IR-B) in HUVEC from GDM is proposed [7]. In this phenomenon insulin would be acting as a factor that restores a potential GDM-associated metabolic phenotype (i.e., preferential activation of $p42/44^{mapk}$ over Akt pathways) to a normal, mitogenic phenotype (i.e., preferential activation of Akt over $p42/44^{mapk}$ pathways) by restoring IR-A expression to values in HUVEC from normal pregnancies [7]. Similar findings have been recently reported for endothelial cells from the microcirculation of the human placenta from GDM pregnancies, where instead a differential role for insulin receptor isoforms is played as modulator of hENT2-mediated adenosine transport [39].

In a recent study it has been proposed that diabetes mellitus is not triggered in experimental animals where arginases activity is increased, a phenomenon proposed to be due to reduced NO synthesis [71]. These findings highlight the importance of the counterregulatory effect of arginases and NOS in pathologies where vascular tone regulation is altered [72]. It is likely that increased arginase activity leads to lower L-arginine bioavailability for eNOS impairing NO synthesis in the endothelium (see Figure 4). Interestingly,

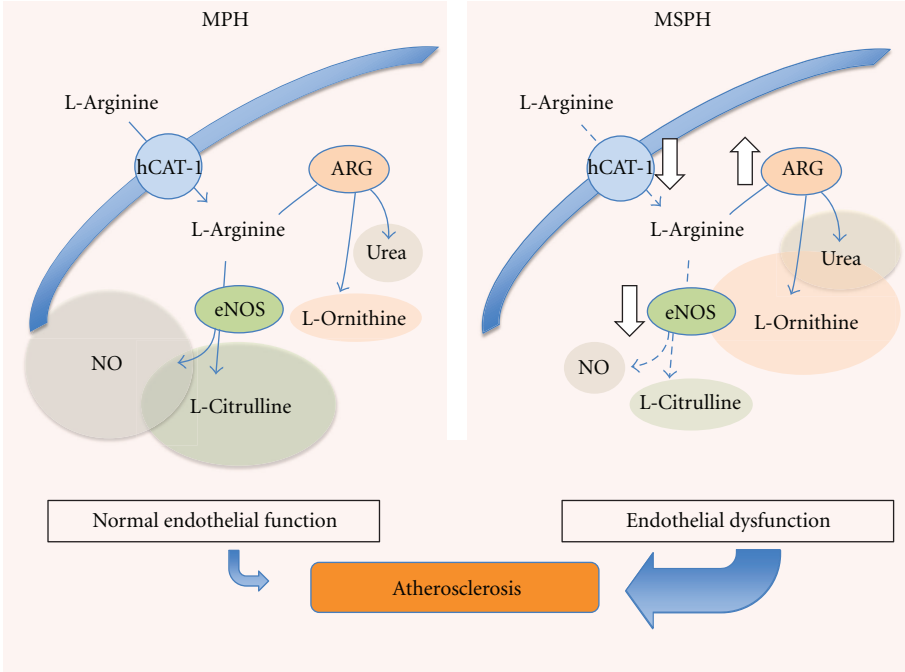


Figure 4: L-Arginine metabolism in hypercholesterolaemia. In human endothelial cells, L-arginine is taken up via cationic amino acid transporter 1 (hCAT-1) which is then metabolized by either the endothelial nitric oxide synthase (eNOS) into L-citrulline and nitric oxide (NO), or via arginases (ARG) into L-ornithine and urea, phenomena conforming a normal endothelial function phenotype. These mechanisms occur in a condition recognized as maternal physiological hypercholesterolaemia (MPH), which has been shown to be associated with early states of fetal vasculature atherosclerosis. However, in a state of maternal supraphysiological hypercholesterolaemia (MSPH) (see text), hCAT-1 and eNOS expression and activity are reduced (white down arrow) leading to reduced (segmented light-blue arrows) L-arginine uptake and NO synthesis, respectively. However, a higher (white up arrow) expression and activity of ARG (most likely arginase 2) leads to increased formation of L-ornithine and urea. The alterations seen in endothelial cells from pregnancies with MSPH result in endothelial dysfunction contributing in a larger proportion to fetal vasculature atherosclerosis compared with MPH. From data in [129, 130, 136, 138].

exogenous L-citrulline, but not L-arginine, and inhibition of arginases induce a diabetic phenotype in rats [71]. Therefore, it is also feasible that recycling of L-citrulline to L-arginine could also be involved in this phenomenon. The fact that L-arginine does not induce diabetes could mean that L-arginine availability for NOS is compartmentalized at such degree that it could not reach appropriate concentrations to activate NOS (K_m of eNOS for L-arginine ranges 1–10 μM) [5], thus limiting the use of this amino acid in the treatment of GDM. What will be the impact of these mechanisms in the fetoplacental circulation, and whether these mechanisms will be associated with programming of adulthood diseases, is unknown.

3.2. Dyslipidaemia. GDM is a pathological condition also characterized by maternal dyslipidaemia, alteration directly affecting fetal development and growth [56]. Dyslipidaemia is defined as elevated levels of triglycerides (hypertriglyceridemia) and total blood cholesterol (hypercholesterolemia), including increased low-density lipoprotein (LDL) and reduced high-density lipoprotein (HDL) levels [73]. This phenomenon is associated with the development of endothelial dysfunction and atherosclerosis (a progressive disease characterized by formation of lipid plaques in arteries) [73, 74]. Dyslipidaemia is the main risk factor for development of CVD [73, 75, 76]. Additionally, GDM is a risk factor to fetal programming due apparently to metabolic syndrome [77–79] and, thus, predisposes to an accelerated development of CVD in adult life [78–83]. Interestingly, most of pregnancies with GDM course with dyslipidaemia, thus making feasible a pathological link (i.e., most likely potentiation) between dyslipidaemia in GDM pregnancies and development of CVD later in life. In fact, GDM could play a role in fetal programming of adult CVD not only by alterations in endothelial function of the placenta (mainly triggered by hyperinsulinemia, hyperglycaemia, and changes in nucleoside extracellular concentration) but also by dyslipidaemia associated with this pathology [79, 84].

3.2.1. Hypertriglyceridemia. Pregnancy is a physiological condition characterized by a progressive weeks of gestation-dependent increase (reaching 100–200%) in the maternal blood level of triglycerides [85, 86]. These changes promote accumulation of maternal fat stores in early and mid pregnancy, so to metabolize and use it in late pregnancy. The very-low-density lipoprotein (VLDL) is the type of

triglycerides carrier that increases in major proportion in the plasma in hypertriglyceridemia. This phenomenon results from an enhanced VLDL production by the liver and decreased removal of this lipoprotein from the circulation as a consequence of pregnancy-associated hormonal changes, including insulin-resistant condition and elevated plasma oestrogen [85, 87]. The characteristic fetal macrosomia in GDM is also a phenomenon related with alterations in lipid metabolism leading to increased supply of nutrients to the fetus favouring its growth [88]. The association between dyslipidaemia and macrosomia regards hypertriglyceridemia more than hypercholesterolemia; in fact, a positive correlation between maternal triglycerides and neonatal body weight or fat mass has been found in GDM [86, 88, 89]. Furthermore, since triglycerides cross the placenta [1] and contribute to fetal macrosomia [87], maternal plasma concentration of these lipids in the third trimester of gestation, which could result from higher concentration of fatty acids derived from maternal triacylglycerol, is considered as a strong predictor of birth weight in women with GDM [90–92]. This phenomenon is related with altered placenta expression of key proteins involved in *de novo* lipid synthesis (fatty acid synthase and sterol regulatory element-binding protein 2) [93], triglycerides metabolism (placental fatty acid-binding protein) [94, 95], and genes related with placental lipid pathways accounting for placental lipid metabolism and transport (e.g., *PLA2G5* for phospholipase A_2, *LPL* for lipoprotein lipase, *FACL3* for fatty acid-coenzyme A ligase) [96]. It is accepted that regulation of these genes in GDM alters placenta and fetus lipid metabolism leading to altered fetal development and size, a condition potentiating fetal hyperinsulinemia's biological effects and contributing to the development of the metabolic syndrome and CVD later in life [79, 96].

3.2.2. Hypercholesterolemia. Pregnancy is also characterized by a progressive and weeks of gestation-dependent increase (40%–50%) in the maternal blood level of cholesterol [85, 97, 98]. This phenomenon is known as maternal physiological hypercholesterolemia in pregnancy (MPH) and is considered to be an adaptive response of the mother to satisfy the high lipids demand by the growing fetus [85, 86]. However, when a maternal misadaptation to the cholesterol demands by the fetus occurs, a group of these women develop a pathological condition referred to as maternal supraphysiological hypercholesterolemia (MSPH). This condition is characterized by maternal blood cholesterol level to be over the 95th percentile or following the establishment of a cut-point >280 mg/dL [93, 99–101]. Sources of cholesterol for fetal metabolism along with endogenous production by fetal tissues include transplacental mother-*to*-fetus transport of maternal cholesterol [93, 100–106]. Although lipid traffic through the placenta is restrictive, a correlation between maternal and fetal blood cholesterol in the first and second trimesters of pregnancy has been established [100, 107]. These studies suggest that maternal cholesterol level alters normal development of the fetus. In fact, it has been reported that, due to altered lipid metabolism in the placenta as a result of high maternal blood cholesterol, atherogenesis, a clinical complication commonly appearing in adults, probably begins in fetal life with likely similar factors altered in the mother, the fetus, and the placenta (see Figure 5) [100, 108–111]. This phenomenon was for the first time referred to as the "foetal hypothesis of atherosclerosis" [100, 112]. Interestingly, a strong correlation between maternal cholesterolaemia before and during pregnancy and the size of atherosclerotic lesions in arteries of fetus, children, and young adults has been shown [100, 101, 111, 112]. This is apparently crucial regarding fetal programming of CVD [109–113]. Potential clinical implications for this foetal hypothesis of atherosclerosis were further contextualised with the FELIC ("Fate or Early Lesions in Children") study [101] where the possibility of applying a therapy to mothers with hypercholesterolaemia during pregnancy complemented with described pathogenic insights in the primary prevention of CVD, including stem cell therapy [114], is suggested as a potential way to improve health in their children [101]. Alternatively, C-reactive protein blood levels were described as higher in mothers with hypercholesterolaemia during pregnancy, and this finding was proposed to be used as a predictor of increased atherogenesis in children [115]; however, even when this information is of relevance for preventive medicine, maternal cholesterolaemia seems to be a stronger predictor.

Placental vascular dysfunction, including altered macro- and microvascular endothelial altered function, is associated with higher risk of developing CVD in adulthood [16, 57]. Cumulative evidence shows that high levels of blood cholesterol modify the endothelial function in different vascular beds [116], mostly associated with reduced vascular NO bioavailability and elevated oxidative stress (Table 1). Unfortunately, nothing is reported regarding whether abnormal maternal blood cholesterol level, including MSPH, leads to placental vascular endothelial dysfunction [109, 117]. GDM correlates with placental macro- and microvascular endothelial dysfunction [16], also considered as early marker of atherosclerosis [77]. Neonates with macrosomia from GDM pregnancies show a significant increase in the aortic intima-media thickness and higher lipid content, both conditions considered as subclinical markers of atherosclerosis [110, 118] and that will potentially increase the atherosclerotic process later in life. Nothing is yet available regarding the potential effect of MSPH in normal or GDM pregnancies regarding development of atherosclerosis in the fetoplacental vasculature in humans [16, 118]. Preliminary findings from our group suggest that MSPH is associated with reduced (in fact almost abolished) vasodilatation of human umbilical vein rings in response to insulin (Figure 6), a phenomenon that could be mediated by endothelial dysfunction since NO synthesis is also altered in HUVEC from these patients [119]. Thus, we speculate that MSPH becomes a pathological condition triggering potentiation of GDM effect on fetal programming of CVD.

Reduced vascular NO bioavailability and elevated oxidative stress alter vascular reactivity in the placenta [120], as well as in children [121, 122] and adults [120, 123–125], phenomena including downregulation of L-arginine transport and eNOS activity in endothelial cells. Several

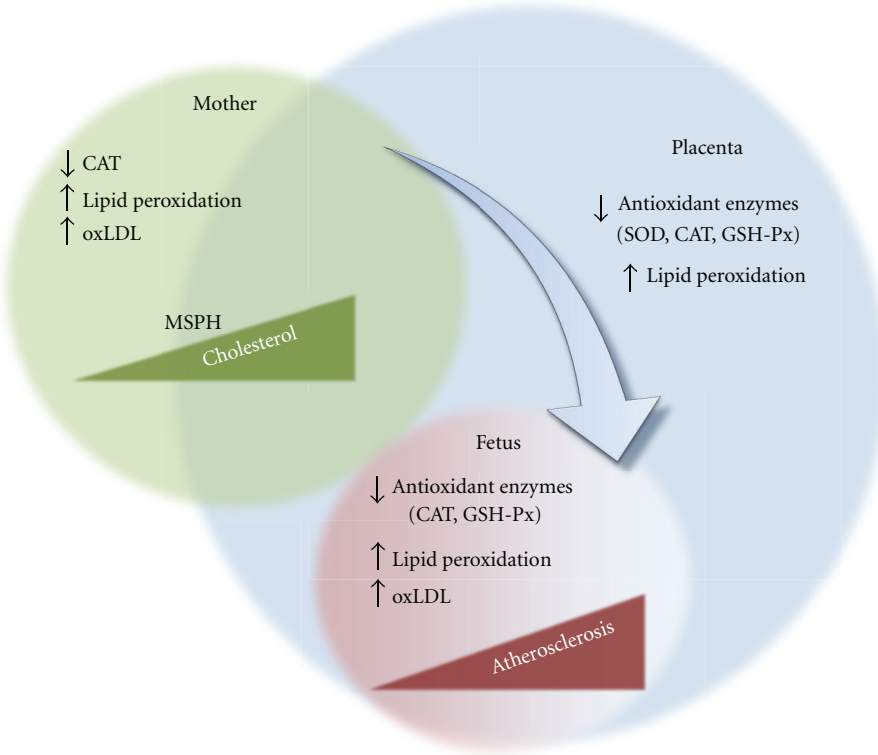


Figure 5: Potential pathophysiological interaction between the mother, the placenta, and the fetus in fetal atherosclerosis. Maternal factors, including reduced (↓) catalase (CAT) activity, increased (↑) lipid peroxidation, and oxidized low density lipoproteins (oxLDL), associated with increased cholesterol content at the mother circulation, generate a state of maternal supraphysiological hypercholesterolaemia (MSPH). This phenomenon leads to similar alterations in the placenta (reduced CAT, superoxide dismutase (SOD), glutathione-peroxidase (GSH-Px) activity) and the fetus (with reduced CAT and GSH-Px and increased lipid peroxidation and oxLDL). Therefore, atherosclerosis in the fetus is identified. Data taken from [88, 100, 101, 109, 110].

alterations caused by hypercholesterolemia could explain these changes in vascular reactivity [126]. To date, (a) cholesterol-enriched diet [127] or oxidized low-density lipoproteins (oxLDLs) [128] cause a posttranscriptional downregulation of hCATsmediated L-arginine transport in rat aortic rings and in the human endothelial cell line EAhy926, (b) hypercholesterolemia leads to reduced NOS expression in human saphenous vein endothelial cell, rabbit aortic segments, and HUVEC [129–131], the latter likely due to increased expression of eNOS mRNA destabilizing cytosolic proteins [130, 131], and (c) eNOS cofactor tetrahydrobiopterin (BH_4) expression is reduced in mice and rabbit aortic rings [132, 133] most likely due to downregulation of guanosine triphosphate cyclohydrolase I (GTPCH, a key enzyme involved in the BH_4 synthesis) [134, 135]. In addition, hypercholesterolemia is also associated with increased expression and activity of arginases resulting in reduced NO synthesis in human and mice aortic endothelial cells [136–138]. Preliminary results show that in fact arginase II protein abundance is increased in HUVEC from patients with MSPH compared with normal pregnancies (A. Leiva, P. Casanello, and L. Sobrevia, *unpublished results*). Therefore, we speculate that similar mechanisms may be either triggered or potentiated by MSPH with direct consequences in the fetoplacental endothelial L-arginine/NO pathway (Figure 4), a phenomenon not at all evaluated in pregnancies coursing with GDM [16, 86].

4. Obesity in Pregnancy

Obesity is a syndrome estimated to be pandemic with a large fraction of children now diagnosed as obese, where causes, other than malnutrition after birth, are not fully explanatory [139]. Obesity is a pathology resulting from a misbalance between the energy intake and energy used, with an overstorage of lipids in adipose tissue [140]. This pathology also courses with systemic metabolic misbalance leading to occurrence of multiple complications, such us dyslipidaemia and insulin resistance [141], and endothelial dysfunction leading to hypertensive disorders (Figure 1) [142, 143]. Incidence of obesity in the world is currently increasing reaching up to ~12% of the population [143]. Worryingly, increased obesity incidence includes ~29% of women in their reproductive age [144]. Much evidence now available involves differential contribution of genetic and environmental factors in the development of obesity, diabetes mellitus, or CVD. Thus, prevention of childhood and adult obesity may require beginning even before conception [145–147].

