Obstetrics and Gynecology International

Drugs during Pregnancy and Lactation: New Solutions to Serious Challenges

Guest Editors: Gideon Koren, Shannon Clark, and Doreen Matsui

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Editorial

Drugs during Pregnancy and Lactation: New Solutions to Serious Challenges

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Ethically, it is very difficult to use the classical paradigms of drug studies in pregnancy, due to the potential fetal risks of prospective exposure of the mother and fetus to chemicals for which safety has not been confirmed. This special issue presents new approaches and offers novel solutions to serious challenges, from the use of antidepressants in pregnancy to domperidone in enhancing lactation, from the potential fetal advantages of polyunsaturated fatty acids to the potential risk of drugs of abuse.

The majority of pregnant women use medications during pregnancy either before recognizing they have conceived or due to the need to treat medical conditions that may affect maternal and fetal well-being. Due to the potential fetal risks of drugs, very few randomized controlled trials are being conducted in early pregnancy, and the numbers are scarce even after embryogenesis has been completed. As a result, women are typically orphaned from the benefits of new therapeutic modalities. Yet, with women tending to postpone the age of starting a family, substantially larger numbers of women experience chronic conditions that necessitate drug therapy.

This issue focuses on major challenges in the area of drug therapy during pregnancy and lactation, looking for evidence of safety and effectiveness with the use of a variety of research methodologies that try to replace the gold standard of randomized clinical trials.

O. Diav-Citrin and A. Ornoy tackle what is probably the biggest contemporary controversy—the fetal safety of antidepressants. Through painstaking review of over 30 studies, they come to the conclusion that fetal and neonatal risks, even if they exist, occur at very low rates and are outweighed by the maternal benefits of these drugs.

M. Moretti and colleagues focus on another controversial area—the fetal safety of ACE inhibitors, commonly used for hypertension. By including a control group matched for the hypertensive morbidity, they strengthen the growing body of evidence suggesting no increased fetal risks after first trimester exposure to ACE inhibitors. With convincing evidence that neonatal folic acid supplementation and fortification can prevent neural tube defects, a fear has emerged that too much circulating folate may increase the risk of cancer as an adverse effect of unmetabolized folic acid. C. Tam and colleagues document that levels of unmetabolized folic acid do not increase in women even when taking 5 mg daily. This detailed biochemical study adds important reassurance that short period use of even 5 mg folate (which is needed in groups of women at high risk for neural tube defects) is safe to the expecting mother.

S. M. Clark and colleagues update the reader on the advances in treating the most common condition in pregnancy—morning sickness. Even today, a large proportion of pregnant women are afraid to treat the symptoms of nausea and vomiting of pregnancy due to unjustified perception of fetal risks. S. M. Clark et al. match the evidence of effectiveness with that of fetal safety, documenting that in 2012 there is no logical reason for a woman not to be managed safely for this condition.

Breastfeeding is the ideal method of infant nutrition; however, not rarely women cannot establish effective milk flow to ensure optimal feeding. Two research papers in

this special issue address this problem, relating directly to the dopaminergic agent domperidone. A. Osadschy and colleagues use a meta-analytic technique to provide evidence that the existing, small studies prove the effectiveness of the drug in improving milk production. C. Mannion et al., bringing the important angle of lactation consultants, explore in a pilot study determinants of success and failure in establishing breastfeeding.

Three papers in this issue explore in-depth methodological issues which challenge different aspects of drug therapy in pregnancy. B. Källén brings his many years of experience in pharmacoepidemiology to the critical discussion of confounders which may affect the interpretation of administrative data bases. These prescription databases, when linked with databases of pregnancy outcome, create a potentially powerful tool in exploring fetal safety of drugs. However, this method is challenged by a large number of serious confounders that must be considered and addressed.

D. Matsui tackles one of the most serious issues in drug therapy in pregnancy—patient compliance. Due to fears of teratogenicity, expecting women tend not to take their medications as prescribed, even in cases of life-threatening conditions. Deeper understanding of these issues is critical if we are to improve drug therapy in pregnancy.

One of the biggest ethical issues in pregnancy is how to gain knowledge on fetal exposure to drugs, when many of these drugs may be unsafe. C. Gedeon and colleagues explore the ethical and practical implications of giving the mother a drug just before an elective pregnancy termination and measuring its kinetics in the abortus.

It appears that scores of such studies have been conducted by scientists in different countries, but this practice has not been accompanied by in-depth discussion on its ethical and legal implication.

Over the last 2 decades a large body of experimental animal research has documented the role of polyunsaturated fatty acids (PUFAs) in ensuring normal fetal brain development. This research has been mirrored by human studies suggesting that offspring of women who suffer from deficits in PUFA are lagging in their visual development. This has led to the commonly held suggestion that enriching the diets of healthy women who do not exhibit PUFA deficiency may improve offspring brain function. Lo and colleague offer the first systematic review of all randomized studies in pregnancy looking at the potential benefits of PUFA supplementation. The results bring into question voices calling for sweeping recommendation to supplement with PUFA women who enjoy normal nutrition.

Lastly, a unique paper by Unger and colleagues tackles the issues of drug exposure and therapy for women suffering from addiction. With increasing numbers of drug-dependent women of reproductive age, optimal care of these women and their unborn children, neonates, and infants should be a major focus.

We hope that you, the reader, will find this special issue stimulating and, as important, relevant to your practice.

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Research Article

Circulating Unmetabolized Folic Acid: Relationship to Folate Status and Effect of Supplementation

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There are increasing concerns that exposure to unmetabolized folic acid, which results from folic acid intakes that overwhelm the liver's metabolic capacity, may be associated with adverse effects. In this paper, we examined the folic acid status of women of reproductive age in relation to dietary intake and the effect of folic acid supplementation (1.1 mg or 5 mg). Plasma unmetabolized folic acid was not significantly correlated with folate intake estimated by food frequency questionnaire or biomarkers. The proportion of women with detectable levels of unmetabolized folic acid increased from 65% to 100% after twelve weeks of supplementation ($P < 0.05$); however, the increase in concentrations did not reach statistical significance and the effect was not sustained. Moreover, there were no significant differences between the two doses. This suggests that there are mechanisms by which the body adapts to high folic acid intakes to limit exposure to unmetabolized folic acid.

1. Introduction

The term "folate" describes the group of B vitamers that share the same vitamin activity based on the parent structure of folic acid. The parent structure consists of an aromatic pteridine ring joined by a methylene bridge to para-aminobenzoic acid (PABA), which in turn is attached to glutamic acid by a peptide bond (Figure 1) [1]. Folate vitamers differ in the oxidation state of the pteridine ring and substitution on the N5 and/or N10 nitrogen atoms. In addition, a polyglutamate tail consisting of up to nine glutamate residues, each one joined via amide linkage to the γ-carboxyl group of the preceding residue, may be added [1, 2].

By convention, the term "folic acid" refers specifically to the fully oxidized and most stable form of the vitamin that is used in supplements and fortified foods.

Biologically, these groups of vitamins are critical in DNA synthesis and repair, and as cofactors in biological reactions involving folate sources. Folate exists naturally in foods as reduced folate polyglutamate conjugates. In addition, folic acid is added as a fortificant to certain foods. As of 2007, fifty-two countries worldwide had national regulations mandating folic acid fortification of wheat flour [3]. Folic acid is also found in supplements and multivitamins.

In general, the bioavailability of folic acid is higher than that of the naturally occurring food folates. Under fasting conditions, the bioavailability of folic acid approaches 100% [4]. When consumed with food, folic acid (either supplemental or as a fortificant) is about 85% bioavailable [4]. The bioavailability of naturally occurring food folates depends on whether folate is present primarily as a monoglutamate or polyglutamate (with the former being more bioavailable) and the presence or absence of dietary and nondietary factors that can facilitate or inhibit folate absorption; on average, it is estimated to be 50%, although it can be as high as 60 to 90% from some fruits and vegetables [5].

Neural tube defects (NTDs) are congenital malformations produced by failure of the neural tube to form and close properly during embryonic development. The most common types of NTDs include spina bifida and anencephaly [6].

A relationship between folate deficiency and malformations of the central nervous system was first suggested in the 1960s by Smithells et al. [7].

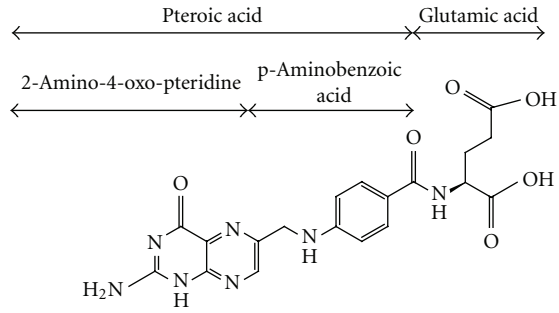

Figure 1: Structure of folic acid [1]. The three parts of the parent structure include 2-amino-4-oxo-pteridine, p-aminobenzoic acid, and glutamic acid. Substitutions (one-carbon groups) occur at the N5 and/or N10 positions.

To clarify the issue, the Medical Research Council of the United Kingdom initiated a multicentre, double-blind, randomized controlled trial (the "MRC Vitamin Study") to evaluate the effect of folic acid with or without other vitamins on the rate of NTD recurrence among women who had a previous pregnancy complicated by an NTD [8]. Among 1195 informative pregnancies, the prevalence of NTDs among women allocated to receive folic acid was 1.0%, compared to 3.5% among women in the other groups. Thus folic acid reduced the risk of NTD recurrence by 72% (relative risk, RR, 0.28; 95% confidence interval (CI), 0.12–0.71). The effect of the "other vitamins" on the risk of NTD recurrence was nonsignificant (RR 0.80; 95% CI, 0.32–1.72).

In parallel to the MRC Vitamin Study, a single-centre, double-blind, randomized controlled trial (the "Hungarian randomized controlled trial") was conducted to evaluate the effect of multivitamin supplementation on first occurring NTDs. There were no NTDs among 2104 pregnancies in the multivitamin/mineral group ($P = 0.029$). The protective effect of the multivitamin (containing 0.8 mg of folic acid) on first occurrent NTDs was estimated to be 90% [9].

In contrast to natural food folates, folic acid is a non-coenzymatic form of folate. Folic acid metabolism involves conversion of folic acid to coenzymatic tetrahydrofolate derivatives, primarily 5-CH_3-H_4PteGlu. The first and rate-limiting step is catalyzed by DHFR, which reduces folic acid to H_2PteGlu (and subsequently to H_4PteGlu) [10]. The expression and activity of DHFR in human liver is relatively low, such that oral doses greater than 260 to 280 μg can saturate the hepatic metabolic capacity, resulting in the appearance of "unmetabolized" folic acid in plasma [11–13]. With single doses, however, folic acid is rapidly cleared from plasma through a combination of uptake into peripheral tissues and renal excretion [14]. On the other hand, two studies have demonstrated the presence of detectable levels of unmetabolized folic acid in fasting plasma samples after eight to 14 weeks of supplementation with 400 μg/day of folic acid [15, 16]. This suggests that daily ingestion of more than 400 μg of folic acid saturates not only hepatic DHFR activity, but also cellular uptake and renal clearance mechanisms.