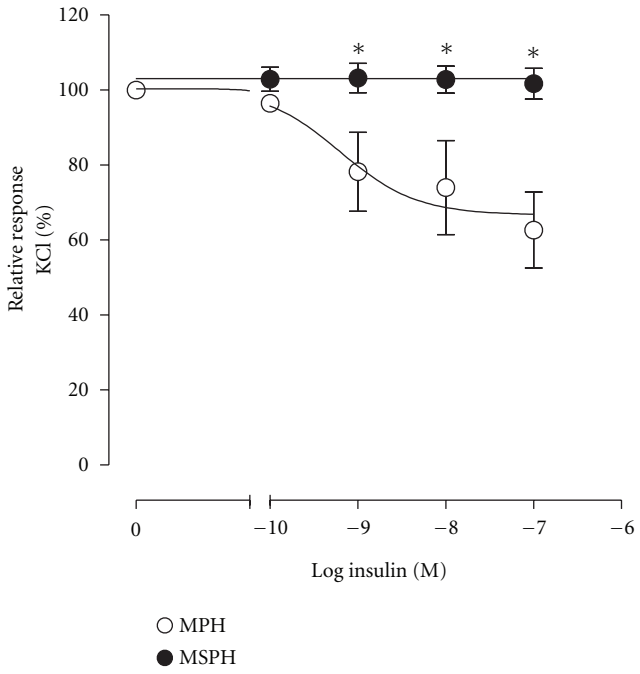


Figure 6: Insulin effect on human umbilical vein ring reactivity. Endothelium-intact human umbilical vein rings were isolated from umbilical veins taken from pregnancies with maternal physiological hypercholesterolaemia (MPH) or maternal supraphysiological hypercholesterolaemia (MSPH). Umbilical vessel ring segments (2–4 mm length) were mounted in a myograph for isometric force measurements with optimal diameter adjusted from maximal active response to 62.5 mM KCl as previously described [28, 107]. Acute response to insulin (3 minutes) was determined in KCl-preconstricted vessels in preparations incubated in Krebs. Values are mean ± SEM ($n = 7$). $^*P < 0.05$ versus corresponding values in MPH.

Obesity in pregnancy is associated with fetal mortality and morbidity, congenital malformations, macrosomia, and increased incidence of caesarean delivery [148–151], thus making this syndrome a condition that once declared in pregnancy alters foetal growth and development. Even when an inflammatory profile in placental tissue from obese women has been described [152–154], the consequences of OP on fetoplacental vasculature function, including expression and function of the endothelial L-arginine/NO signalling pathway, remain mostly unknown (Figure 2, Table 1) [16]. Even when GDM [6, 16, 56, 155] and obesity [142, 156, 157] are syndromes associated with altered human vascular function, there are no studies addressing a potential link between placental dysfunction in GDM and OP. However, it is known that OP is associated with higher risk of developing GDM [158], a possibility supported by findings showing that OP correlates with overgrown fetuses [149], intrauterine growth restriction [154], and preeclampsia [159–161]. These results are demonstrative that OP is a key risk factor for pregnancy and fetal development, a condition that could lead to programming of diseases of the adulthood (Figure 1).

4.1. Endothelial Dysfunction in Obesity in Pregnancy. Several studies associate obesity with chronic inflammation since blood markers, such as the proinflammatory cytokine interleukin 6 (IL-6) and tumour necrosis factor α (TNFα), are increased in these patients [162–166]. The endothelium is the first cell line exposed to these cytokines [167–170] leading to altered eNOS expression and activity and reduced NO bioavailability [171–174]. Moreover, placentas from patients with OP exhibit a higher inflammatory profile with increased expression of interleukin 1 (IL-1), IL-8, and chemoattractant protein 1, compared with lean women [153]. These findings are complemented by reports showing obesity-associated increase of IL-6 and TNFα level, with higher heterogeneous macrophage infiltration in the human placenta [152]. In addition, in a sheep model of OP describing this inflammatory profile, JNK and NFκB signalling pathway involvement in the placental tissue has been reported [175]. Thus, OP could become a condition altering placental endothelial function with consequences to the fetus at birth and potentially in the adulthood.

Leptin, a hormone whose circulating level is increased in obesity [176], increases system A transport activity through activation of STAT3 and activation of JAK-STAT signalling pathway in human placental villous [177]. However, hyperleptinaemia in obese pregnant women was also shown to correlate with reduced activity of system A, an effect most likely due to increased leptin resistance by the placental tissue [178]. Regarding nucleoside transport, there are no studies addressing this phenomenon, including hENT activity and/or expression, in obese subjects, including pregnant women [142]. Interestingly, NO level is higher in obese subjects [179] and rats [180], and the transcription factor complex hCHOP-C/EBPα, known to cause NO-dependent downregulation of *SLC29A1* expression in HUVEC from GDM pregnancies (see above) [51], is also expressed in human adipocytes and involved in the downregulation of expression of other membrane transporters, such as *SCL2A4* (for GLUT4) [181]. In addition, obesity is also associated with altered insulin signalling in several tissues and activates MAPK signalling cascades enhancing insulin resistance [182]. Even when the above-described mechanisms are involved in downregulation of hENT1 expression in the human placental vascular endothelium from GDM, nothing is reported regarding OP effect in this phenomenon.

4.2. Postnatal Outcome in Offspring in Obesity in Pregnancy. Prepregnancy obesity and excessive gestational weight gain have been implicated in an intergenerational "vicious cycle" of obesity, since overweight or obese women give birth to macrosomic girls, who are more likely to become obese themselves and deliver large-sized neonates [183]. In fact, gestational weight gain and birth weight were directly associated with the body mass index and the risk of obesity in adolescence [184, 185]. The relationship described was independent of parental characteristics, potentially mediating peripartum factors, child obesogenic behaviour, and weight at birth, suggesting a role of the intrauterine environment on long-term offspring weight regulation. Interestingly, an association between weight gain of the mother during

pregnancy and increased risk of greater adiposity in the offspring has been shown at ages of infancy as early as 7 [186] or 3 years old [187]. Considering the high prevalence of OP and its potential association with GDM [158], there is an increasing interest in considering a potentially negative influence of maternal overnutrition and raised birth weight on the risk of disease in childhood and adulthood [148, 183, 188]. Children of obese women exhibiting increased risk of diabetes in pregnancy are more likely to develop insulin resistance later in life [189] (Figure 1). An association between maternal weight gain during pregnancy and prepregnancy weight with offspring cardiovascular risk factors in 9 years old children has been proposed (Avon Longitudinal Study of Parents and Children, ALSPAC) [190]. This study shows that women gaining more than recommended weight during gestation were more prone to have offspring with greater body mass index, waist, fat mass, leptin, systolic blood pressure, C-reactive protein, and interleukin-6 levels but lower HDL cholesterol and apolipoprotein A levels than women with a physiological weight gain. Additionally, greater prepregnancy weight was independently associated with greater offspring adiposity and adverse cardiovascular risk factors, agreeing with previous studies [191–195]. Epidemiological studies show that OP increases the incidence of metabolic syndrome in children [188]. Interestingly, OP is related to neonatal metabolic compromise already apparent at birth, characterized by reduced insulin sensitivity and increased serum inflammatory markers [13]. Since OP effect on the susceptibility to obesity in offspring is apparently independent of GDM, as obese women with normal blood glucose have babies with increased adiposity [196], OP and excessive maternal weight gain during pregnancy are independent factors leading to increased risk of obesity, insulin resistance, and early markers of CVD in the offspring. All this evidence shifts our attention towards the gestational period as an extremely key interventional target in the prevention of obesity and associated consequences such as insulin resistance and cardiovascular risk.

4.2.1. Mechanisms of Adverse Postnatal Outcome. The molecular mediators and signalling pathways from the mother to program the metabolic phenotype (i.e., obesity and insulin resistance) of the developing offspring are not fully elucidated. Hormones, such as leptin and insulin, or nutrients, such as D-glucose, free fatty acids, and triglycerides, and multiple inflammatory cytokines could be implicated. During normal intrauterine life, maternal insulin does not cross the placenta, whereas maternal D-glucose is actively transferred to the fetus [197]. The developing fetal pancreas responds to a D-glucose load by increasing synthesis and release of insulin, which acts as a fetal growth hormone. This is the basic concept of the "Pedersen's hyperglycaemia-hyperinsulinism hypothesis" (where fetal overgrowth due to hyperinsulinemia in response to increased transplacental D-glucose transfer is proposed, as recently reviewed [224]) explaining observations showing that offspring of diabetic mothers exhibit high birth weight [225]. Further analysis expanded this theory to include the possibility that other insulin secretagogues, including free fatty acids, ketone bodies, and amino acids [197]. Maternal overnutrition produces hyperglycaemia, which leads to increased fetal insulin secretion in a similar manner as seen in GDM [226]. Thus, secondary fetal hyperinsulinemia is believed to be involved in the intrauterine programming of obesity and diabetes [188]. Prospective studies indicate that at birth and at 6 years old the greatest increase in weight to height relation (relative obesity) was seen in children who experienced the greatest exposures to insulin in uterus (as judged by amniotic fluid insulin concentration) [197].

Leptin is also implicated in programming obesity. In humans, leptin is increased in OP and maternal diabetes and is reduced in intrauterine growth restriction [227]. Although the placental transfer of leptin has been demonstrated *in vivo* [228], it is believed that umbilical blood level of this circulating peptide is a marker of neonatal adiposity more than a relevant modulator of fetal growth [227]. Additionally, several inflammatory cytokines levels are elevated in obese pregnant women [229], changes that are proposed as potential mediators of metabolic programming. Thus, altered metabolic phenotypes, such as obesity and insulin resistance seen in offspring in OP, could partially be explained by the involvement of multiple mediators. Probably, a multifactorial contribution of nutrient- (e.g., D-glucose, fatty acids, amino acids) and hormone- (e.g., insulin, leptin) triggered signals between the obese mother and the developing fetus would better describe the involved mechanisms. Recent studies suggest a strict metabolic control of the mother with GDM in order to overcome the adverse effects of this pathology on the fetal outcome [46, 230–232]. However, adverse effects of GDM environment on fetal tissues persist in time, and multiple studies show increased risk to develop metabolic syndrome in offspring of GDM pregnancies [70, 169, 192]. More recently it was shown that individuals born from GDM pregnancies are prone to develop obesity and D-glucose intolerance compared with offspring from normal pregnancies [198, 199]. However, further research is needed to understand the specific mechanisms of metabolic programming in response to altered intrauterine environment derived from OP and GDM.

5. Concluding Remarks

Fetoplacental endothelial dysfunction is a common characteristic of several diseases in pregnancy limiting the function of the placenta vasculature leading to altered fetal growth and development. These phenomena involve altered capacity of one of the essential functions of the endothelium, that is, the synthesis of vasoactive molecules, including NO. It is now established that GDM and OP are pathological conditions altering hCAT-mediated L-arginine transport and eNOS-synthesis of NO (i.e., the "endothelial L-arginine/NO signalling pathway") in the human fetoplacental vasculature. This phenomenon results in abnormal function of the endothelial L-arginine/NO signalling pathway leading to altered vascular reactivity and changes in umbilical vessels blood flow from and to the fetus with serious consequences on its growth. Abnormalities in the endothelial L-arginine/NO signalling pathway are also dependent of several

regulatory mechanisms, including up-regulation caused by activation of A_{2A}-adenosine receptors in the micro- and macrovasculature of the human placenta in GDM (and perhaps in OP) due to accumulation of extracellular adenosine resulting from reduced hENT expression and activity. Interestingly, GDM pregnancies course with dyslipidaemia (hypertriglyceridemia and hypercholesterolemia) and a pathological link between this condition and development of CVD later in life is likely. A proper management of GDM and OP would be of benefit for the actual newborn's health condition and is crucial for the developing of diseases in the adulthood. Altered function of fetal endothelium at birth is a "metabolic altered state" associated with GDM and OP. We hypothesize that this phenomenon is a potential characteristic (or "*at birth* metabolic marker") that could be considered as predictor of diseases of the adulthood (e.g., CVD, obesity, diabetes mellitus, metabolic syndrome) resulting from a programmed state due to diseases of pregnancy.

Conflict of Interests

Authors declare that they have no conflict of interest.

Acknowledgments

This research supported by Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1110977, 1080534, 11110059), Chile, Programa de Investigación Interdisciplinario (PIA) from Comisión Nacional de Investigación en Ciencia y Tecnología (CONICYT) (Anillos ACT-73), Chile, and Dirección de Investigación (DI-4061-08, DI-340-09, VRA-2009) and Vicerrectoría Académica (Anillos ACT-73 MA Ramírez Postdoctoral Research Associate at CMPL-PRL, Pontificia Universidad Católica de Chile) from Universidad de Antofagasta, Chile. Authors thank Mrs. Ninoska Muñoz for excellent secretarial assistance and the personnel of the Hospital Clínico Pontificia Universidad Católica de Chile labour ward for supply of placentas.

References

[1] L. Sobrevia and P. Casanello, "Placenta," in *Obstetricia*, A. Pérez-Sánchez and E. Donoso-Siña, Eds., pp. 136–176, Mediterráneo, Santiago, Chile, 2011.

[2] P. Casanello, C. Escudero, and L. Sobrevia, "Equilibrative nucleoside (ENTs) and cationic amino acid (CATS) transporters: implications in foetal endothelial dysfunction in human pregnancy diseases," *Current Vascular Pharmacology*, vol. 5, no. 1, pp. 69–84, 2007.

[3] L. Myatt, "Review: reactive oxygen and nitrogen species and functional adaptation of the placenta," *Placenta*, vol. 31, pp. S66–S69, 2010.

[4] L. J. Ignarro and C. Napoli, "Novel features of nitric oxide, endothelial nitric oxide synthase, and atherosclerosis," *Current Diabetes Reports*, vol. 5, no. 1, pp. 17–23, 2005.

[5] S. Moncada and E. A. Higgs, "The discovery of nitric oxide and its role in vascular biology," *British Journal of Pharmacology*, vol. 147, supplement 1, pp. S193–S201, 2006.

[6] F. Westermeier, C. Puebla, J. L. Vega et al., "Equilibrative nucleoside transporters in fetal endothelial dysfunction in diabetes mellitus and hyperglycaemia," *Current Vascular Pharmacology*, vol. 7, no. 4, pp. 435–449, 2009.

[7] F. Westermeier, C. Salomón, M. González et al., "Insulin restores gestational diabetes mellitus-reduced adenosine transport involving differential expression of insulin receptor isoforms in human umbilical vein endothelium," *Diabetes*, vol. 60, no. 6, pp. 1677–1687, 2011.

[8] M. A. Read, I. M. Leitch, W. B. Giles, A. M. Bisits, A. L. Boura, and W. A. Walters, "U46619-mediated vasoconstriction of the fetal placental vasculature in vitro in normal and hypertensive pregnancies," *Journal of Hypertension*, vol. 17, no. 3, pp. 389–396, 1999.

[9] H. K. Eltzschig, "Adenosine: an old drug newly discovered," *Anesthesiology*, vol. 111, no. 4, pp. 904–915, 2009.

[10] D. J. Barker, "Fetal programming of coronary heart disease," *Trends in Endocrinology and Metabolism*, vol. 13, no. 9, pp. 364–368, 2002.

[11] K. L. Thornburg, P. F. O'Tierney, and S. Louey, "Review: the placenta is a programming agent for cardiovascular disease," *Placenta*, vol. 31, pp. S54–S59, 2010.

[12] K. D. Bruce and M. A. Hanson, "The developmental origins, mechanisms, and implications of metabolic syndrome," *Journal of Nutrition*, vol. 140, no. 3, pp. 648–652, 2010.

[13] P. M. Catalano, L. Presley, J. Minium, and S. Hauguel de Mouzon, "Fetuses of obese mothers develop insulin resistance in utero," *Diabetes Care*, vol. 32, no. 6, pp. 1076–1080, 2009.

[14] R. H. Jones and S. E. Ozanne, "Intra-uterine origins of type 2 diabetes," *Archives of Physiology and Biochemistry*, vol. 113, no. 1, pp. 25–29, 2007.

[15] C. L. Wei, W. M. Hon, K. H. Lee, and H. E. Khoo, "Chronic administration of aminoguanidine reduces vascular nitric oxide production and attenuates liver damage in bile duct-ligated rats," *Liver International*, vol. 25, no. 3, pp. 647–656, 2005.

[16] L. Sobrevia, F. Abarzúa, J. K. Nien et al., "Review: differential placental macrovascular and microvascular endothelial dysfunction in gestational diabetes," *Placenta*, vol. 25, pp. S159–S164, 2011.

[17] C. Escudero and L. Sobrevia, "A hypothesis for preeclampsia: adenosine and inducible nitric oxide synthase in human placental microvascular endothelium," *Placenta*, vol. 29, no. 6, pp. 469–483, 2008.

[18] R. M. Barbosa, C. F. Lourenço, R. M. Santos et al., "Chapter 20 *in vivo* real-time measurement of nitric oxide in anesthetized rat brain," *Methods in Enzymology*, vol. 441, pp. 351–367, 2008.

[19] S. B. Fox and T. Y. Khong, "Lack of innervation of human umbilical cord. An immunohistological and histochemical study," *Placenta*, vol. 11, no. 1, pp. 59–62, 1990.

[20] J. Deanfield, A. Donald, C. Ferri et al., "Endothelial function and dysfunction. Part I: methodological issues for assessment in the different vascular beds: a statement by the working group on endothelin and endothelial factors of the European society of hypertension," *Journal of Hypertension*, vol. 23, no. 1, pp. 7–17, 2005.

[21] A. S. Wierzbicki, P. J. Chowienczyk, J. R. Cockcroft et al., "Cardiovascular risk factors and endothelial dysfunction," *Clinical Science*, vol. 107, no. 6, pp. 609–615, 2004.

[22] D. Versari, E. Daghini, A. Virdis, L. Ghiadoni, and S. Taddei, "Endothelium-dependent contractions and endothelial dysfunction in human hypertension," *British Journal of Pharmacology*, vol. 157, no. 4, pp. 527–536, 2009.

[23] P. Libby, P. M. Ridker, and G. K. Hansson, "Progress and challenges in translating the biology of atherosclerosis," *Nature*, vol. 473, no. 7347, pp. 317–325, 2011.

[24] A. Avogaro, G. P. Fadini, A. Gallo, E. Pagnin, and S. de Kreutzenberg, "Endothelial dysfunction in type 2 diabetes mellitus," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 16, supplement 1, pp. S39–S45, 2006.

[25] Z. Cheng, X. Yang, and H. Wang, "Hyperhomocysteinemia and endothelial dysfunction," *Current Hypertension Reviews*, vol. 5, no. 2, pp. 158–165, 2009.

[26] T. Nakagawa, K. Tanabe, B. P. Croker et al., "Endothelial dysfunction as a potential contributor in diabetic nephropathy," *Nature Reviews Nephrology*, vol. 7, no. 1, pp. 36–44, 2011.

[27] K. Enomoto, H. Yamabe, K. Toyama et al., "Improvement effect on endothelial function in patients with congestive heart failure treated with cardiac resynchronization therapy," *Journal of Cardiology*, vol. 58, no. 1, pp. 69–73, 2011.

[28] A. A. Ogonowski, W. H. Kaesemeyer, L. Jin, V. Ganapathy, F. H. Leibach, and R. W. Caldwell, "Effects of NO donors and synthase agonists on endothelial cell uptake of L-Arg and superoxide production," *American Journal of Physiology*, vol. 278, no. 1, pp. C136–C143, 2000.

[29] E. I. Closs, J. S. Scheld, M. Sharafi, and U. Förstermann, "Substrate supply for nitric-oxide synthase in macrophages and endothelial cells: role of cationic amino acid transporters," *Molecular Pharmacology*, vol. 57, no. 1, pp. 68–74, 2000.

[30] L. Sobrevia and M. González, "A role for insulin on L-arginine transport in fetal endothelial dysfunction in hyperglycaemia," *Current Vascular Pharmacology*, vol. 7, no. 4, pp. 467–474, 2009.

[31] R. Devés and C. A. Boyd, "Transporters for cationic amino acids in animal cells: discovery, structure, and function," *Physiological Reviews*, vol. 78, no. 2, pp. 487–545, 1998.

[32] G. E. Mann, D. L. Yudilevich, and L. Sobrevia, "Regulation of amino acid and glucose transporters in endothelial and smooth muscle cells," *Physiological Reviews*, vol. 83, no. 1, pp. 183–252, 2003.

[33] M. González, V. Gallardo, N. Rodríguez et al., "Insulin-stimulated L-arginine transport requires SLC7A1 gene expression and is associated with human umbilical vein relaxation," *Journal of Cellular Physiology*, vol. 226, no. 11, pp. 2916–2924, 2011.

[34] F. Verrey, E. I. Closs, C. A. Wagner, M. Palacin, H. Endou, and Y. Kanai, "CATs and HATs: the SLC7 family of amino acid transporters," *Pflügers Archiv European Journal of Physiology*, vol. 447, no. 5, pp. 532–542, 2004.

[35] C. Flores, S. Rojas, C. Aguayo et al., "Rapid stimulation of L-arginine transport by D-glucose involves p42/44^{mapk} and nitric oxide in human umbilical vein endothelium," *Circulation Research*, vol. 92, no. 1, pp. 64–72, 2003.

[36] J. F. Dye, S. Vause, T. Johnston et al., "Characterization of cationic amino acid transporters and expression of endothelial nitric oxide synthase in human placental microvascular endothelial cells," *The FASEB Journal*, vol. 18, no. 1, pp. 125–127, 2004.

[37] E. Tsitsiou, C. P. Sibley, S. W. D'Souza, O. Catanescu, D. W. Jacobsen, and J. D. Glazier, "Homocysteine transport by systems L, A and y^+L across the microvillous plasma membrane of human placenta," *Journal of Physiology*, vol. 587, no. 16, pp. 4001–4013, 2009.

[38] Y. Arancibia-Garavilla, F. Toledo, P. Casanello, and L. Sobrevia, "Nitric oxide synthesis requires activity of the cationic and neutral amino acid transport system y^+L in human umbilical vein endothelium," *Experimental Physiology*, vol. 88, no. 6, pp. 699–710, 2003.

[39] G. Vásquez, F. Sanhueza, R. Vásquez et al., "Role of adenosine transport in gestational diabetes-induced L-arginine transport and nitric oxide synthesis in human umbilical vein endothelium," *Journal of Physiology*, vol. 560, no. 1, pp. 111–122, 2004.

[40] M. Pastor-Anglada, B. Dérijard, and F. J. Casado, "Mechanisms implicated in the response of system a to hypertonic stress and amino acid deprivation still can be different," *The Journal of General Physiology*, vol. 125, no. 1, pp. 41–42, 2005.

[41] S. A. Baldwin, P. R. Beal, S. Y. Yao, A. E. King, C. E. Cass, and J. D. Young, "The equilibrative nucleoside transporter family, SLC29," *Pflügers Archiv European Journal of Physiology*, vol. 447, no. 5, pp. 735–743, 2004.

[42] C. Aguayo, J. Casado, M. González et al., "Equilibrative nucleoside transporter 2 is expressed in human umbilical vein endothelium, but is not involved in the inhibition of adenosine transport induced by hyperglycaemia," *Placenta*, vol. 26, no. 8-9, pp. 641–653, 2005.

[43] P. Casanello, A. Torres, F. Sanhueza et al., "Equilibrative nucleoside transporter 1 expression is downregulated by hypoxia in human umbilical vein endothelium," *Circulation Research*, vol. 97, no. 1, pp. 16–24, 2005.

[44] C. Salomón, F. Westermeier, P. Casanello, and L. Sobrevia, "Differential modulation of insulin receptor isoforms expression and NOS activity by insulin in human placenta microvascular endothelial cells from gestational diabetes," *Placenta*, vol. 31, 2010.

[45] K. Engel, M. Zhou, and J. Wang, "Identification and characterization of a novel monoamine transporter in the human brain," *Journal of Biological Chemistry*, vol. 279, no. 48, pp. 50042–50049, 2004.

[46] K. Barnes, H. Dobrzynski, S. Foppolo et al., "Distribution and functional characterization of equilibrative nucleoside transporter-4, a novel cardiac adenosine transporter activated at acidic pH," *Circulation Research*, vol. 99, no. 5, pp. 510–519, 2006.

[47] E. Guzmán-Gutiérrez, F. Abarzúa, C. Belmar et al., "Functional link between adenosine and insulin: a hypothesis for fetoplacental vascular endothelial dysfunction in gestational diabetes," *Current Vascular Pharmacology*, vol. 9, no. 6, pp. 750–752, 2011.

[48] R. San Martín and L. Sobrevia, "Gestational diabetes and the adenosine/L-arginine/nitric oxide (ALANO) pathway in human umbilical vein endothelium," *Placenta*, vol. 27, no. 1, pp. 1–10, 2006.

[49] C. Escudero, P. Casanello, and L. Sobrevia, "Human equilibrative nucleoside transporters 1 and 2 may be differentially modulated by A2B adenosine receptors in placenta microvascular endothelial cells from pre-eclampsia," *Placenta*, vol. 29, no. 9, pp. 816–825, 2008.

[50] J. M. Marshall, "The roles of adenosine and related substances in exercise hyperaemia," *Journal of Physiology*, vol. 583, no. 3, pp. 835–845, 2007.

[51] M. Farías, C. Puebla, F. Westermeier et al., "Nitric oxide reduces SLC29A1 promoter activity and adenosine transport involving transcription factor complex hCHOP-C/EBPα in human umbilical vein endothelial cells from gestational diabetes," *Cardiovascular Research*, vol. 86, no. 1, pp. 45–54, 2010.

[52] A. Pandolfi and N. Di Pietro, "High glucose, nitric oxide, and adenosine: a vicious circle in chronic hyperglycaemia?" *Cardiovascular Research*, vol. 86, no. 1, pp. 9–11, 2010.

[53] American Diabetes Association, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 34, supplement 1, pp. S62–S69, 2011.

[54] J. L. Nold and M. K. Georgieff, "Infants of diabetic mothers," *Pediatric Clinics of North America*, vol. 51, no. 3, pp. 619–637, 2004.

[55] M. F. Greene and C. G. Solomon, "Gestational diabetes mellitus—time to treat," *New England Journal of Medicine*, vol. 352, no. 24, pp. 2544–2546, 2005.

[56] G. Desoye and S. Hauguel-De Mouzon, "The human placenta in gestational diabetes mellitus: the insulin and cytokine network," *Diabetes Care*, vol. 30, supplement 2, pp. S120–S126, 2007.

[57] L. Leach, "Placental vascular dysfunction in diabetic pregnancies: intimations of fetal cardiovascular disease?" *Microcirculation*, vol. 18, no. 4, pp. 263–269, 2011.

[58] R. Figueroa, E. Martinez, R. P. Fayngersh, N. Tejani, K. M. Mohazzab-H, and M. S. Wolin, "Alterations in relaxation to lactate and H_2O_2 in human placental vessels from gestational diabetic pregnancies," *American Journal of Physiology*, vol. 278, no. 3, pp. H706–H713, 2000.

[59] M. Farías, R. San Martín, C. Puebla et al., "Nitric oxide reduces adenosine transporter ENT1 gene (SLC29A1) promoter activity in human fetal endothelium from gestational diabetes," *Journal of Cellular Physiology*, vol. 208, no. 2, pp. 451–460, 2006.

[60] M. González, C. Flores, J. D. Pearson, P. Casanello, and L. Sobrevia, "Cell signalling-mediating insulin increase of mRNA expression for cationic amino acid transporters-1 and -2 and membrane hyperpolarization in human umbilical vein endothelial cells," *Pflügers Archiv European Journal of Physiology*, vol. 448, no. 4, pp. 383–394, 2004.

[61] M. Srinivasan, P. Herrero, J. B. McGill et al., "The effects of plasma insulin and glucose on myocardial blood flow in patients with type 1 diabetes mellitus," *Journal of the American College of Cardiology*, vol. 46, no. 1, pp. 42–48, 2005.

[62] L. Sobrevia, S. M. Jarvis, and D. L. Yudilevich, "Adenosine transport in cultured human umbilical vein endothelial cells is reduced in diabetes," *American Journal of Physiology*, vol. 267, no. 1, pp. C39–C47, 1994.

[63] M. Farías, *Intracellular signalling in the reduced expression and activity of the equilibrative nucleoside transporter 1 (hENT1) in human umbilical vein endothelium from gestational diabetes mellitus*, Ph.D. thesis, Pontificia Universidad Católica de Chile, 2008.

[64] L. Sobrevia, C. Puebla, F. Farías, and P. Casanello, "Role of equilibrative nucleoside transporters in fetal endothelial dysfunction in gestational diabetes," in *Membrane Transporters and Receptors in Disease*, L. Sobrevia and P. Casanello, Eds., pp. 1–25, Research Signpost, Kerala, India, 2009.

[65] N. M. Nivillac, K. Wasal, D. F. Villani, Z. Naydenova, W. J. Hanna, and I. R. Coe, "Disrupted plasma membrane localization and loss of function reveal regions of human equilibrative nucleoside transporter 1 involved in structural integrity and activity," *Biochimica et Biophysica Acta*, vol. 1788, no. 10, pp. 2326–2334, 2009.

[66] N. M. Nivillac, J. Bacani, and I. R. Coe, "The life cycle of human equilibrative nucleoside transporter 1: from ER export to degradation," *Experimental Cell Research*, vol. 317, no. 11, pp. 1567–1579, 2011.

[67] Y. Yoneyama, R. Sawa, S. Suzuki et al., "Regulation of plasma adenosine levels in normal pregnancy," *Gynecologic and Obstetric Investigation*, vol. 53, no. 2, pp. 71–74, 2002.

[68] Y. Yoneyama, S. Suzuki, R. Sawa, K. Yoneyama, G. G. Power, and T. Araki, "Increased plasma adenosine concentrations and the severity of preeclampsia," *Obstetrics and Gynecology*, vol. 100, no. 6, pp. 1266–1270, 2002.

[69] M. F. Ethier, V. Chander, and J. G. Dobson Jr., "Adenosine stimulates proliferation of human endothelial cells in culture," *American Journal of Physiology*, vol. 265, no. 1, pp. H131–H138, 1993.

[70] G. Muñoz, R. San Martín, M. Farías et al., "Insulin restores glucose inhibition of adenosine transport by increasing the expression and activity of the equilibrative nucleoside transporter 2 in human umbilical vein endothelium," *Journal of Cellular Physiology*, vol. 209, no. 3, pp. 826–835, 2006.

[71] M. J. Romero, D. H. Platt, H. E. Tawfik et al., "Diabetes-induced coronary vascular dysfunction involves increased arginase activity," *Circulation Research*, vol. 102, no. 1, pp. 95–102, 2008.

[72] S. M. Morris Jr., "Recent advances in arginine metabolism: roles and regulation of the arginases," *British Journal of Pharmacology*, vol. 157, no. 6, pp. 922–930, 2009.

[73] ATP III, "Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.

[74] J. Davignon and P. Ganz, "Role of endothelial dysfunction in atherosclerosis," *Circulation*, vol. 109, no. 23, pp. III27–III32, 2004.

[75] V. L. Roger, A. S. Go, D. M. Lloyd-Jones et al., "Heart disease and stroke statistics-2011 update: a report from the American Heart Association," *Circulation*, vol. 123, pp. e18–e209, 2011.

[76] B. J. Arsenault, S. M. Boekholdt, and J. J. Kastelein, "Lipid parameters for measuring risk of cardiovascular disease," *Nature Reviews Cardiology*, vol. 8, no. 4, pp. 197–206, 2011.

[77] C. M. Boney, A. Verma, R. Tucker, and B. R. Vohr, "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus," *Pediatrics*, vol. 115, no. 3, pp. e290–e296, 2005.

[78] T. D. Clausen, E. R. Mathiesen, T. Hansen et al., "Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 7, pp. 2464–2470, 2009.

[79] T. R. Moore, "Fetal exposure to gestational diabetes contributes to subsequent adult metabolic syndrome," *American Journal of Obstetrics and Gynecology*, vol. 202, no. 6, pp. 643–649, 2010.

[80] B. Isomaa, P. Almgren, T. Tuomi et al., "Cardiovascular morbidity and mortality associated with the metabolic syndrome," *Diabetes Care*, vol. 24, no. 4, pp. 683–689, 2001.

[81] G. M. Egeland and S. J. Meltzer, "Following in mother's footsteps? Mother-daughter risks for insulin resistance and cardiovascular disease 15 years after gestational diabetes," *Diabetic Medicine*, vol. 27, no. 3, pp. 257–265, 2010.

[82] J. Pirkola, M. Vääräsmäki, M. Ala-Korpela et al., "Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle," *American Journal of Epidemiology*, vol. 171, no. 1, pp. 72–82, 2010.

[83] S. Mottillo, K. B. Filion, J. Genest et al., "The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis," *Journal of the American College of Cardiology*, vol. 56, no. 14, pp. 1113–1132, 2010.

[84] E. A. Reece, "The fetal and maternal consequences of gestational diabetes mellitus," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 23, no. 3, pp. 199–203, 2010.

[85] A. Basaran, "Pregnancy-induced hyperlipoproteinemia: review of the literature," *Reproductive Sciences*, vol. 16, no. 5, pp. 431–437, 2009.

[86] E. Herrera and H. Ortega-Senovilla, "Disturbances in lipid metabolism in diabetic pregnancy—are these the cause of the problem?" *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 24, no. 4, pp. 515–525, 2010.

[87] N. F. Butte, "Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus," *American Journal of Clinical Nutrition*, vol. 71, no. 5, pp. 1256–1261, 2000.

[88] A. Zawiejska, E. Wender-Ozegowska, J. Brazert, and K. Sodowski, "Components of metabolic syndrome and their impact on fetal growth in women with gestational diabetes mellitus," *Journal of Physiology and Pharmacology*, vol. 59, supplement 4, pp. S5–S18, 2008.

[89] G. H. Son, J. Y. Kwon, Y. H. Kim, and Y. W. Park, "Maternal serum triglycerides as predictive factors for large-for- gestational age newborns in women with gestational diabetes mellitus," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 89, no. 5, pp. 700–704, 2010.

[90] C. J. Nolan, S. F. Riley, M. T. Sheedy, J. E. Walstab, and N. A. Bescher, "Maternal serum triglyceride, glucose tolerance, and neonatal birth weight ratio in pregnancy: a study within a racially heterogeneous population," *Diabetes Care*, vol. 18, no. 12, pp. 1550–1556, 1995.