There is much debate as to whether exposure to unmetabolized folic acid poses a health risk [17]. Theoretically, folic acid could interfere with normal folate metabolism through competition with reduced, coenzymatic folates for transporters, binding proteins, and folate-dependent enzymes [18–20]. For instance, both folic acid and H_2PteGlu are substrates for DHFR. Although the affinity of DHFR for H_2PteGlu is higher than its affinity for folic acid, in the presence of high concentrations of folic acid, folic acid could competitively inhibit the conversion of H_2PteGlu to H_4PteGlu [19]. As neither folic acid nor H_2PteGlu is metabolically active, this could theoretically create an intracellular folate deficiency [19]. Another study observed a downregulation of folate transporters in intestinal and renal epithelial cells cultured in growth media that were oversupplemented with folic acid [20]. Although it remains to be seen whether these *in vitro* effects also occur *in vivo*, the potential implications of disturbed folate metabolism are wide-ranging; it is, therefore, critical that we gain a better understanding of the pharmacokinetics and pharmacodynamics of unmetabolized folic acid.

At present, there is no conclusive evidence that exposure to unmetabolized folic acid causes adverse health effects. However, potential concerns (i.e., those that appear to be uniquely associated with high folic acid intakes) include negative effects on vitamin B12 deficiency, cancer development, immune function, and epigenetic regulation [21].

The objectives of the present study were twofold.

(1) To examine the relationship between plasma concentration of unmetabolized folic acid and (a) dietary folic acid and total folate intake and (b) plasma and red blood cell total folate concentration.

(2) To examine the effect of folic acid supplementation on fasting plasma concentrations of unmetabolized folic acid.

2. Materials and Methods

2.1. Study Population. The blood samples and dietary data presented herein were collected as part of a prospective, randomized, open-label trial of 30 weeks of daily supplementation with 1.1 mg or 5 mg of folic acid as part of a prenatal/postpartum vitamin-mineral supplement [22]. Participants were recruited through posters displayed at the Hospital for Sick Children (Toronto, ON) and at designated locations on the St. George campus of the University of Toronto, advertisement in the Hospital for Sick Children newsletter, online advertisements published on the Hospital for Sick Children and Motherisk websites, and word-of-mouth. Motherisk is a clinical, research, and teaching program affiliated with the University of Toronto that provides evidence-based information on the safety of medications, infections, and other exposures during pregnancy and lactation.

All participants were healthy women between the ages of 18 and 45 at the time of study enrollment. Eligibility was assessed during an initial telephone or in-person interview. Potential participants were screened for the following conditions and excluded from participation, as appropriate.

(i) Use of folic acid supplements or multivitamin supplements containing folic acid in the six months preceding study enrollment.

(ii) Previous pregnancy in which an NTD was detected

(iii) Family history of NTDs.

(iv) Concurrent use of medications known to affect folate status (e.g., antiseizure medications, folate antagonists, and oral contraceptives).

(v) Allergy or hypersensitivity to any of the ingredients in PregVit or PregVit-Folic5.

The protocol for the trial was approved by the Research Ethics Board at The Hospital for Sick Children. Eligible participants provided *verbal* informed consent to proceed with study enrollment; enrolled participants provided *written* informed consent at the first clinic appointment. Information collected during the enrollment process included:

(i) contact information,

(ii) demographic information (e.g., ethnicity, marital status, education, and employment status),

(iii) history of medication and substance use,

(iv) medical and obstetrical histories.

Randomization was performed by the Hospital for Sick Children research support pharmacists. Participants were randomized to receive either PregVit (containing 1.1 mg of folic acid) or PregVit-Folic5 (containing 5 mg of folic acid). Neither the participants nor the study coordinator were blinded, as it was not feasible to modify the product appearance or packaging.

2.2. Study Drugs. PregVit and PregVit-Folic5 are vitamin-mineral supplements designed for use by planning and pregnant women. Both PregVit and PregVit-Folic5 are formulated as two tablets that are to be taken daily: the pink (am) tablet is taken in the morning and the blue (pm) tablet in the evening. The pink tablet and blue tablet contain different vitamins and minerals (Table 1); specifically, iron is supplied in the pink tablet and calcium is supplied in the blue tablet to facilitate iron absorption and reduce adverse events related to iron supplementation.

2.3. Study Procedures. Study visits were conducted in the Clinical Investigations Unit at the Hospital for Sick Children. All participants provided witnessed, written informed consent at the beginning of the first study visit.

At the first study visit, participants provided a fasting blood sample (5 mL) to measure baseline plasma and RBC folate and plasma vitamin B12. Participants were given an eight-week supply of their assigned multivitamins, which was renewed at subsequent study visits, and instructed to take the multivitamins as per the product monograph (i.e., pink tablet in the morning, blue tablet in the evening). Further instruction was given to leave missed or skipped doses in the blister packaging and to return all packaging, including unused tablets, to the study coordinator. Rates of adherence were determined based on the number of pills returned. Participants returned to the hospital at weeks 2, 4, 6, 12, and 30 (±3 days) to provide fasting blood samples (5 mL) for plasma and RBC folate measurements. Plasma vitamin B12 was measured again at week 30.