[91] M. Kitajima, S. Oka, I. Yasuhi, M. Fukuda, Y. Rii, and T. Ishimaru, "Maternal serum triglyceride at 24–32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens," *Obstetrics and Gynecology*, vol. 97, no. 5, pp. 776–780, 2001.

[92] U. M. Schaefer-Graf, K. Graf, I. Kulbacka et al., "Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus," *Diabetes Care*, vol. 31, no. 9, pp. 1858–1863, 2008.

[93] C. Marseille-Tremblay, M. Ethier-Chiasson, J. C. Forest et al., "Impact of maternal circulating cholesterol and gestational diabetes mellitus on lipid metabolism in human term placenta," *Molecular Reproduction and Development*, vol. 75, no. 6, pp. 1054–1062, 2008.

[94] A. L. Magnusson, I. J. Waterman, M. Wennergren, T. Jansson, and T. L. Powell, "Triglyceride hydrolase activities and expression of fatty acid binding proteins in the human placenta in pregnancies complicated by intrauterine growth restriction and diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 9, pp. 4607–4614, 2004.

[95] C. M. Scifres, B. Chen, D. M. Nelson, and Y. Sadovsky, "Fatty acid binding protein 4 regulates intracellular lipid accumulation in human trophoblasts," *Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 7, pp. E1083–E1091, 2011.

[96] T. Radaelli, J. Lepercq, A. Varastehpour, S. Basu, P. M. Catalano, and S. Hauguel-De Mouzon, "Differential regulation of genes for fetoplacental lipid pathways in pregnancy with gestational and type 1 diabetes mellitus," *American Journal of Obstetrics and Gynecology*, vol. 201, no. 2, pp. 209.e1–209.e10, 2009.

[97] P. Brizzi, G. Tonolo, F. Esposito et al., "Lipoprotein metabolism during normal pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 181, no. 2, pp. 430–434, 1999.

[98] H. J. Avis, B. A. Hutten, M. T. Twickler et al., "Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn?" *Current Opinion in Lipidology*, vol. 20, no. 6, pp. 484–490, 2009.

[99] A. Montes, C. E. Walden, and R. H. Knopp, "Physiologic and supraphysiologic increases in lipoprotein lipids and apoproteins in late pregnancy and postpartum. Possible markers for the diagnosis of "prelipemia"," *Arteriosclerosis*, vol. 4, no. 4, pp. 407–417, 1984.

[100] C. Napoli, F. P. D'Armiento, F. P. Mancini et al., "Fatty streak formation occurs in human fetal aortas and is greatly enhanced maternal, hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atheroeclerotic lesions," *Journal of Clinical Investigation*, vol. 100, no. 11, pp. 2680–2690, 1997.

[101] C. Napoli, C. K. Glass, J. L. Witztum, R. Deutsch, F. P. D'Armiento, and W. Palinski, "Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study," *The Lancet*, vol. 354, no. 9186, pp. 1234–1241, 1999.

[102] K. P. Battaile and R. D. Steiner, "Smith-Lemli-Opitz syndrome: the first malformation syndrome associated with defective cholesterol synthesis," *Molecular Genetics and Metabolism*, vol. 71, no. 1-2, pp. 154–162, 2000.

[103] C. Wadsack, A. Hammer, S. Levak-Frank et al., "Selective cholesteryl ester uptake from high density lipoprotein by human first trimester and term villous trophoblast cells," *Placenta*, vol. 24, no. 2-3, pp. 131–143, 2003.

[104] K. T. Jenkins, L. S. Merkens, M. R. Tubb et al., "Enhanced placental cholesterol efflux by fetal HDL in Smith-Lemli-Opitz syndrome," *Molecular Genetics and Metabolism*, vol. 94, no. 2, pp. 240–247, 2008.

[105] J. Stefulj, U. Panzenboeck, T. Becker et al., "Human endothelial cells of the placental barrier efficiently deliver cholesterol to the fetal circulation via ABCA1 and ABCG1," *Circulation Research*, vol. 104, no. 5, pp. 600–608, 2009.

[106] L. A. Woollett, "Review: transport of maternal cholesterol to the fetal circulation," *Placenta*, vol. 32, supplement 2, pp. S218–S221, 2011.

[107] S. H. Badruddin, R. Lalani, M. Khurshid, A. Molla, R. Qureshi, and M. A. Khan, "Serum cholesterol in neonates and their mothers. A pilot study," *Journal of the Pakistan Medical Association*, vol. 40, no. 5, pp. 108–109, 1990.

[108] A. Liguori, F. P. D'Armiento, A. Palagiano et al., "Effect of gestational hypercholesterolaemia on omental vasoreactivity, placental enzyme activity and transplacental passage of normal and oxidised fatty acids," *An International Journal of Obstetrics and Gynaecology*, vol. 114, no. 12, pp. 1547–1556, 2007.

[109] W. Palinski and C. Napoli, "The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis," *The FASEB Journal*, vol. 16, no. 11, pp. 1348–1360, 2002.

[110] M. R. Skilton, "Intrauterine risk factors for precocious atherosclerosis," *Pediatrics*, vol. 121, no. 3, pp. 570–574, 2008.

[111] C. Napoli, L. O. Lerman, F. de Nigris, M. Gossl, M. L. Balestrieri, and A. Lerman, "Rethinking primary prevention of atherosclerosis-related diseases," *Circulation*, vol. 114, no. 23, pp. 2517–2527, 2006.

[112] C. Napoli and W. Palinski, "Maternal hypercholesterolemia during pregnancy influences the later development of

atherosclerosis: clinical and pathogenic implications," *European Heart Journal*, vol. 22, no. 1, pp. 4–9, 2001.

[113] W. Palinski, E. Nicolaides, A. Liguori, and C. Napoli, "Influence of maternal dysmetabolic conditions during pregnancy on cardiovascular disease," *Journal of Cardiovascular Translational Research*, vol. 2, no. 3, pp. 277–285, 2009.

[114] C. Napoli and F. Cacciatore, "Novel pathogenic insights in the primary prevention of cardiovascular disease," *Progress in Cardiovascular Diseases*, vol. 51, no. 6, pp. 503–523, 2009.

[115] A. Liguori, F. P. D'Armiento, A. Palagiano, W. Palinski, and C. Napoli, "Maternal C-reactive protein and developmental programming of atherosclerosis," *American Journal of Obstetrics and Gynecology*, vol. 198, no. 3, pp. 281.e1–281.e5, 2008.

[116] P. A. Stapleton, A. G. Goodwill, M. E. James, R. W. Brock, and J. C. Frisbee, "Hypercholesterolemia and microvascular dysfunction: interventional strategies," *Journal of Inflammation*, vol. 7, article 54, 2010.

[117] J. A. Joles, "Crossing borders: linking environmental and genetic developmental factors," *Microcirculation*, vol. 18, no. 4, pp. 298–303, 2011.

[118] E. Koklu, M. Akcakus, S. Kurtoglu et al., "Aortic intima-media thickness and lipid profile in macrosomic newborns," *European Journal of Pediatrics*, vol. 166, no. 4, pp. 333–338, 2007.

[119] A. Leiva, E. Guzmán-Gutiérrez, F. Abarzúa, P. Casanello, and L. Sobrevia, "Maternal supraphysiologicalhypercholesterolemia leads to reduced endothelium-dependent vasodilation of umbilical vein and increased L-arginine transport in HUVEC," *Journal of Developmental Origins of Health and Disease*, vol. 2, supplement 1, p. S95, 2011.

[120] M. González, E. Muñoz, C. Puebla et al., "Maternal and fetal metabolic dysfunction in pregnancy diseases associated with vascular oxidative and nitrative stress," in *The Molecular Basis for Origin of Fetal Congenital Abnormalities and Maternal Health: An overview of Association with Oxidative Stress*, B. M. Matata and M. Elahi, Eds., Bentham, USA, 2011.

[121] Y. Aggoun, I. Szezepanski, and D. Bonnet, "Noninvasive assessment of arterial stiffness and risk of atherosclerotic events in children," *Pediatric Research*, vol. 58, no. 2, pp. 173–178, 2005.

[122] S. Riggio, G. Mandraffino, M. A. Sardo et al., "Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children," *European Journal of Clinical Investigation*, vol. 40, no. 3, pp. 250–257, 2010.

[123] M. A. Creager, J. P. Cooke, M. E. Mendelsohn et al., "Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans," *Journal of Clinical Investigation*, vol. 86, no. 1, pp. 228–234, 1990.

[124] K. Egashira, T. Inou, Y. Hirooka et al., "Impaired coronary blood flow response to acetylcholine in patients with coronary risk factors and proximal atherosclerotic lesions," *Journal of Clinical Investigation*, vol. 91, no. 1, pp. 29–37, 1993.

[125] T. Münzel, C. Sinning, F. Post, A. Warnholtz, and E. Schulz, "Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction," *Annals of Medicine*, vol. 40, no. 3, pp. 180–196, 2008.

[126] S. Kawashima and M. Yokoyama, "Dysfunction of endothelial nitric oxide synthase and atherosclerosis," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 6, pp. 998–1005, 2004.

[127] I. F. Schwartz, M. Ingbir, T. Chernichovski et al., "Arginine uptake is attenuated, through post-translational regulation of cationic amino acid transporter-1, in hyperlipidemic rats," *Atherosclerosis*, vol. 194, no. 2, pp. 357–363, 2007.

[128] W. Z. Zhang, K. Venardos, S. Finch, and D. M. Kaye, "Detrimental effect of oxidized LDL on endothelial arginine metabolism and transportation," *International Journal of Biochemistry and Cell Biology*, vol. 40, pp. 920–928, 2008.

[129] J. K. Liao, W. S. Shin, W. Y. Lee, and S. L. Clark, "Oxidized low-density lipoprotein decreases the expression of endothelial nitric oxide synthase," *Journal of Biological Chemistry*, vol. 270, no. 1, pp. 319–324, 1995.

[130] F. Vidal, C. Colomé, J. Martínez-González, and L. Badimon, "Atherogenic concentrations of native low-density lipoproteins down- regulate nitric-oxide-synthase mRNA and protein levels in endothelial cells," *European Journal of Biochemistry*, vol. 252, no. 3, pp. 378–384, 1998.

[131] A. Jiménez, M. M. Arriero, A. López-Blaya et al., "Regulation of endothelial nitric oxide synthase expression in the vascular wall and in mononuclear cells from hypercholesterolemic rabbits," *Circulation*, vol. 104, no. 15, pp. 1822–1830, 2001.

[132] M. Ozaki, S. Kawashima, T. Yamashita et al., "Overexpression of endothelial nitric oxide synthase accelerates atherosclerotic lesion formation in apoE-deficient mice," *Journal of Clinical Investigation*, vol. 110, no. 3, pp. 331–340, 2002.

[133] F. T. Tang, Z. Y. Qian, P. Q. Liu et al., "Crocetin improves endothelium-dependent relaxation of thoracic aorta in hypercholesterolemic rabbit by increasing eNOS activity," *Biochemical Pharmacology*, vol. 72, no. 5, pp. 558–565, 2006.

[134] J. Dulak, M. Polus, I. Guevara, A. Polus, J. Hartwich, and A. Dembińska-Kieć, "Regulation of inducible nitric oxide synthase (iNOS) and GTP cyclohydrolase I (GTP-CH I) gene expression by OX-LDL in rat vascular smooth muscle cells," *Journal of Physiology and Pharmacology*, vol. 48, no. 4, pp. 689–697, 1997.

[135] J. Dulak, M. Polus, I. Guevara et al., "Oxidized low density lipoprotein inhibits inducible nitric oxide synthase, GTP cyclohydrolase I and transforming growth factor beta gene expression in rat macrophages," *Journal of Physiology and Pharmacology*, vol. 50, no. 3, pp. 429–441, 1999.

[136] S. Ryoo, C. A. Lemmon, K. G. Soucy et al., "Oxidized low-density lipoprotein-dependent endothelial arginase II activation contributes to impaired nitric oxide signaling," *Circulation Research*, vol. 99, no. 9, pp. 951–960, 2006.

[137] S. Ryoo, G. Gupta, A. Benjo et al., "Endothelial arginase II: a novel target for the treatment of atherosclerosis," *Circulation Research*, vol. 102, no. 8, pp. 923–932, 2008.

[138] S. Ryoo, A. Bhunia, F. Chang, A. Shoukas, D. E. Berkowitz, and L. H. Romer, "OxLDL-dependent activation of arginase II is dependent on the LOX-1 receptor and downstream RhoA signaling," *Atherosclerosis*, vol. 214, no. 2, pp. 279–287, 2011.

[139] D. Spruijt-Metz, "Etiology, treatment, and prevention of obesity in childhood and adolescence: a decade in review," *Journal of Research on Adolescence*, vol. 21, no. 1, pp. 129–152, 2011.

[140] S. E. Shoelson, L. Herrero, and A. Naaz, "Obesity, Inflammation, and Insulin Resistance," *Gastroenterology*, vol. 132, no. 6, pp. 2169–2180, 2007.

[141] S. Nishimura, I. Manabe, and R. Nagai, "Adipose tissue inflammation in obesity and metabolic syndrome," *Discovery Medicine*, vol. 8, no. 41, pp. 55–60, 2009.

[142] M. Tesauro and C. Cardillo, "Obesity, blood vessels and metabolic syndrome," *Acta Physiologica*, vol. 203, no. 1, pp. 279–286, 2011.

[143] World Health Organization, "Obesity and Overweight," Fact Sheet N°311, March 2011.

[144] A. A. Hedley, C. L. Ogden, C. L. Johnson, M. D. Carroll, L. R. Curtin, and K. M. Flegal, "Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002," *Journal of the American Medical Association*, vol. 291, no. 23, pp. 2847–2850, 2004.

[145] A. M. Magarey, L. A. Daniels, T. J. Boulton, and R. A. Cockington, "Predicting obesity in early adulthood from childhood and parental obesity," *International Journal of Obesity*, vol. 27, no. 4, pp. 505–513, 2003.

[146] S. Danielzik, M. Czerwinski-Mast, K. Langnäse, B. Dilba, and M. J. Müller, "Parental overweight, socioeconomic status and high birth weight are the major determinants of overweight and obesity in 5-7 y-old children: baseline data of the Kiel Obesity Prevention Study (KOPS)," *International Journal of Obesity*, vol. 28, no. 11, pp. 1494–1502, 2004.

[147] P. J. Salsberry and P. B. Reagan, "Dynamics of early childhood overweight," *Pediatrics*, vol. 116, no. 6, pp. 1329–1338, 2005.

[148] H. M. Ehrenberg, C. P. Durnwald, P. Catalano, and B. M. Mercer, "The influence of obesity and diabetes on the risk of cesarean delivery," *American Journal of Obstetrics and Gynecology*, vol. 191, no. 3, pp. 969–974, 2004.

[149] B. Rosenn, "Obesity and diabetes: a recipe for obstetric complications," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 21, no. 3, pp. 159–164, 2008.

[150] J. M. Salbaum and C. Kappen, "Diabetic embryopathy: a role for the epigenome?" *Birth Defects Research Part A*, vol. 91, no. 8, pp. 770–780, 2011.

[151] V. O'Dwyer, N. Farah, C. Fattah, N. O'Connor, M. M. Kennelly, and M. J. Turner, "The risk of caesarean section in obese women analysed by parity," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 158, no. 1, pp. 28–32, 2011.

[152] J. C. Challier, S. Basu, T. Bintein et al., "Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta," *Placenta*, vol. 29, no. 3, pp. 274–281, 2008.

[153] K. A. Roberts, S. C. Riley, R. M. Reynolds et al., "Placental structure and inflammation in pregnancies associated with obesity," *Placenta*, vol. 32, no. 3, pp. 247–254, 2011.

[154] L. Higgins, S. L. Greenwood, M. Wareing, C. P. Sibley, and T. A. Mills, "Obesity and the placenta: a consideration of nutrient exchange mechanisms in relation to aberrant fetal growth," *Placenta*, vol. 32, no. 1, pp. 1–7, 2011.

[155] U. Hiden, I. Lang, N. Ghaffari-Tabrizi, M. Gauster, U. Lang, and G. Desoye, "Insulin action on the human placental endothelium in normal and diabetic pregnancy," *Current Vascular Pharmacology*, vol. 7, no. 4, pp. 460–466, 2009.

[156] T. Becker, M. J. Vermeulen, P. R. Wyatt, C. Meier, and J. G. Ray, "Maternal obesity and the risk of placental vascular disease," *Journal of Obstetrics and Gynaecology Canada*, vol. 30, no. 12, pp. 1132–1136, 2008.

[157] F. C. Denison, J. Price, C. Graham, S. Wild, and W. A. Liston, "Maternal obesity, length of gestation, risk of postdates pregnancy and spontaneous onset of labour at term," *An International Journal of Obstetrics and Gynaecology*, vol. 115, no. 6, pp. 720–725, 2008.

[158] S. Y. Chu, W. M. Callaghan, S. Y. Kim et al., "Maternal obesity and risk of gestational diabetes mellitus," *Diabetes Care*, vol. 30, no. 8, pp. 2070–2076, 2007.

[159] J. Lepercq, M. Cauzac, N. Lahlou et al., "Overexpression of placental leptin in diabetic pregnancy: a critical role for insulin," *Diabetes*, vol. 47, no. 5, pp. 847–850, 1998.

[160] M. A. Williams, P. J. Havel, M. W. Schwartz et al., "Pre-eclampsia disrupts the normal relationship between serum leptin concentrations and adiposity in pregnant women," *Paediatric and Perinatal Epidemiology*, vol. 13, no. 2, pp. 190–204, 1999.

[161] T. Reimer, D. Koczan, B. Gerber, D. Richter, H. J. Thiesen, and K. Friese, "Microarray analysis of differentially expressed genes in placental tissue of pre-eclampsia: up-regulation of obesity-related genes," *Molecular Human Reproduction*, vol. 8, no. 7, pp. 674–680, 2002.

[162] P. A. Kern, S. Ranganathan, C. Li, L. Wood, and G. Ranganathan, "Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance," *American Journal of Physiology*, vol. 280, no. 5, pp. E745–E751, 2001.

[163] A. D. Pradhan, J. E. Manson, N. Rifai, J. E. Buring, and P. M. Ridker, "C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus," *Journal of the American Medical Association*, vol. 286, no. 3, pp. 327–334, 2001.

[164] B. Vozarova, C. Weyer, K. Hanson, P. A. Tataranni, C. Bogardus, and R. E. Pratley, "Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion," *Obesity Research*, vol. 9, no. 7, pp. 414–417, 2001.

[165] P. Dandona, R. Weinstock, K. Thusu, E. Abdel-Rahman, A. Aljada, and T. Wadden, "Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss," *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 8, pp. 2907–2910, 1998.

[166] P. Dandona, A. Aljada, and A. Bandyopadhyay, "Inflammation: the link between insulin resistance, obesity and diabetes," *Trends in Immunology*, vol. 25, no. 1, pp. 4–7, 2004.

[167] S. P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R. L. Leibel, and A. W. Ferrante Jr., "Obesity is associated with macrophage accumulation in adipose tissue," *Journal of Clinical Investigation*, vol. 112, no. 12, pp. 1796–1808, 2003.

[168] G. Fantuzzi, "Adipose tissue, adipokines, and inflammation," *Journal of Allergy and Clinical Immunology*, vol. 115, no. 5, pp. 911–920, 2005.

[169] H. Tilg and A. R. Moschen, "Adipocytokines: mediators linking adipose tissue, inflammation and immunity," *Nature Reviews Immunology*, vol. 6, no. 10, pp. 772–783, 2006.

[170] K. Meijer, M. de Vries, S. Al-Lahham et al., "Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages," *PLoS One*, vol. 6, no. 3, Article ID e17154, 2011.

[171] J. A. Suwaidi, S. Hamasaki, S. T. Higano, R. A. Nishimura, D. R. Holmes, and A. Lerman, "Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction," *Circulation*, vol. 101, no. 9, pp. 948–954, 2000.

[172] F. Kim, M. Pham, E. Maloney et al., "Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 11, pp. 1982–1988, 2008.

[173] E. Yamamoto, T. Nakamura, K. Kataoka et al., "Nifedipine prevents vascular endothelial dysfunction in a mouse model of obesity and type 2 diabetes, by improving eNOS dysfunction and dephosphorylation," *Biochemical and Biophysical Research Communications*, vol. 403, no. 3-4, pp. 258–263, 2010.

[174] T. B. Nascimento, R. D. Baptista, P. C. Pereira et al., "Vascular alterations in high-fat diet-obese rats: role of Endothelial L-arginine/NO Pathway," *Arquivos Brasileiros de Cardiologia*, vol. 97, no. 1, pp. 40–45, 2011.

[175] M. J. Zhu, M. Du, P. W. Nathanielsz, and S. P. Ford, "Maternal obesity up-regulates inflammatory signaling pathways and enhances cytokine expression in the mid-gestation sheep placenta," *Placenta*, vol. 31, no. 5, pp. 387–391, 2010.

[176] P. Singla, A. Bardoloi, and A. A. Parkash, "Metabolic effects of obesity: a review," *World Journal of Diabetes*, vol. 1, pp. 76–88, 2010.

[177] F. von Versen-Höynck, A. Rajakumar, M. S. Parrott, and R. W. Powers, "Leptin affects system a amino acid transport activity in the human placenta: evidence for STAT3 dependent mechanisms," *Placenta*, vol. 30, no. 4, pp. 361–367, 2009.

[178] D. M. Farley, J. Choi, D. J. Dudley et al., "Placental amino acid transport and placental leptin resistance in pregnancies complicated by maternal obesity," *Placenta*, vol. 31, no. 8, pp. 718–724, 2010.

[179] K. Fujita, K. Wada, Y. Nozaki et al., "Serum nitric oxide metabolite as a biomarker of visceral fat accumulation: clinical significance of measurement for nitrate/nitrite," *Medical Science Monitor*, vol. 17, no. 3, pp. 123–131, 2011.

[180] L. Rong-Na, Z. Xiang-Jun, C. Yu-Han, L. Ling-Qiao, and H. Gang, "Interaction between hydrogen sulfide and nitric oxide on cardiac protection in rats with metabolic syndrome," *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, vol. 33, no. 1, pp. 25–32, 2011.

[181] R. S. Miller, D. Diaczok, and D. W. Cooke, "Repression of GLUT4 expression by the endoplasmic reticulum stress response in 3T3-L1 adipocytes," *Biochemical and Biophysical Research Communications*, vol. 362, no. 1, pp. 188–192, 2007.

[182] N. Shen, X. Yu, F. Y. Pan, X. Gao, B. Xue, and C. J. Li, "An early response transcription factor, Egr-1, enhances insulin resistance in type 2 diabetes with chronic hyperinsulinism," *Journal of Biological Chemistry*, vol. 286, no. 16, pp. 14508–14515, 2011.

[183] P. M. Catalano, "Obesity and pregnancy—the propagation of a viscous cycle?" *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 8, pp. 3505–3506, 2003.

[184] G. C. Curhan, W. C. Willett, E. B. Rimm, D. Spiegelman, A. L. Ascherio, and M. J. Stampfer, "Birth weight and adult hypertension, diabetes mellitus, and obesity in US men," *Circulation*, vol. 94, no. 12, pp. 3246–3250, 1996.

[185] E. Oken, S. L. Rifas-Shiman, A. E. Field, A. L. Frazier, and M. W. Gillman, "Maternal gestational weight gain and offspring weight in adolescence," *Obstetrics and Gynecology*, vol. 112, no. 5, pp. 999–1006, 2008.

[186] B. H. Wrotniak, J. Shults, S. Butts, and N. Stettler, "Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1818–1824, 2008.

[187] E. Oken, E. M. Taveras, K. P. Kleinman, J. W. Rich-Edwards, and M. W. Gillman, "Gestational weight gain and child adiposity at age 3 years," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 4, pp. 322.e1–322.e8, 2007.

[188] E. Oken and M. W. Gillman, "Fetal origins of obesity," *Obesity Research*, vol. 11, no. 4, pp. 496–506, 2003.

[189] G. Dorner and A. Plagemann, "Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life," *Hormone and Metabolic Research*, vol. 26, no. 5, pp. 213–221, 1994.

[190] A. Fraser, K. Tilling, C. MacDonald-Wallis et al., "Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood," *Circulation*, vol. 121, no. 23, pp. 2557–2564, 2010.

[191] B. M. Margetts, M. G. Rowland, F. A. Foord, A. M. Cruddas, T. J. Cole, and D. J. Barker, "The relation of maternal weight to the blood pressures of Gambian children," *International Journal of Epidemiology*, vol. 20, no. 4, pp. 938–943, 1991.

[192] K. M. Godfrey, T. Forrester, D. J. Barker et al., "Maternal nutritional status in pregnancy and blood pressure in childhood," *British Journal of Obstetrics and Gynaecology*, vol. 101, no. 5, pp. 398–403, 1994.

[193] A. Laor, D. K. Stevenson, J. Shemer, R. Gale, and D. S. Seidman, "Size at birth, maternal nutritional status in pregnancy, and blood pressure at age 17: population based analysis," *British Medical Journal*, vol. 315, no. 7106, pp. 449–453, 1997.

[194] P. M. Clark, C. Atton, C. M. Law, A. Shiell, K. Godfrey, and D. J. Barker, "Weight gain in pregnancy, triceps skinfold thickness, and blood pressure, in offspring," *Obstetrics and Gynecology*, vol. 91, no. 1, pp. 103–107, 1998.

[195] A. A. Mamun, M. O'Callaghan, L. Callaway, G. Williams, J. Najman, and D. A. Lawlor, "Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of ageevidence from a birth cohort study," *Circulation*, vol. 119, no. 13, pp. 1720–1727, 2009.

[196] M. F. Sewell, L. Huston-Presley, D. M. Super, and P. Catalano, "Increased neonatal fat mass, not lean body mass, is associated with maternal obesity," *American Journal of Obstetrics and Gynecology*, vol. 195, no. 4, pp. 1100–1103, 2006.

[197] B. E. Metzger, B. L. Silverman, N. Freinkel, S. L. Dooley, E. S. Ogata, and O. C. Green, "Amniotic fluid insulin concentration as a predictor of obesity," *Archives of Disease in Childhood*, vol. 65, no. 10, pp. 1050–1052, 1990.

[198] M. W. Gillman, S. Rifas-Shiman, C. S. Berkey, A. E. Field, and G. A. Colditz, "Maternal gestational diabetes, birth weight, and adolescent obesity," *Pediatrics*, vol. 111, no. 3, pp. 221–226, 2003.

[199] D. Dabelea, "The predisposition to obesity and diabetes in offspring of diabetic mothers," *Diabetes Care*, vol. 30, supplement 2, pp. S169–S174, 2007.

[200] D. Dabelea, R. L. Hanson, P. H. Bennett, J. Roumain, W. C. Knowler, and D. J. Pettitt, "Increasing prevalence of type II diabetes in American Indian children," *Diabetologia*, vol. 41, no. 8, pp. 904–910, 1998.

[201] D. Dabelea, W. C. Knowler, and D. J. Pettitt, "Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 9, no. 1, pp. 83–88, 2000.

[202] T. D. Clausen, E. R. Mathiesen, T. Hansen et al., "High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia," *Diabetes Care*, vol. 31, no. 2, pp. 340–346, 2008.

[203] D. J. Pettitt and W. C. Knowler, "Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians," *Diabetes Care*, vol. 21, supplement 2, pp. B138–B141, 1998.

[204] Y. Yogev and G. H. Visser, "Obesity, gestational diabetes and pregnancy outcome," *Seminars in Fetal and Neonatal Medicine*, vol. 14, no. 2, pp. 77–84, 2009.

[205] L. Schack-Nielsen, K. F. Michaelsen, M. Gamborg, E. L. Mortensen, and T. I. Sørensen, "Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood," *International Journal of Obesity*, vol. 34, no. 1, pp. 67–74, 2010.

[206] J. A. Armitage, L. Poston, and P. D. Taylor, "Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity," *Frontiers of Hormone Research*, vol. 36, pp. 73–84, 2008.

[207] T. A. Hillier, K. L. Pedula, M. M. Schmidt, J. A. Mullen, M. A. Charles, and D. J. Pettitt, "Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia," *Diabetes Care*, vol. 30, no. 9, pp. 2287–2292, 2007.

[208] M. W. Gillman, H. Oakey, P. A. Baghurst, R. E. Volkmer, J. S. Robinson, and C. A. Crowther, "Effect of treatment of gestational diabetes mellitus on obesity in the next generation," *Diabetes Care*, vol. 33, no. 5, pp. 964–968, 2010.

[209] I. Rogers, "The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life," *International Journal of Obesity*, vol. 27, no. 7, pp. 755–777, 2003.

[210] M. A. Charles, D. J. Pettitt, R. L. Hanson et al., "Familial and metabolic factors related to blood pressure in Pima Indian children," *American Journal of Epidemiology*, vol. 140, no. 2, pp. 123–131, 1994.

[211] C. S. Wright, S. L. Rifas-Shiman, J. W. Rich-Edwards, E. M. Taveras, M. W. Gillman, and E. Oken, "Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure," *American Journal of Hypertension*, vol. 22, no. 2, pp. 215–220, 2009.

[212] E. P. Gunderson, C. P. Quesenberry, D. R. Jacobs, J. Feng, C. E. Lewis, and S. Sidney, "Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: the CARDIA study," *American Journal of Epidemiology*, vol. 172, no. 10, pp. 1131–1143, 2010.

[213] C. R. Assumpção, T. M. Brunini, N. R. Pereira et al., "Insulin resistance in obesity and metabolic syndrome: is there a connection with platelet l-arginine transport?" *Blood Cells, Molecules, and Diseases*, vol. 45, no. 4, pp. 338–342, 2010.

[214] K. Kikuta, T. Sawamura, S. Miwa, N. Hashimoto, and T. Masaki, "High-affinity arginine transport of bovine aortic endothelial cells is impaired by lysophosphatidylcholine," *Circulation Research*, vol. 83, no. 11, pp. 1088–1096, 1998.

[215] K. Posch, S. Simecek, T. C. Wascher et al., "Glycated low-density lipoprotein attenuates shear stress-induced nitric oxide synthesis by inhibition of shear stress-activated L-arginine uptake in endothelial cells," *Diabetes*, vol. 48, no. 6, pp. 1331–1337, 1999.

[216] M. T. Jay, S. Chirico, R. C. Siow et al., "Modulation of vascular tone by low density lipoproteins: effects on L-arginine transport and nitric oxide synthesis," *Experimental Physiology*, vol. 82, no. 2, pp. 349–360, 1997.

[217] A. Nuszkowski, R. Gräbner, G. Marsche, A. Unbehaun, E. Malle, and R. Heller, "Hypochlorite-modified low density lipoprotein inhibits nitric oxide synthesis in endothelial cells via an intracellular dislocalization of endothelial nitric-oxide synthase," *Journal of Biological Chemistry*, vol. 276, no. 17, pp. 14212–14221, 2001.

[218] W. G. Rossmanith, U. Hoffmeister, S. Wolfahrt et al., "Expression and functional analysis of endothelial nitric oxide synthase (eNOS) in human placenta," *Molecular Human Reproduction*, vol. 5, no. 5, pp. 487–494, 1999.

[219] J. Ketonen, T. Pilvi, and E. Mervaala, "Caloric restriction reverses high-fat diet-induced endothelial dysfunction and vascular superoxide production in C57Bl/6 mice," *Heart and Vessels*, vol. 25, no. 3, pp. 254–262, 2010.

[220] S. Kagota, E. Chia, and J. J. McGuire, "Preserved arterial vasodilation via endothelial protease-activated receptor-2 in obese type 2 diabetic mice," *British Journal of Pharmacology*, vol. 164, no. 2, pp. 358–371, 2011.

[221] S. Fatani, I. Itua, P. Clark, C. Wong, and E. K. Naderali, "The effects of diet-induced obesity on hepatocyte insulin signaling pathways and induction of non-alcoholic liver damage," *International Journal of General Medicine*, vol. 4, pp. 211–219, 2011.

[222] J. L. Di Iulio, N. M. Gude, R. G. King, C. G. Li, M. J. Rand, and S. P. Brennecke, "Human placental nitric oxide synthase activity is not altered in diabetes," *Clinical Science*, vol. 97, no. 1, pp. 123–128, 1999.

[223] H. B. Eccleston, K. K. Andringa, A. M. Betancourt et al., "Chronic exposure to a high-fat diet induces hepatic steatosis, impairs nitric oxide bioavailability, and modifies the mitochondrial proteome in mice," *Antioxidants and Redox Signaling*, vol. 15, no. 2, pp. 447–459, 2011.

[224] P. M. Catalano and S. Hauguel-De Mouzon, "Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic?" *American Journal of Obstetrics and Gynecology*, vol. 204, no. 6, pp. 479–487, 2011.

[225] J. Pedersen, *Diabetes and pregnancy: blood sugar of newborn infants*, Ph.D. thesis, Danish Science Press, Copenhagen, Denmark, 1952.

[226] T. W. Leung and T. T. Lao, "Placental size and large-for-gestational-age infants in women with abnormal glucose tolerance in pregnancy," *Diabetic Medicine*, vol. 17, no. 1, pp. 48–52, 2000.

[227] S. Hauguel-de Mouzon, J. Lepercq, and P. Catalano, "The known and unknown of leptin in pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 194, no. 6, pp. 1537–1545, 2006.

[228] J. T. Smith and B. J. Waddell, "Leptin distribution and metabolism in the pregnant rat: transplacental leptin passage increases in late gestation but is reduced by excess glucocorticoids," *Endocrinology*, vol. 144, no. 7, pp. 3024–3030, 2003.

[229] F. M. Stewart, D. J. Freeman, J. E. Ramsay, I. A. Greer, M. Caslake, and W. R. Ferrell, "Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 3, pp. 969–975, 2007.

[230] D. J. Tuffnell, J. West, and S. A. Walkinshaw, "Treatments for gestational diabetes and impaired glucose tolerance in pregnancy," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD003395, 2003.

[231] C. A. Crowther, J. E. Hiller, J. R. Moss, A. J. McPhee, W. S. Jeffries, and J. S. Robinson, "Effect of treatment of gestational diabetes mellitus on pregnancy outcomes," *New England Journal of Medicine*, vol. 352, no. 24, pp. 2477–2486, 2005.

[232] A. Burguet, "Long term outcome in children of mothers with gestational diabetes," *Journal de Gynecologie Obstetrique et Biologie de la Reproduction*, vol. 39, no. 8, supplement 2, pp. S322–S337, 2010.