A validated FFQ [23] was administered during the first and final study visits to assess usual dietary folate intake during the six months prior to study participation and during the 30 weeks (approximately seven months) of study participation, respectively.

2.4. Blood Folate Analyses

2.4.1. Blood Sample Preparation. Venous blood samples were collected in ethylenediaminetetraacetic acid- (EDTA-) treated blood collection tubes (BD Vacutainer K2 EDTA; BD Biosciences, Franklin Lakes NJ) after a minimum six-hour fast. Samples were shielded from light, placed near ice, and processed within two hours of collection.

To determine the hematocrit (Hct), whole blood was drawn into 75 mm heparinized capillary tubes (Allied Corp., Fisher Scientific; Pittsburgh PA) and centrifuged for 3 minutes (Hettich Haematokrit; Tuttlingen, Germany). Hct was reported as the mean of at least two determinations.

Whole blood samples were prepared in triplicate in 2 mL polypropylene microtubes (Sarstedt, Inc., Montréal, QC). Aliquots (100 μL) of EDTA-anticoagulated whole blood were diluted 10-fold in 1% (wt : vol) ascorbic acid (A7631; Sigma-Aldrich Canada Ltd.; Oakville, ON) in deionized water. Samples were vortexed and incubated at 37°C for 30 minutes to allow for lysis of red blood cells and deconjugation of polyglutamylated folates by plasma GGH.

The remaining whole blood was centrifuged at 1500 g for 20 minutes at 4°C (Allegra 21R Centrifuge; Beckman Coulter, Inc., Fullerton, CA) to separate plasma from RBCs. The plasma layer was removed to a 14 mL polypropylene tube (Falcon; BD Biosciences, Franklin Lakes NJ). Aliquots (500 μL) of plasma were transferred to two 2 mL polypropylene microtubes for vitamin B12 analysis. Sodium ascorbate (134032; Sigma-Aldrich Canada Ltd.; Oakville, ON) was added to the remaining plasma to a final concentration of 1% (wt : vol) to prevent oxidative degradation of folate.

All samples were frozen immediately after processing and stored at −80°C.

2.4.2. Affinity-HPLC Assay for Oxidized Folic Acid. Plasma concentrations of oxidized folic acid were measured by the affinity-HPLC method with electrochemical detection described by Bagley and Selhub [24] and Belz and Nau [25].

The affinity column consisted of immobilized FBP that was isolated from dried whey powder. To isolate FBP, 50 g of dried whey powder (ADM Nutraceuticals; Decatur, IL) was suspended in 500 mL of water and the pH was adjusted to pH 9 with 5 mol/L sodium hydroxide. The suspension was refrigerated overnight and then centrifuged at 10 000 g for 30 minutes at 4°C. To prepare the column matrix, the supernatant fraction was allowed to react with Affi-Prep 10 affinity chromatography support (Bio-Rad Laboratories;

Table 1: Composition of study drugs, PregVit and PregVit-Folic5.

Pink (morning) tablet		Blue (evening) tablet	
Vitamin A (as beta-carotene)	2700 IU	Folic acid	
Vitamin B1 (thiamin mononitrate)	3 mg	(PregVit)	1.1 mg
Vitamin B2 (riboflavin)	3.4 mg	(PregVit-Folic5)	5 mg
Vitamin B3 (niacinamide)	20 mg	Vitamin B12 (cyanocobalamin)	12 μg
Vitamin B5 (pantothenate calcium)	5 mg	Vitamin D3 (cholecalciferol)	250 IU
Vitamin B6 (as pyridoxine)	10 mg	Calcium (calcium carbonate)	300 mg
Vitamin E (dL-α-tocopheryl acetate)	30 IU		
Copper (cupric oxide)	2 mg		
Iodine (potassium iodine)	0.15 mg		
Iron (ferrous fumarate)	35 mg		
Magnesium (magnesium oxide)	50 mg		
Zinc (zinc oxide)	15 mg		

Mississauga, ON) overnight at 4°C. The FBP-Affi-Prep 10 slurry was washed sequentially with 20 mmol/L trifluoroacetic acid, 1 mol/L potassium phosphate, and deionized water. To prepare the column, 1 mL of the slurry was transferred to a glass Pasteur pipette packed with glass wool. Folate recovery from the prepared column, determined using [^{3}H]-folic acid (Amersham Biosciences; GE Healthcare; Piscataway, NJ), was 95 ± 2% (n = 10).

To prepare the samples for HPLC analysis, frozen plasma samples were placed in a water bath set at 100°C for 10 minutes to denature plasma proteins. Denatured samples were loaded on the prepared FBP-Affi-Prep 10 column, which was washed sequentially with deionized water to remove nonfolate compounds and then mobile phase (equal proportions of A, B, and C; described in further detail below) to elute the purified folates.

Folic acid was quantified in affinity-purified samples by reversed-phase HPLC with electrochemical detection. The HPLC system consisted of a low-pressure gradient pump (P580A LPG) fitted with an automated sample injector (ASI-100 Autosampler) set at 4°C to minimize sample degradation, phenyl analytical column (250 mm × 4.6 mm internal diameter, 5 μm particle size; BetaSil* Phenyl HPLC Column) installed in an oven set at 30°C (STH 585), and ED50 electrochemical detector with Ag/AgCl reference electrode managed by a computer running Chromeleon software (Version 6.2). The analytical column was purchased from Keystone Scientific (Thermo Fisher Scientific, Inc., Waltham, MA). All other parts and software were purchased from Dionex Corp. (Oakville, CA).