Hindawi Publishing Corporation
Experimental Diabetes Research
Volume 2011, Article ID 585749, 10 pages
doi:10.1155/2011/585749

Review Article

Maternal Obesity and the Early Origins of Childhood Obesity: Weighing Up the Benefits and Costs of Maternal Weight Loss in the Periconceptional Period for the Offspring

Song Zhang, Leewen Rattanatray, Janna L. Morrison, Lisa M. Nicholas, Shervi Lie, and I. Caroline McMillen

Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5001, Australia

Correspondence should be addressed to I. Caroline McMillen, caroline.mcmillen@unisa.edu.au

Received 28 June 2011; Revised 21 August 2011; Accepted 23 August 2011

Academic Editor: Christine Maric-Bilkan

There is a need to understand the separate or interdependent contributions of maternal prepregnancy BMI, gestational weight gain, glycaemic control, and macronutrient intake on the metabolic outcomes for the offspring. Experimental studies highlight that there may be separate influences of maternal obesity during the periconceptional period and late gestation on the adiposity of the offspring. While a period of dietary restriction in obese mothers may ablate the programming of obesity, it is associated with an activation of the stress axis in the offspring. Thus, maternal obesity may result in epigenetic changes which predict the need for efficient fat storage in postnatal life, while maternal weight loss may lead to epigenetic changes which predict later adversity. Thus, development of dietary interventions for obese mothers during the periconceptional period requires a greater evidence base which allows the effective weighing up of the metabolic benefits and costs for the offspring.

1. Introduction

As the prevalence of obesity has increased in the developed world, more women are entering pregnancy with a high body mass index (BMI) in the overweight (BMI > 25 kg/m^2) or obese (BMI > 30 kg/m^2) range. As discussed in this paper, clinical and population studies have shown that maternal obesity results in fertility problems and suboptimal outcomes for the mother and her fetus during and after pregnancy [1]. It is also the case that maternal obesity is associated with an increase in BMI in the offspring during infancy, childhood, and later life. A recent scientific statement from the American Heart Association Council on Epidemiology and Prevention included a summary of the evidence for the prenatal determinants of obesity and highlighted that "*obesity among girls and women of childbearing age is producing a concomitant increase in rates of gestational diabetes which in turn is likely to lead to more obesity in the next generation. This vicious cycle may well fuel the obesity epidemic for decades to come*" [2]. This places a focus on the nutritional health of women before pregnancy and on the development of optimal weight loss interventions in overweight or obese women in the preconceptional period to improve pregnancy outcomes. This paper highlights recent evidence that suggests that the periconceptional period may represent a critical window during which exposure of the oocyte and/or embryo can independently contribute to an increased risk of obesity in the offspring. Further, this paper summarises evidence from experimental studies of the potential metabolic benefits and costs of weight loss during the periconceptional period in overweight and obese mothers for the offspring.

2. Maternal Prepregnancy BMI, Gestational Weight Gain, and Pregnancy Outcomes

During the past decade, the obesity epidemic in the developed world has resulted in an increase in the number of women entering pregnancy with a high body mass index (BMI) in the overweight (BMI > 25 kg/m^2) or obese (BMI > 30 kg/m^2) range. In the US, UK, and Australia, the prevalence of obesity in women aged between 20 and 39 years is around

28%, 20%, and 15%, respectively, as determined in studies carried out between 2000 and 2009 [1–5]. In the US, La Coursiere and colleagues [6] found that the incidence of women being either overweight or obese at the start of pregnancy increased from 25% to 35% between 1991 and 2001, and that the incidence of maternal obesity at delivery rose from 29% to 39% across the same period [6]. Although the proportion of women of reproductive age in the US who are overweight or obese appears to have plateaued recently, the proportion that is severely obese (BMI $\geq$ 40 kg/m^2) is increasing. Similarly, two recent reports from different states in Australia found that the prevalence of maternal overweight and obesity was 34% in a population giving birth between 1998 and 2002 and 43% in a population measured at their first antenatal visit between 2001 and 2005 [7, 8]. Obese women are at increased risk of a range of pregnancy complications including gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), delivery of a large-for-gestational-age (LGA) infant, and an increase in Caesarean section rate [9].

In addition to the focus on the impact of maternal prepregnancy BMI on pregnancy outcomes, there has been a range of observational studies which suggest that there is also an association between gestational weight gain with short- and longer-term maternal outcomes [10]. The Institute of Medicine (IOM) in the US has recently revised its 1990 guidelines for gestational weight gain in underweight, normal weight, overweight, and obese women [11]. The new guidelines were developed based on a systematic evidence-based review [12] which found that the evidence that gestational weight gain was related to maternal pregnancy and postpartum outcomes was weak. There was, however, a moderate association between gestational weight gain and both Caesarean section delivery and maternal postpartum weight retention [12]. Some recent observational studies in obese women report better pregnancy outcomes at lower or negative gestational weight gains than in the revised IOM guidelines [10], but there are concerns that striving to achieve a lower gestational weight gain than that recommended in the new guidelines may have adverse outcomes [1]. The recent International Life Sciences Institute (ILSI) Europe Workshop on obesity in pregnancy concluded that given that the new IOM guidelines were based on observational studies, there was a pressing requirement for large randomised control trials which are adequately powered to test the validity of the recommendations [1]. Currently, it appears that for obese women, prepregnancy BMI is more associated with an increased risk of preeclampsia, GDM, and the delivery of an LGA infant than is gestational weight gain [9]. This places a focus on the nutritional health of women in the preconceptional period and on what weight loss interventions can be safely introduced in the obese woman seeking to become pregnant.

3. Maternal Prepregnancy BMI, Gestational Weight Gain, and Childhood Obesity

While it is not unexpected that the maternal nutritional and hormonal environment would determine fetal nutrient supply, fetal growth, and the body composition of the infant, the effects of the nutritional environment experienced *in utero* persist beyond fetal life. There is a U-shaped relationship between birth weight, and adult fat mass, with a higher prevalence of adult obesity occurring in individuals with birth weights at either the low or high end of the birth weight distribution [13–16]. A study in a large British cohort found that babies who were in the heaviest quintile of birth weight tended to have a high BMI in adult life independent of gender and that this relationship was largely accounted for by maternal weight [15]. A recent Danish study of 300,000 children also reported a remarkably stable association between having a birth weight greater than 4000 g and being overweight at 6–13 years of age in both girls and boys [17]. A retrospective US study of 8494 low-income families found that children (both boys and girls) born to obese mothers were twice as likely to be obese by 2 years of age [16]. There was a greater than 2-fold increase in the prevalence of obesity observed in children of obese mothers compared to those with mothers whose BMI was in the normal range.

Recent studies have investigated how a high maternal prepregnancy BMI, poor maternal glycaemic control, and total gestational weight gain may each contribute to a range of outcomes including an LGA baby and child obesity. In one report, siblings born to women who had undergone bariatric surgery for the treatment of severe obesity had a lower BMI and obesity risk than their siblings who were born prior to maternal surgery and weight loss [18]. In this latter study, it was not possible, due to the sample size, to determine whether there was any difference in the impact of a reduction in maternal weight on the metabolic outcomes in the male or female offspring. The findings of this latter study suggest that exposure to a high maternal BMI before and during pregnancy has important consequences for the metabolic health of the offspring. While some observational studies have found that there is an impact of gestational weight gain on outcomes including child obesity, the effect of gestational weight gain, independent of maternal prepregnancy BMI on offspring obesity, is not clear [10].

A high prepregnancy BMI is also associated with an increased risk of poor glucose tolerance and GDM, and recent randomised control trials provide evidence that there is a causal relationship between maternal glucose intolerance and the delivery of a macrosomic infant [19, 20]. A study on Pima Indians reported that there was an increased risk of obesity in offspring (male and female) born after the mother was diagnosed with diabetes compared with their siblings who were born before the mothers were diagnosed with diabetes [21]. Thus, exposure to an increase in high maternal glucose and insulin concentrations from conception results in a larger and fatter infant who is at increased risk of obesity in later life. Interestingly in a recent follow-up study of children whose mothers participated in a randomised control trial, treatment of mild GDM resulted in a reduction in macrosomia at birth but not in the BMI of offspring at 4-5 years of age [22]. While this null effect may be a consequence of the early age at which the children were studied, it is also possible that there are separate effects of exposure to

GDM on fetal body growth and on the risk of increased adiposity in childhood. In this context, it is of note that maternal pre pregnancy weight and the associated level of maternal insulin resistance are strongly correlated with an infant's fat mass at birth, whereas the level of maternal insulin resistance in later pregnancy is correlated with birth weight and an infant's "fat-free" mass [23]. Thus, better glycaemic control in later pregnancy may have a greater impact on infant body growth than on the propensity for childhood obesity. Similarly, other studies have shown that there appear to be independent contributions of maternal pre pregnancy weight and maternal glucose intolerance during pregnancy to birth weight and the risk of adolescent obesity [24].

Finally, the role of maternal macronutrient and energy intakes during pregnancy on the subsequent development of appetite and food choices of her offspring has also been investigated. Maternal glucose concentrations are influenced by her total energy intake and by the proportions of carbohydrate, fat, and protein in her diet. A recent study investigated the association of maternal macronutrient and energy intake during pregnancy with the macronutrient and energy intake of her offspring [25]. Maternal dietary intakes of protein, fat, and carbohydrate in pregnancy were positively associated with the dietary intake of the same nutrients in both male and female offspring, and these associations were greater than those observed for paternal dietary intakes [25]. Furthermore, associations of maternal prenatal-offspring intakes were stronger than those for maternal postnatal-offspring intakes for protein and fat [25]. Thus, this study supports the conclusion which has also been drawn from a range of experimental animal studies as cited below, that there may be *in utero* programming of offspring appetite by maternal intake during pregnancy in the human.

4. Maternal Overnutrition: Critical Periods for the Development of Postnatal Obesity

There is a need to understand the separate or interdependent contributions of maternal pre pregnancy BMI, gestational weight gain, glycaemic control, and maternal macronutrient intake on the longer-term metabolic outcomes for the offspring, including the metabolic responses to an obesogenic diet. This understanding would help inform the evidence base for effective nutritional interventions in women before and during pregnancy. It is clearly difficult in human populations to determine the impact of exposure to a high maternal BMI during the preconceptional period separately from exposure to a high maternal BMI during any subsequent stage of pregnancy on the metabolic outcomes for the offspring. Most women who enter pregnancy heavy remain so during pregnancy and are also at greater risk of development of glucose intolerance during late gestation.

A range of experimental animal studies have provided insights into the mechanisms that may underpin the early programming of a life of obesity, but as highlighted below there are relatively few experimental studies which have addressed the impact of maternal dietary interventions imposed during different periods of pregnancy on the metabolic outcomes for the offspring.

5. Animal Models of Maternal Overnutrition

5.1. The Early Programming of Obesity in the Rodent. The effects of obesity on oocyte quality and early embryo development have been assessed by Minge and colleagues using a mouse model of diet-induced obesity [26]. Embryos isolated from either obese or control-mated females were cultured *in vitro* in order to monitor their development. Although a difference in fertilisation rates was not observed, embryos from obese females exhibited slower development to the four- to eight-cell stage and through to the blastocyst stage. It was also reported in this study that defects in oocyte developmental competence caused by obesity were reversed by treatment with insulin sensitisers before conception. Thus, maternal obesity and peripheral insulin sensitivity are important from as early as the preconceptional period in determining developmental outcomes. This is important in the context that most animal models of maternal overnutrition include exposure to an increase in energy intake and/or a diet which is high in fat and/or sugar including exposure to "junk food" style diets from before conception and throughout pregnancy [27–31].

There have been several excellent recent papers of the impact of maternal overnutrition in rodents on the postnatal metabolic phenotype of the pups and offspring in later life [32–34]. In most instances, it has been reported that maternal overnutrition in the rat leads to a consistent increase in body fat mass, poor glucose tolerance, insulin resistance, and an increase in appetite in the offspring [32–35]. These studies provide important information on the metabolic signalling pathways that are perturbed in skeletal muscle, liver, and in visceral and subcutaneous adipose tissue. Interestingly, however, a recent systematic paper of those animals models which have used exposure to maternal high-fat feeding throughout pregnancy identified that there was a paucity of data which characterised what aspects of the maternal metabolic state were related to the specific postnatal outcomes. The authors of this paper commented that this limited the capacity to draw links between the maternal phenotype and the metabolic outcomes in the offspring in these models [36]. Important outcomes from this systematic paper were firstly that all offspring born to obese mothers had perturbed glycaemic control in postnatal life and secondly that poor glycaemic control was also observed in offspring from nonobese, high-fat-fed mothers [36]. Importantly, there was not convincing evidence that there was a hyperphagic phenotype in offspring exposed to a maternal diet which was high in fat and low in carbohydrate [36]. In contrast, there is consistent evidence for a hyperphagic phenotype in offspring exposed to a maternal diet that is high in sugar including "junk food" and cafeteria-style diets [27–31]. This is consistent with a wide range of studies in the rodent that have reported that exposure of the fetal and neonatal brain to conditions in which there is hyperglycaemia, hyperinsulinaemia, and/or hyperleptinaemia can result in the programming of postnatal appetite [37].

One important study determined the impact of feeding nonpregnant rats with 15% excess calories/day for 3 weeks

prior to mating such that dams entered pregnancy obese or lean [38]. After mating, the dams were all placed on the same diet for the remainder of pregnancy, and the pups were cross-fostered at birth to normal-weight mothers to ensure that the nutritional intervention was restricted to pregnancy. Offspring from the obese dams gained greater body weight and had a higher percentage body fat than the offspring from lean dams when fed a high-fat diet in postnatal life. While the nutritional intervention in this study was restricted to the 3-week period prior to conception, the dams which entered pregnancy obese remained obese throughout pregnancy, and the increase in offspring adiposity might therefore reflect the impact of overnutrition and obesity in both the periconceptional period and the remainder of of pregnancy. Another key study placed obese female rats on a control chow diet from one month before mating for the remainder of pregnancy and lactation and compared the outcomes with those from obese female rats maintained on a high fat diet from before and during pregnancy and throughout lactation [39]. At 21 days after birth, serum triglycerides, leptin and insulin were increased in the offspring from the obese mother on a high fat diet, but not the offspring of the obese mother fed on the control diet. An increase in body fat mass in the offspring of high fat fed mothers at 5 months of age was partially "reversed" in offspring of the chow fed, previously obese mothers [39]. This study demonstrates the effectiveness of a weight loss intervention which extends from before and throughout pregnancy. It is not possible, however, to conclude whether the impact of the dietary intervention on the previously obese rat was a consequence of the decrease in her pre pregnancy weight and fat mass, gestational weight gain, or exposure to a high-fat diet during lactation.

5.2. The Early Programming of Obesity in the Sheep. There have been a range of studies using the sheep as a large animal model of pregnancy on the impact of exposure to maternal obesity on the fetal and postnatal lamb. The sheep is an excellent model for the study of the early development of later obesity. In the sheep, as in the human, the development of adipose tissue and of the hypothalamic neural network which regulates appetite and energy balance in later life occur before birth. This is unlike the rodent, where fat development and the appetite regulatory system in the hypothalamus each develop after birth [37, 40]. In an important series of studies, it has been reported that exposure of ewes to a diet containing 150% metabolic requirements from 60 days before conception and extending throughout pregnancy resulted in changes in adipose tissue development, glucose tolerance, and appetite regulation in the adult offspring [41]. In these studies, the adult offspring from obese and control-fed mothers were exposed to a 3-month "feeding challenge." During the feeding challenge, offspring from obese ewes consumed more food and at the end of the challenge had a higher percentage of body fat than offspring from control ewes. There was also a decrease in insulin sensitivity in the offspring from obese ewes compared with their control counterparts [41]. In this study, body fat mass was measured using dual X-ray absorptiometry, and so it was not possible to determine whether the increase in body fat mass after the feeding challenge was a result of an increase in the visceral or subcutaneous fat depots.

We have developed a model of maternal overnutrition in which pregnant ewes were overfed for the last month of pregnancy to determine whether exposure of the fetus to increased maternal glucose concentrations during late pregnancy would result in an increase in postnatal adiposity [42–44]. We found that maternal overnutrition imposed in this period resulted in an increase in fetal glucose and insulin concentrations and an upregulation of key adipogenic and lipogenic genes, including peroxisome-proliferator activator receptor γ (PPAR γ), leptin, and adiponectin within the perirenal fat depot of the late gestation sheep fetus [44]. We also found that there was an increased mass of subcutaneous, but not visceral fat present in the male and female lambs of these overnourished ewes at one month of age [42]. Furthermore, in the lambs of overnourished ewes, there was a decrease in the hypothalamic expression of the leptin receptor with increasing body fat mass and a loss of the positive relationship between the expression of a hypothalamic appetite inhibitory peptide (cocaine amphetamine-regulated transcript) and body fat mass [42].

Thus, it appears that exposure to maternal and fetal hyperglycaemia in late pregnancy alone can result in an increase in adiposity and in changes in the hypothalamic neural network which would limit the appropriate response to an increase in body fat mass and energy intake in the postnatal animal.