The mobile phase was delivered at a flow rate of 0.75 mL/min and maintained at 25% A (112 mmol/L potassium phosphate, 240 mmol/L phosphoric acid), 7% B (80% (vol : vol) acetonitrile in HPLC-grade water), and 68% C (HPLC-grade water) for the first 10 minutes. Between 10 and 40 minutes, the concentration of B was raised linearly to 20%, providing the gradient. The folic acid derivative was identified on the basis of retention time and comparison to the electrochemical response of the peak of the folic acid standard (F8798; Sigma-Aldrich Canada Ltd.; Oakville, ON).

The limit of detection (signal-to-noise ratio = 3) of our HPLC setup was 100 pg of folic acid. Samples for which measured values were below the limit of quantification were spiked with a known quantity of folic acid standard and reassayed.

Assay performance was evaluated using the standard curve that was generated at the beginning of each assay by injecting the folic acid standard in increasing volumes within the linear range of the assay. Injector precision and retention time reproducibility were within the specified limits (relative standard deviation ≤ 1%).

2.4.3. Microbiological Assay for Total Folate. Plasma and whole blood total folate concentrations were measured using the microtitre plate method described by Molloy and Scott [26], with modification, using the test organism *Lactobacillus rhamnosus* (ATCC 7469; American Type Culture Collection, Manassas, VA), which was reconstituted (thawed) daily from a cryopreserved stock.

To prepare the assay medium, 5.7 g of dehydrated assay medium (Difco Folic Acid Casei Medium; BD Biosciences, Franklin Lakes, NJ) was reconstituted in 100 mL of deionized water. Ascorbic acid was added to a final concentration of 0.05% (wt : vol) and the mixture was heated. When the mixture was hot, but not boiling, 30 μL of Tween 80 (P8074; Sigma-Aldrich Canada Ltd.; Oakville, ON) was added and the mixture was brought to the boil for 2 to 3 minutes. After cooling slightly, 0.075 mg of ascorbic acid was added. The medium was shielded from light and held in an incubator at 37°C while the standards and test samples were prepared and deposited. When ready, thawed *L. rhamnosus* suspension (20 μL) was added to 50 mL of assay medium.

Frozen plasma and whole blood samples were thawed at room temperature, shielded from light. Thawed samples were diluted 80-fold in 1% (wt : vol) sodium ascorbate in deionized water. Aliquots of 20, 40, and 60 μL were deposited in triplicate. 1% sodium ascorbate was added to a volume of 100 μL followed by 200 μL of prepared assay medium.

Microtitre plates were covered with aluminum sealing tape (Corning; Sigma-Aldrich Canada Ltd.; Oakville, ON) and incubated at 37°C for 42 hours (Revco Ultima; Thermo Fisher Scientific, Inc., Waltham, MA). After 42 hours, the plates were inverted and agitated to resuspend the cells, and the sealing tape was removed. The optical density at 590 nm was determined using a 96-well microtiter plate reader (Opsys MR; DYNEX Technologies; Chantilly, VA) linked to a computer running the supplied software for data collection and analysis (Revelation Quicklink; DYNEX Technologies; Chantilly, VA). Folate concentrations were determined based on the standard curve that was generated for each plate. The standard curve was based on a folic acid standard (0.5 ng/mL) that was prepared daily from a frozen stock and deposited in triplicate in aliquots of 0 to 100 μL (0 to 50 pg of folic acid).

All samples for a given subject were analyzed as a set to reduce intraperson variability. Measurements were discarded if the coefficient of variation for the triplicate exceeded 5% or if the measurements did not fall in linear range of the standard curve (7–21 pg); if no usable values remained for one or more weeks from a given subject, all samples from that subject were reassayed, adjusting the dilutions as needed. Otherwise, reported values (in picograms) were plotted against the volume of the initial aliquot (i.e., 20, 40, and 60 μL); the slope of the line of best fit gave the folate concentration in the reaction well, which was multiplied by the dilution factor to determine the folate concentration in the plasma or whole blood sample. RBC folate was calculated according to the following equation:

$$\text{RBC folate} = \frac{\text{whole blood folate} - [(1 - \text{Hct}) \times \text{plasma folate}]}{\text{Hct}}. \quad (1)$$

Assay performance (accuracy and interassay variability) was assessed using a certified whole blood folate standard (95/528; National Institute for Biological Standards and Control, Hertfordshire, UK) that was analyzed in triplicate at two different dilutions on each plate. Reported values were checked against a quality control chart prepared in advance from twenty consecutive assays in which the standard was similarly analyzed. The acceptable limits were defined as ±1 standard deviation from the mean of these twenty determinations. Our analyses yielded an overall interassay coefficient of variation of 3.4% and a measured concentration of 30.6 ± 1.0 nmol/L (stated value: 29.5 nmol/L; [27]).

2.5. Dietary Folate Analyses. The Block Folic Acid/Dietary Folate Equivalents (DFE) Screener (NutritionQuest; Berkeley CA) was administered to assess dietary folate intake. The DFE Screener is an abbreviated folate-targeted food and supplement screening tool that was developed based on dietary data from NHANES 1999-2000 and designed to assess usual and customary folate intake in women [27–29]. It includes 19 food groups and two supplement questions.