Relatively few animal studies have attempted to determine the impact of maternal obesity restricted to the "periconceptional period" alone on the development of adiposity in the offspring. The periconceptional period is an important period for intervention because as highlighted earlier there appears to be an association between maternal pre pregnancy BMI and an increased body fat mass in the offspring. Furthermore, dietary intervention in overweight or obese women is relatively more feasible in the pre- or periconceptional period.

5.2.1. Definition of What Constitutes the "Periconceptional Period". The periconceptional period includes the period extending from oocyte maturation to early gestation. In a number of studies in the sheep, nutritional interventions are imposed during a periconceptional period which extends from around 60 days before to 30 days after conception which covers the period of oocyte maturation, implantation, and placentation [45, 46]. Nutritional interventions which extend into the placentation period may affect placental growth and the placental transfer efficiency of substrates to the fetus during early or late pregnancy [47]. We have proposed therefore that the term "periconceptional" should be used to refer to the developmental stages which include some or all of the following early events: oocyte maturation, follicular development, conception, and embryo/blastocyst growth up until implantation [48]. When maternal nutritional interventions extend beyond implantation to include early

placentation, then it may be more appropriate to describe these interventions as occurring during "early gestation."

5.2.2. Exposure to Maternal Overnutrition in the Periconceptional Period and Programming of Later Obesity in the Sheep. We have developed a model in which nonpregnant ewes were either overnourished or normally nourished for at least 4 months before artificial insemination [49, 50]. In two subgroups of non pregnant ewes, a 4-week period of dietary restriction was imposed before and after artificial insemination to result in 4 periconceptional treatment groups: periconceptional overnutrition with (HR) or without (HH) dietary restriction and control nutrition with (CR) or without (CC) dietary restriction [49]. Around a week after conception, single embryos were transferred from these donor ewes to nonobese recipient ewes which were then maintained on a control diet for the remainder of pregnancy. The ewes which were overnourished during the periconceptional period were heavier than the control ewes during this period (Figure 1). Recipient nonobese ewes were maintained at a normal body condition score from the start of the donor ewe feeding regime to the time of conception. This model therefore isolates the effect of exposure to maternal obesity during the periconceptional period alone.

We found that there was a gender-specific effect of periconceptional overnutrition on the body fat mass of the 4-month-old lambs. Periconceptional overnutrition resulted in an increase in total fat mass in female, but not male lambs [49]. Interestingly, maternal dietary restriction imposed in the overnourished ewe during the periconceptional period ablated the development of an increase in total body fat in the female lambs (Figure 2). There was also a significant relationship between the total fat mass of female lambs at 4 months of age and the weight of the donor ewe at conception. The greatest impact of periconceptional overnutrition was on the perirenal and omental fat depots in the female lamb and the weights of these depots were also higher in female than male lambs in all nutritional groups. The greater impact of periconceptional overnutrition in the female lamb, may be related to the higher level of expression of adipogenic and lipogenic genes, for example, G3PDH and lipoprotein lipase (LPL) present in adipose tissue in female, compared to male lambs.

Exposure of the oocyte and early embryo to a high plane of maternal nutrition therefore resulted in a greater postnatal capacity to synthesise and store triglycerides in female lambs. We have speculated that the early embryo may respond to maternal overnutrition to program changes within metabolic pathways which ultimately result in a more efficient deposition of fat in visceral fat depots in postnatal life. It may be that this early response is on the basis that the postnatal nutritional environment will match the high nutritional environment experienced by the embryo and that an increased capacity to store fat will be required in postnatal life.

Interestingly we found that there was no effect of periconceptional overnutrition on the level of expression of PPAR γ, leptin, and adiponectin in the perirenal, omental, or subcutaneous fat depots in lambs at 4 months of age [49]. Thus, exposure of the sheep embryo to periconceptional overnutrition results in an increased visceral adiposity with no increase in adipose PPAR γ or leptin expression, whereas exposure to maternal overnutrition in late gestation results in an increase in PPAR γ and leptin expression in fetal visceral fat and an increase in subcutaneous fat mass in postnatal life. These differences may reflect differences in timing between the study endpoints (4- versus 1-month postnatal age, resp.), or it may be that different signalling systems are activated in adipocytes after exposure to maternal overnutrition during the periconceptional and late gestational periods. Periconceptional overnutrition may result in epigenetic changes induced in the germ layers of the embryo associated with an increase in the differentiation, proliferation, and/or hypertrophy of visceral adipocytes.

Thus, the early programming of later obesity may result from "two hits," the first occurring as a result of maternal overnutrition during the periconceptional period and the second occurring as a result of increased fetal nutrition in late pregnancy [51].

5.2.3. Dietary Intervention during the Periconceptional Period: Metabolic Benefits. As noted above, we found that placing the obese ewe on a dietary regime where the energy intake was reduced to 70% of normal for one month before and one week after conception only resulted in an ablation of the effects of maternal overnutrition on the total fat mass in the female lamb [49]. This is an important finding as it highlights that nutritional intervention in the periconceptional period can ablate the effects of a high maternal pre pregnancy weight on offspring adiposity. One issue, however, is whether such a dietary restriction regime has any other positive or negative metabolic or endocrine consequences for the offspring.

5.2.4. Dietary Intervention during the Periconceptional Period: Metabolic and Endocrine "Costs". It has previously been shown that a severe nutritional restriction imposed in ewes with a body weight in the normal range across both the periconceptional and early gestation periods (from 60 days before until 30 days after mating) resulted in a decreased glucose tolerance in the 10-month-old offspring [45]. In this latter study, this period of undernutrition resulted in an increase in the glucose and insulin areas under the curve in response to a glucose tolerance test at 4 and at 10 months postnatal age [45]. It is not known, however, whether a similar period of dietary restriction in obese ewes would have similar metabolic consequences in the offspring. It has also been demonstrated that moderate dietary restriction imposed during the periconceptional period results in an increase in fetal arterial blood pressure and in an earlier activation of the fetal prepartum cortisol surge [52, 53].

We have recently determined whether exposure to a moderate restriction of energy intake in obese and normal weight ewes results in changes in the development of the hypothalamo-pituitary-adrenal axis and the stress response in the offspring. We have found that dietary restriction imposed during the periconceptional period in either normal weight or obese ewes resulted in an enhanced cortisol response to stress in female lambs at 3-4 months of age

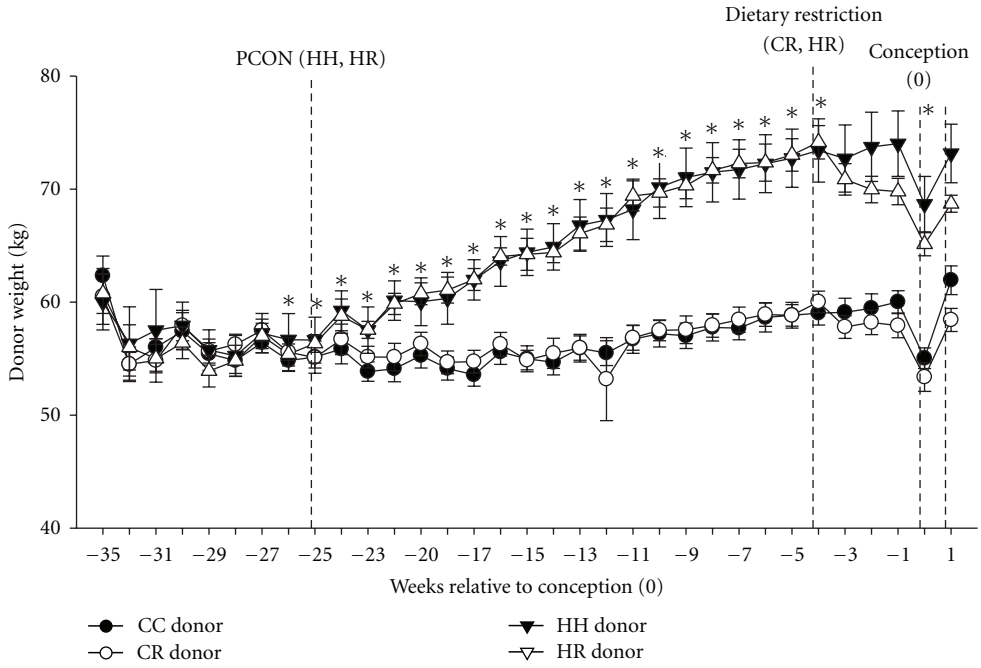


Figure 1: Weight of donor ewes during the nutritional feeding protocol from 35 weeks before conception to 1 week after conception (CC: closed circle; CR: open circle; HH: closed triangle; HR: open triangle). *denotes a significant difference between the weight of the donor ewes in the HH and HR groups compared to the CC and CR groups ($P < 0.05$) (reprinted from Rattanatray et al., 2010 [49]).

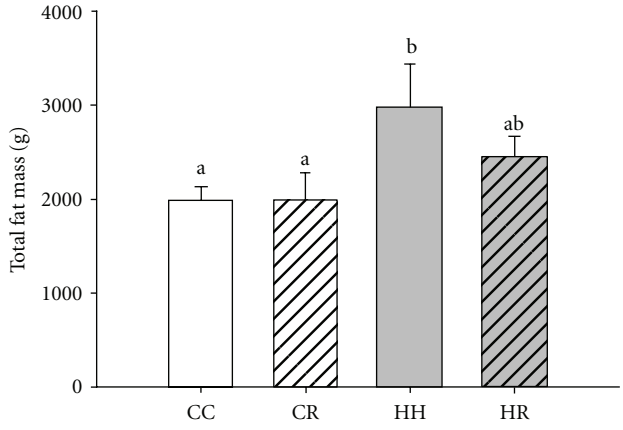


Figure 2: Effect of periconceptional overnutrition and/or dietary restriction on the total fat mass of female lambs at 4 months of age (CC: open bar; CR: striped bar; HH: grey bar; HR: grey striped bar). Different superscripts (e.g., a, b) denote a significant difference of total fat mass between the treatment groups ($P < 0.05$) (reprinted from Rattanatray et al. 2010 [49]).

(Figure 3) [50]. In this study, the adrenal gland was also bigger at 4 months of age in male and female lambs which were conceived in either normal weight or obese ewes which had been exposed to dietary restriction during the periconceptional period. The increase in adrenal growth was associated with a decrease in the adrenal expression of the insulin-like growth factor 2 (IGF 2). IGF2 is expressed in a parent-of-origin-specific manner from the paternal gene and has been implicated in the regulation of adrenal growth and steroidogenesis in the fetal sheep [54]. Epigenetic modifications play a vital role in the transmission of the parental identity of particular alleles through the germline; this is achieved through complex mechanisms typified by cytosine methylation of "imprinting control regions" (ICR). For *IGF2*, the ICR resides within a differentially methylated region (DMR) 4 kb upstream of the neighbouring nonprotein coding *H19* gene. When the DMR is methylated, *IGF2* is expressed, and conversely when the DMR is unmethylated, *IGF2* expression is repressed by *H19* [55]. Using combined bisulphite restriction analysis (COBRA), we found that the lamb adrenals in the CR group carried significantly less methylation in the *IGF2/H19* DMR when compared to the CC and HH groups, and this effect was present in both male and female lambs [50]. Bisulphite sequencing of a subset of animals from each group revealed that the loss of methylation observed in the CR group was marked, with most animals exhibiting a complete loss of methylation. It was also of note that some animals in the HR group exhibited loss of *IGF2/H19* DMR methylation. Thus, the increase in adrenal weight in the CR and HR lambs was paradoxically associated with a decrease in the expression of an adrenal growth factor which in turn was associated with decreased level of methylation in the proximal CTCF binding site in the DMR region of the *IGF2/H19* gene in these groups. There was no change, however, in the methylation status of *IGF2R* or in IGF2R mRNA expression in the adrenals of the lambs in either the CR or HR groups. It remains to be determined

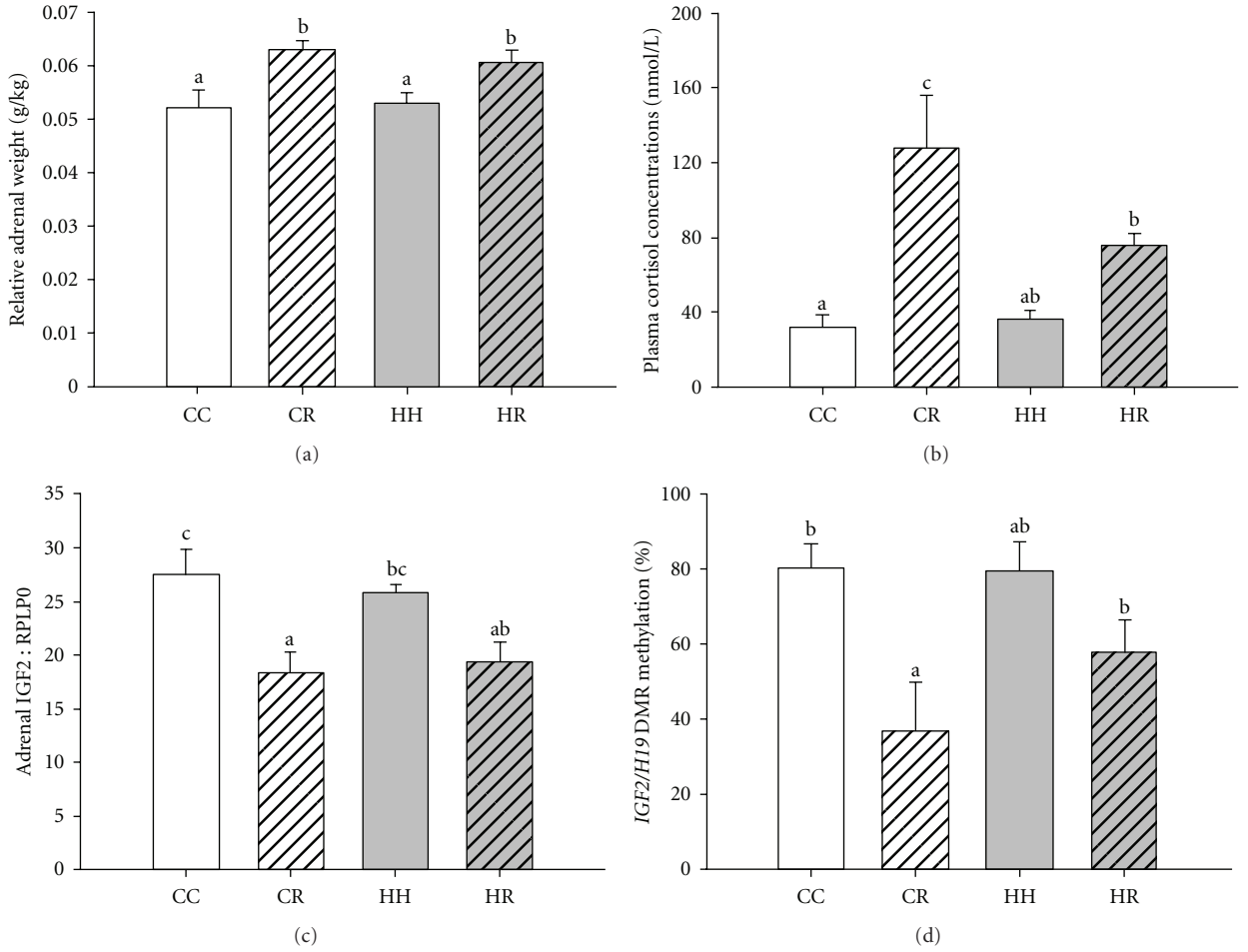


Figure 3: Relative adrenal weight (a) in the CC, CR, HH, and HR lambs (CC: open bar; CR: striped bar; HH: grey bar; HR: grey striped bar), plasma cortisol concentrations (b) in response to stress in female lambs at postnatal week 12, adrenal IGF2 mRNA expression (c), and IGF2/H19 DMR methylation levels (d) in lambs at postnatal week 16 (from Zhang et al., 2010 [50]). Different superscripts a, b, and c denote treatment groups which are significantly different from each other ($P < 0.05$).

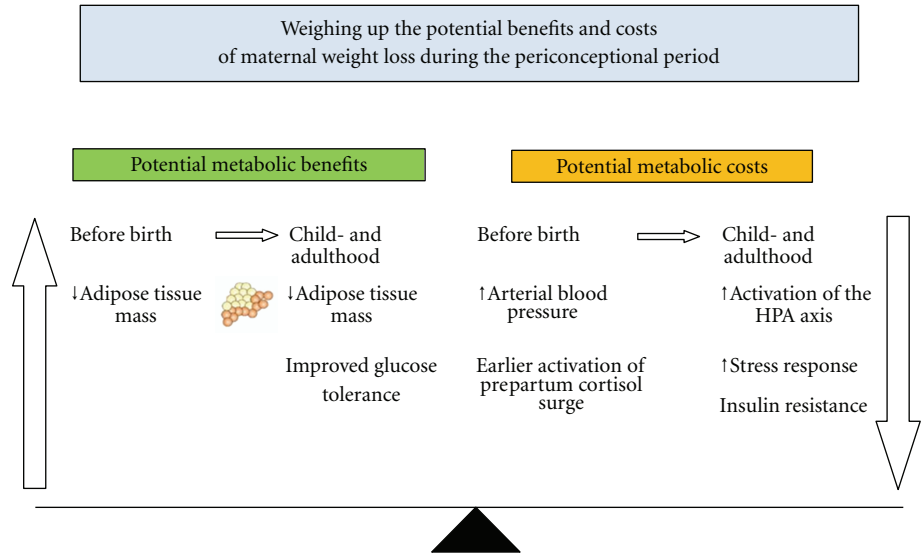


Figure 4: Diagram summarising the potential benefits and costs of maternal weight loss during the periconceptional period.

whether the decrease in adrenal IGF2 mRNA expression is a consequence of the epigenetic changes in adrenal *IGF2* or whether there are other factors driving adrenal growth in these animals which in turn suppress IGF2 gene expression within the adrenal. It has recently been reported that people whose mothers were exposed to famine during the Dutch Hunger Winter in 1944-1945 had less *IGF2* methylation in blood cells in adult life compared with their unexposed same-sex siblings [56]. In particular, epigenetic changes were found among individuals who had been exposed to famine in early gestation and who had a normal birth weight. In contrast, exposure to famine in late gestation was associated with a low birth weight, but not with epigenetic changes in the blood cells in later life [56].