Questionnaires were processed and analyzed by NutritionQuest (Berkeley, CA). The results were reported as:

(a) naturally occurring food folates (μg),

(b) folic acid from folic acid-fortified foods (μg),

(c) total food folate, μg (sum of (a) and (b)),

(d) total food folate, μg DFE (μg DFE = (a) + (b) × 1.7).

2.6. Statistical Analyses. Data were tested for normality using the Shapiro-Wilk test, and parametric or nonparametric tests were performed as appropriate. All statistical analyses were performed using SAS for Windows (Version 9.1; SAS Institute, Inc.; Cary NC), except for the Friedman test due to the lack of posthoc analysis options in SAS. Results were considered statistically significant at a P value of ≤0.05.

Subject characteristics are presented as mean ± standard deviation or median (range). Between-group comparisons were performed using Student's t-test, Wilcoxon-Mann-Whitney test, or Fisher's exact test. Dietary folic acid intake and dietary total folate intake were compared between groups and over time by using the MIXED procedure (PROC MIXED) in SAS for Windows. The MIXED procedure fits mixed linear models to data and estimates and tests the significance of between- and within-subject effects.

The relationships between plasma unmetabolized folic acid and (i) dietary folic acid intake, (ii) dietary total folate intake, (iii) total plasma folate concentration, and (iv) total RBC folate concentration were evaluated by calculating Kendall's tau-b rank correlation coefficient, which measures association based on concordance and discordance between paired observations. Kendall's tau-b was seen as preferable to Spearman's rho due to the number of tied ranks (i.e., samples that were below the LOD).

Frequency data, including the proportion of women with detectable concentrations of unmetabolized folic acid, were analyzed by Fisher's exact test for between-group comparisons or Cochran's Q test for within-group comparisons (i.e., change over time). A significant Q statistic was investigated further by planned posthoc pair-wise comparisons using McNemar's test with Bonferroni correction for multiple testing to maintain a procedure-wise type I error rate of 0.05.

As unmetabolized folic acid concentrations were not normally distributed and it was not feasible to transform the data to fit a normal distribution, the effect of folic acid supplementation on plasma folic acid was analyzed using the Friedman test in WINKS SDA 6.0 (TexaSoft; Cedar Hill TX). A significant χ^2 statistic was investigated further by nonparametric posthoc pair-wise comparisons with Tukey adjustment for multiple testing.

3. Results

3.1. Study Population. Between March 2007 and February 2008, sixty-three healthy, nonpregnant women of reproductive age were approached for participation in this study (Figure 2). Twenty-three women were excluded, either because they did not meet the inclusion criteria ($n = 21$) or because they did not wish to participate ($n = 2$); thus

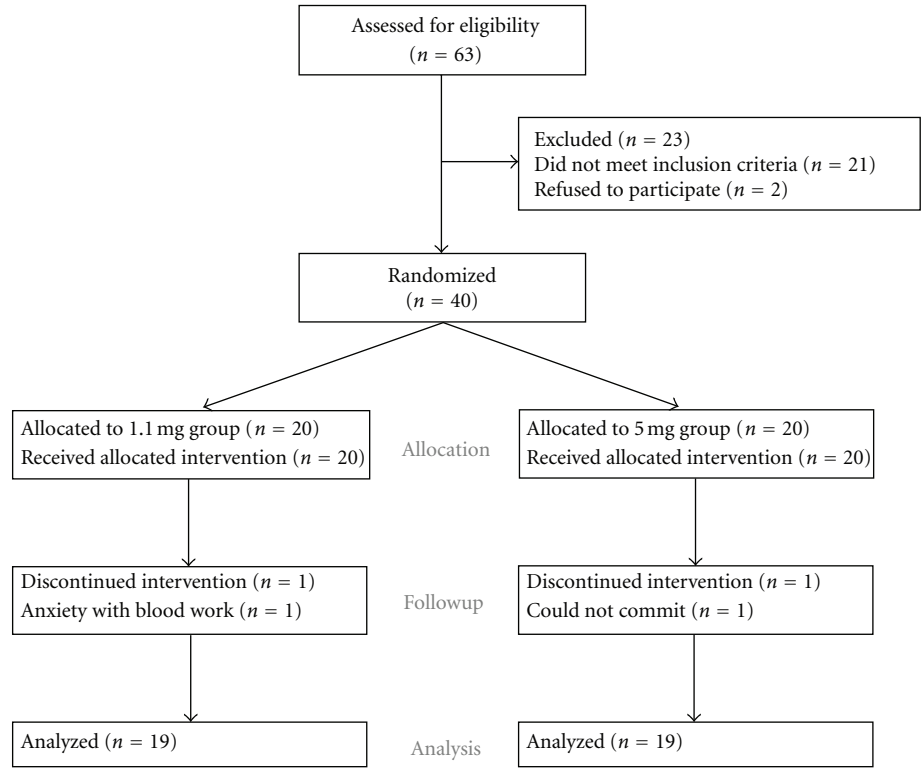

Figure 2: Consolidated Standards of Reporting Trials (CONSORT) patient flow diagram.

40 women were enrolled. Twenty women were randomized to take the multivitamin containing 1.1 mg of folic acid; twenty women were randomized to take the multivitamin containing 5 mg of folic acid. One woman from each group withdrew from the study after the baseline measurement due to anxiety with the blood work ($n = 1$) or inability to commit to the study timeline ($n = 1$). Nineteen women in each group completed the study protocol and were included in the analyses.