Thus, studies on the effects of maternal undernutrition imposed during the periconceptional period highlight the need to be cautious about the level and length of any dietary intervention regime imposed around the time of conception as not all of the metabolic and endocrine effects of dietary restriction in this period may be beneficial in the longer term.

Thus, there appear to be a series of changes including epigenetic modifications in a number of key genes induced in the embryo after exposure to either maternal over- or undernutrition. These may result in metabolic and endocrine changes which result in responses consistent with the expectation of either a "life of adversity" or of a "life of plenty" with high levels of postnatal nutrition. Critically, there is evidence that metabolic and endocrine changes may be induced in offspring after imposition of dietary restriction during the pre pregnancy period in either normal weight or obese mothers. This is important in the context of the dietary advice given to overweight or obese women who are seeking to become pregnant as it is critical that any dietary intervention imposed during the periconceptional period is evidence based and does not incur a further metabolic or endocrine cost in the offspring.

6. Summary

It is clear that further work is required to determine the separate or interdependent contributions of maternal pre pregnancy BMI and gestational weight gain, glycaemic control, and macronutrient intake during pregnancy on the metabolic outcomes in the offspring. It appears from recent studies in the sheep that the early programming of later obesity may result from "two hits" related to the separate influences of maternal obesity experienced during the periconceptional period and during late gestation. Each of these exposures may act through different mechanisms to alter the propensity for triglyceride storage in specific fat depots after birth. While a period of dietary restriction in overweight mothers may ablate the impact of maternal BMI on the programming of postnatal obesity, it is associated with an activation of the stress axis and a potential impact on glucose tolerance in the offspring (Figure 4). Thus, a high maternal pre pregnancy BMI may result in epigenetic changes within the embryo which predict the need for efficient fat storage in postnatal life. In contrast, weight loss in mothers with either a high or normal BMI may lead to epigenetic changes within the stress axis which predict the likely need to respond to adversity in later life. Thus, it is important to ensure that any dietary restriction interventions recommended for overweight or obese mothers are evidence based to allow an effective weighing up of the potential metabolic benefits and costs (Figure 4) for the offspring.

Conflict of Interests

The authors declare that there is no conflict of interests.

Acknowledgments

The work reported from this laboratory in this paper was supported by funding awarded by the National Health and Medical Research Council of Australia (I. C. McMillen, J. L. Morrison) and the Brailsford RobertsonTrust (I. C. McMillen). J. L. Morrison is supported by the South Australian Cardiovascular Research Network. S. Zhang and L. Rattanatray contributed equally to the paper.

References

[1] L. Poston, L. F. Harthoorn, E. M. Van Der Beek, and on behalf of contributors to the ILSI Europe Workshop, "Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement," *Pediatric Research*, vol. 69, no. 2, pp. 175–180, 2011.

[2] S. Kumanyika, E. Obarzanek, N. Stettler et al., "Population-based prevention of obesity: the need for comprehensive promotion of healthful eating, physical activity, and energy balance: a scientific statement from American heart association council on epidemiology and prevention, interdisciplinary committee for prevention (formerly the expert panel on population and prevention science)," *Circulation*, vol. 118, no. 4, pp. 428–464, 2008.

[3] Australian Bureau of Statistics, "Australian Social Trends," ABS: Canberra, Cat No 4102.0, 2007.

[4] K. Flegal, M. Carroll, C. Ogden, and C. Johnson, "Prevalence and trends in obesity among US adults, 1999-2000," *Journal of the American Medical Association*, vol. 288, no. 14, pp. 1723–1727, 2002.

[5] C. L. Ogden, S. Z. Yanovski, M. D. Carroll, and K. M. Flegal, "The epidemiology of obesity," *Gastroenterology*, vol. 132, no. 6, pp. 2087–2102, 2007.

[6] D. La Coursiere, L. Bloebaum, J. Duncan, and M. Varner, "Population-based trends and correlates of maternal overweight and obesity, Utah 1991–2001," *American Journal of Obstetrics and Gynecology*, vol. 192, no. 3, pp. 832–839, 2005.

[7] C. Athukorala, A. R. Rumbold, K. J. Willson, and C. A. Crowther, "The risk of adverse pregnancy outcomes in women who are overweight or obese," *BioMed Central*, vol. 10, no. 56, pp. 1–8, 2010.

[8] L. K. Callaway, J. B. Prins, A. M. Chang, and H. D. McIntyre, "The prevalence and impact of overweight and obesity in an Australian obstetrics population," *Medical Journal of Australia*, vol. 184, no. 2, pp. 56–59, 2006.

[9] E. A. Nohr, M. Vaeth, J. L. Baker, T. I. A. Sorensen, J. Olsen, and K. M. Rasmussen, "Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy," *American Journal of Clinical Nutrition*, vol. 87, no. 6, pp. 1750–1759, 2008.

[10] E. Oken, K. P. Kleinman, M. B. Belfort, J. K. Hammitt, and M. W. Gillman, "Associations of gestational weight gain with short- and longer-term maternal and child health outcomes," *American Journal of Epidemiology*, vol. 170, no. 2, pp. 173–180, 2009.

[11] K. Rasmussen and A. Yaktine, *Weight Gain During Pregnancy: Reexamining the Guidelines*, The National Academies Press, Washington, DC, USA, 2009.

[12] A. M. Siega-Riz, M. Viswanathan, M. K. Moos et al., "A systematic review of outcomes of maternal weight gain according to the institute of medicine recommendations: birthweight, fetal growth, and postpartum weight retention," *American Journal of Obstetrics and Gynecology*, vol. 201, no. 4, pp. 339.e1–339.e14, 2009.

[13] G. Curhan, W. Willett, E. Rimm, D. Spiegelman, A. Ascherio, and M. Stampfer, "Birth weight and adult hypertension, diabetes mellitus, and obesity in US men," *Circulation*, vol. 94, no. 12, pp. 3246–3250, 1996.

[14] E. Oken, E. Taveras, K. Kleinman, J. Rich-Edwards, and M. Gillman, "Gestational weight gain and child adiposity at age 3 years," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 4, pp. 322.e1–322.e8, 2007.

[15] T. J. Parsons, C. Power, and O. Manor, "Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal," *British Medical Journal*, vol. 323, no. 7325, pp. 1331–1335, 2001.

[16] R. C. Whitaker, "Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy," *Pediatrics*, vol. 114, no. 1, pp. e29–e36, 2004.

[17] S. Rugholm, J. L. Baker, L. W. Olsen, L. Schack-Nielsen, J. Bua, and T. I. A. Sorensen, "Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic," *Obesity Research*, vol. 13, no. 12, pp. 2187–2194, 2005.

[18] J. Smith, K. Cianflone, S. Biron et al., "Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 11, pp. 4275–4283, 2009.

[19] C. A. Crowther, J. E. Hiller, J. R. Moss, A. J. McPhee, W. S. Jeffries, and J. S. Robinson, "Effect of treatment of gestational diabetes mellitus on pregnancy outcomes," *The New England Journal of Medicine*, vol. 352, no. 24, pp. 2477–2486, 2005.

[20] M. B. Landon, C. Y. Spong, E. Thom et al., "A multicenter, randomized trial of treatment for mild gestational diabetes," *The New England Journal of Medicine*, vol. 361, no. 14, pp. 1339–1348, 2009.

[21] D. Dabelea, R. L. Hanson, R. S. Lindsay et al., "Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships," *Diabetes*, vol. 49, no. 12, pp. 2208–2211, 2000.

[22] M. W. Gillman, H. Oakey, P. A. Baghurst, R. E. Volkmer, J. S. Robinson, and C. A. Crowther, "Effect of treatment of gestational diabetes mellitus on obesity in the next generation," *Diabetes Care*, vol. 33, no. 5, pp. 964–968, 2010.

[23] P. M. Catalano and H. M. Ehrenberg, "The short- and long-term implications of maternal obesity on the mother and her offspring," *British Journal of Obstetrics and Gynaecology*, vol. 113, no. 10, pp. 1126–1133, 2006.

[24] O. Langer, Y. Yogev, E. Xenakis, and L. Brustman, "Overweight and obese in gestational diabetes: the impact on pregnancy outcome," *American Journal of Obstetrics and Gynecology*, vol. 192, no. 6, pp. 1768–1776, 2005.

[25] M. J. Brion, A. R. Ness, I. Rogers et al., "Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 y: exploring parental comparisons and prenatal effects," *American Journal of Clinical Nutrition*, vol. 91, no. 3, pp. 748–756, 2010.

[26] C. Minge, B. Bennett, R. Norman, and R. Robker, "Peroxisome proliferator-activated receptor-γ agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality," *Endocrinology*, vol. 149, no. 5, pp. 2646–2656, 2008.

[27] P. Nivoit, C. Morens, F. A. Van Assche et al., "Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance," *Diabetologia*, vol. 52, no. 6, pp. 1133–1142, 2009.

[28] S. A. Bayol, S. J. Farrington, and N. C. Stickland, "A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring," *British Journal of Nutrition*, vol. 98, no. 4, pp. 843–851, 2007.

[29] M. J. Morris and H. Chen, "Established maternal obesity in the rat reprograms hypothalamic appetite regulators and leptin signaling at birth," *International Journal of Obesity*, vol. 33, no. 1, pp. 115–122, 2009.

[30] S. Rajia, H. Chen, and M. J. Morris, "Maternal overnutrition impacts offspring adiposity and brain appetite markers-modulation by postweaning diet," *Journal of Neuroendocrinology*, vol. 22, no. 8, pp. 905–914, 2010.

[31] S. L. Kirk, A. M. Samuelsson, M. Argenton et al., "Maternal obesity induced by diet in rats permanently influences central processes regulating food intake in offspring," *Plos One*, vol. 4, no. 6, Article ID e5870, 2009.

[32] K. Rooney and S. E. Ozanne, "Maternal over-nutrition and offspring obesity predisposition: targets for preventative interventions," *International Journal of Obesity*, vol. 35, no. 7, pp. 883–890, 2011.

[33] J. A. Armitage, P. D. Taylor, and L. Poston, "Experimental models of developmental programming: consequences of exposure to an energy rich diet during development," *Journal of Physiology*, vol. 565, no. 1, pp. 3–8, 2005.

[34] J. A. Armitage, L. Poston, and P. D. Taylor, "Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity," *Frontiers of Hormone Research*, vol. 36, pp. 73–84, 2008.

[35] J. A. Armitage, I. Y. Khan, P. D. Taylor, P. W. Nathanielsz, and L. Poston, "Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals?" *Journal of Physiology*, vol. 561, no. 2, pp. 355–377, 2004.

[36] H. Ainge, C. Thompson, S. E. Ozanne, and K. B. Rooney, "A systematic review on animal models of maternal high fat feeding and offspring glycaemic control," *International Journal of Obesity*, vol. 35, no. 3, pp. 325–335, 2010.

[37] I. C. McMillen and J. S. Robinson, "Developmental origins of the metabolic syndrome: prediction, plasticity, and programming," *Physiological Reviews*, vol. 85, no. 2, pp. 571–633, 2005.

[38] K. Shankar, A. Harrell, X. Liu, J. M. Gilchrist, M. J. J. Ronis, and T. M. Badger, "Maternal obesity at conception programs obesity in the offspring," *American Journal of Physiology*, vol. 294, no. 2, pp. R528–R538, 2008.

[39] E. Zambrano, P. M. Martinez-Samayoa, G. L. Rodriguez-Gonzalez, and P. W. Nathanielsz, "Dietary intervention prior

to pregnancy reverses metabolic programming in male offspring of obese rats," *Journal of Physiology*, vol. 588, no. 10, pp. 1791–1799, 2010.

[40] I. C. McMillen, L. Rattanatray, J. A. Duffield et al., "The early origins of later obesity: pathways and mechanisms," *Advances in Experimental Medicine and Biology*, vol. 646, pp. 71–81, 2009.

[41] N. M. Long, L. A. George, A. B. Uthlaut et al., "Maternal obesity and increased nutrient intake before and during gestation in the ewe results in altered growth, adiposity, and glucose tolerance in adult offspring," *Journal of Animal Science*, vol. 88, no. 11, pp. 3546–3553, 2010.

[42] B. S. Muhlhausler, C. L. Adam, P. A. Findlay, J. A. Duffield, and I. C. McMillen, "Increased maternal nutrition alters development of the appetite-regulating network in the brain," *Journal of the Federation of American Societies for Experimental Biology*, vol. 20, no. 8, pp. 1257–1259, 2006.

[43] B. S. Muhlhausler, C. T. Roberts, B. S. J. Yuen et al., "Determinants of fetal leptin synthesis, fat mass, and circulating leptin concentrations in well-nourished ewes in late pregnancy," *Endocrinology*, vol. 144, no. 11, pp. 4947–4954, 2003.

[44] B. S. Muhlhausler, J. A. Duffield, and I. C. McMillen, "Increased maternal nutrition stimulates peroxisome proliferator activated receptor-γ, adiponectin, and leptin messenger ribonucleic acid expression in adipose tissue before birth," *Endocrinology*, vol. 148, no. 2, pp. 878–885, 2007.

[45] S. Todd, M. Oliver, A. Jaquiery, F. Bloomfield, and J. Harding, "Periconceptional undernutrition of ewes impairs glucose tolerance in their adult offspring," *Pediatric Research*, vol. 65, no. 4, pp. 409–413, 2009.

[46] F. H. Bloomfield, M. H. Oliver, P. Hawkins et al., "A periconceptional nutritional origin for noninfectious preterm birth," *Science*, vol. 300, no. 5619, p. 606, 2003.

[47] S. M. MacLaughlin, S. K. Walker, C. T. Roberts, D. O. Kleemann, and I. C. McMillen, "Periconceptional nutrition and the relationship between maternal body weight changes in the periconceptional period and feto-placental growth in the sheep," *Journal of Physiology*, vol. 565, no. 1, pp. 111–124, 2005.

[48] S. M. MacLaughlin, B. S. Muhlhausler, S. Gentili, and I. C. McMillen, "When in gestation do nutritional alterations exert their effects? A focus on the early origins of adult disease," *Current Opinion in Endocrinology and Diabetes*, vol. 13, no. 6, pp. 516–522, 2006.

[49] L. Rattanatray, S. M. MacLaughlin, D. O. Kleemann, S. K. Walker, B. S. Muhlhausler, and I. C. McMillen, "Impact of maternal periconceptional overnutrition on fat mass and expression of adipogenic and lipogenic genes in visceral and subcutaneous fat depots in the postnatal lamb," *Endocrinology*, vol. 151, no. 11, pp. 5195–5205, 2010.

[50] S. Zhang, L. Rattanatray, S. M. MacLaughlin et al., "Periconceptional undernutrition in normal and overweight ewes leads to increased adrenal growth and epigenetic changes in adrenal IGF2/H19 gene in offspring," *Journal of the Federation of American Societies for Experimental Biology*, vol. 24, no. 8, pp. 2772–2782, 2010.

[51] S. Zhang, L. Rattanatray, I. C. McMillen, C. M. Suter, and J. L. Morrison, "Periconceptional nutrition and the early programming of a life of obesity or adversity," *Progress in Biophysics and Molecular Biology*, vol. 106, no. 1, pp. 307–314, 2011.

[52] L. J. Edwards and I. C. McMillen, "Periconceptional nutrition programs development of the cardiovascular system in the fetal sheep," *American Journal of Physiology*, vol. 283, no. 3, pp. R669–R679, 2002.

[53] L. J. Edwards and I. C. McMillen, "Impact of maternal undernutrition during the periconceptional period, fetal number, and fetal sex on the development of the hypothalamo-pituitary adrenal axis in sheep during late gestation," *Biology of Reproduction*, vol. 66, no. 5, pp. 1562–1569, 2002.

[54] J. T. Ross, I. C. McMillen, F. Lok, A. G. Thiel, J. A. Owens, and C. L. Coulter, "Intrafetal insulin-like growth factor-I infusion stimulates adrenal growth but not steroidogenesis in the sheep fetus during late gestation," *Endocrinology*, vol. 148, no. 11, pp. 5424–5432, 2007.

[55] A. J. Wood and R. J. Oakey, "Genomic imprinting in mammals: emerging themes and established theories," *Plos Genetics*, vol. 2, no. 11, pp. 1677–1685, 2006.

[56] B. T. Heijmans, E. W. Tobi, A. D. Stein et al., "Persistent epigenetic differences associated with prenatal exposure to famine in humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 44, pp. 17046–17049, 2008.