There were no significant differences between the two groups of women in the collected patient characteristics (Table 2). Except for one woman who was a student pursuing postsecondary education, all of the women had earned a postsecondary degree (either college or university). The majority of the women were employed—either part time or full time. As per the inclusion criteria, all participants were healthy and were not taking any medications on a chronic basis. In the 1.1 mg folic acid group, one woman used acetaminophen or ibuprofen for infrequent migraine headaches and one used minocycline for acne on an "as needed" basis. In the 5 mg folic acid group, two women reported occasional use of salbutamol for asthma and one received desensitization shots for seasonal allergies. Occasional (social) alcohol consumption was reported by the majority of the women and did not differ significantly between the two groups. One woman in the 5 mg group reported light cigarette smoking.

3.2. Relationship between Plasma Folic Acid and Other Indicators of Folate Status. The relationships between plasma concentration of unmetabolized folic acid and dietary folate intakes and between plasma folic acid and total blood folate concentrations were evaluated by calculating Kendall's tau-b rank correlation coefficient. Correlation coefficients were calculated within each group and for pooled data from both groups, as these analyses were performed on baseline data (i.e., samples collected before supplementation was started).

Plasma folic acid was not found to be significantly correlated with dietary folic acid or dietary total folate (Figure 3) when analyzed by group or in pooled data. A significant negative correlation was observed between plasma folic acid and RBC total folate in the 1.1 mg group (Kendall's $\tau_b = -0.36$, $P = 0.04$), but not in the 5 mg group or in pooled data. After Bonferroni correction for multiple testing, however, the correlation did not retain statistical significance (critical P value = $0.05 \div 12 = 0.004$). No other significant correlations were observed between plasma folic acid and plasma total folate (Figure 4) or RBC total folate (Figure 5).

Subjects were then grouped according to whether or not unmetabolized folic acid was detectable at baseline and compared on the same dietary and biochemical variables (Table 3). Neither dietary folic intake nor dietary total folate intake was significantly higher among individuals with

Table 2: Patient characteristics.

	PregVit (1.1 mg folic acid) ($n = 19$)	PregVit-Folic5 (5 mg folic acid) ($n = 19$)	P[a]
Age (years)	33.4 ± 5.5	35.1 ± 7.0	0.40
Weight (kg)	54.5 (45.5–90.9)	61.8 (50.08–6.36)[b]	0.98
Gravidity[c]	0 (0–4)	1 (0–6)	0.86
Ethnicity			0.29
Caucasian	14	14	
Hispanic	1	0	
South Asian	3	1	
Oriental Asian	1	4	
Education			0.78
High school	0	1	
College	6	4	
University	12	12	
Postgraduate	1	2	
Employment			0.73
Student	2	4	
Part time	2	1	
Full time	14	14	
Homemaker	1	0	
Substance use			
Alcohol	11	15	0.29
Cigarettes	0	1	>0.99

[a] P value, as determined by Student's t-test, Wilcoxon-Mann-Whitney test, or Fisher's exact test.
[b] Data was missing for one patient (i.e., $n = 18$).
[c] The proportion of women who had been pregnant before was not significantly different between the two groups (9/19 versus 10/19; Fisher's exact test, $P > 0.99$).

Table 3: Baseline dietary and biochemical data for participants with detectable or undetectable (i.e., below the LOD) plasma concentrations of unmetabolized folic acid.

	Undetectable ($n = 13$)	Detectable ($n = 25$)	P[a]
Plasma folic acid (nmol/L)	—	8.8 (0.27–41.9)	—
Dietary folic acid (μg/day)	188.5 (56.8–380.0)	191.8 (70.6–395.8)	>0.99
Dietary total folate (μg DFE/day)	477.5 (181.9–849.2)	450.4 (231.9–979.4)	0.52
Plasma total folate (nmol/L)	48.7 (30.3–87.7)	43.7 (27.4–84.8)	0.27
RBC folate (nmol/L)	969.2 (761.0–1777.5)	1018.61 (710.3–2355.1)	0.88

[a] P value, as determined by Wilcoxon-Mann-Whitney test (due to unequal sample sizes).

detectable folic acid compared to those with undetectable levels; similarly, neither plasma nor RBC total folate concentrations were significantly different between the two groups.

3.3. Effect of Folic Acid Supplementation on Plasma Concentrations of Unmetabolized Folic Acid

3.3.1. Adherence to Multivitamin Supplementation. Adverse events were reported by fourteen women (37%) over the course of 30 weeks of multivitamin supplementation, including nausea ($n = 5$), constipation ($n = 3$), abdominal discomfort ($n = 3$), diarrhea ($n = 1$), difficulty swallowing ($n = 1$), and heartburn ($n = 1$). All adverse events were mild in nature, however, and none of the women discontinued supplementation or withdrew from the study as a result of the event. Moreover, there was no significant difference in adverse events between the two groups.

The median rate of adherence was 88.8% (29.8–100%) in the 1.1 mg group and 89.8% (range 37.9–99.5%) in the 5 mg group (Figure 6). The difference was not significant ($z = -0.37$; $P = 0.71$).

3.3.2. Proportion of Plasma Samples with Detectable Folic Acid. The limit of detection (LOD) of our affinity chromatography-HPLC assay was 100 pg (0.18 nmol/L). Before supplementation, the proportion of women with a plasma concentration of unmetabolized folic acid that was above the LOD was 0.63 (95% CI, 0.39–0.83) in the 1.1 mg group and 0.68 (95% CI, 0.44–0.86) in the 5 mg group (Figure 7). There was a significant change in the proportion of women with detectable concentrations of folic acid over time in both the 1.1 mg group (Cochran's $Q = 33.89$; df = 3; $P < 0.001$) and the 5 mg group (Cochran's $Q = 33.69$; df = 3; $P < 0.001$). Posthoc comparisons to baseline were

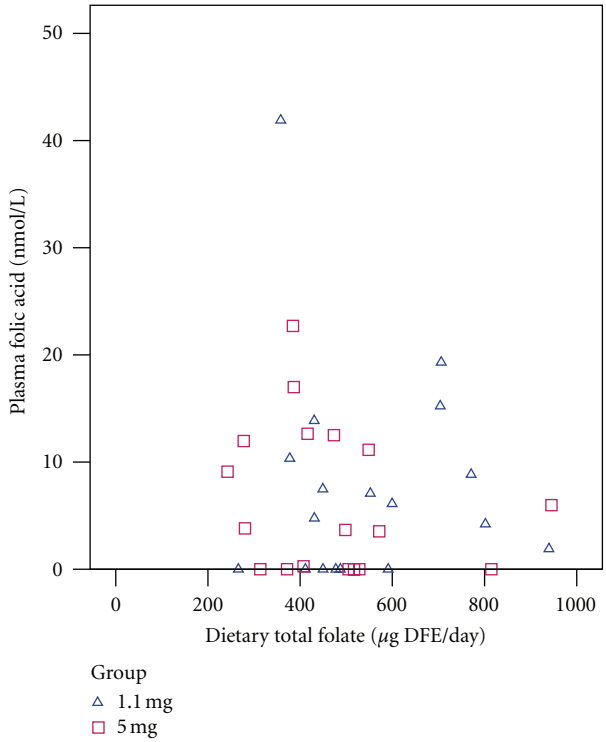

Figure 3: Relationship between plasma folic acid and dietary folic acid intake. 1.1 mg group (triangles): Kendall's $\tau_b = 0.12$, $P = 0.47$. 5 mg group (squares): Kendall's $\tau_b = -0.18$, $P = 0.29$. Pooled: Kendall's $\tau_b = -0.026$, $P = 0.83$.

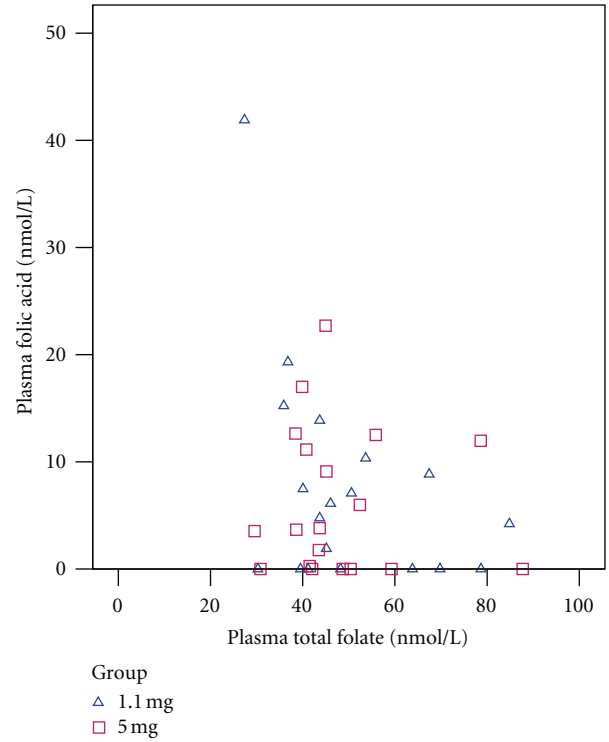

Figure 4: Relationship between plasma folic acid and plasma total folate. 1.1 mg group (triangles): Kendall's $\tau_b = -0.26$, $P = 0.14$. 5 mg group (squares): Kendall's $\tau_b = -0.073$, $P = 0.67$. Pooled data: Kendall's $\tau_b = -0.16$, $P = 0.18$.

statistically significant for week 6 and week 12 ($P < 0.017$) but not week 30 in both groups (1.1 mg: $P = 0.32$, 5 mg: $P = 0.32$; Table 4). Comparing the proportions at each time point, there were no significant differences between the 1.1 mg and 5 mg groups (Fisher's exact test; $P > 0.99$).

In the 1.1 mg group, of the seven women who had *undetectable* plasma concentrations of folic acid at baseline, all had undetectable concentrations of folic acid at week 30; of the 12 women who had *detectable* folic acid at baseline, eleven had detectable concentrations of folic acid at week 30 (kappa = 0.89; 95% CI, 0.68–1.00). A slightly lower level of agreement was observed in the 5 mg group of the six women who had *undetectable* plasma concentrations of folic acid at baseline, five had undetectable concentrations at week 30; of the thirteen women who had detectable folic acid at baseline, ten had detectable concentrations at week 30 (kappa = 0.55; 95% CI, 0.18–0.93).

3.3.3. Plasma Concentrations of Unmetabolized Folic Acid. The distribution of plasma concentrations of unmetabolized folic acid was not normal, nor was it feasible to transform the data to fit a normal distribution due to the proportion of samples that were below the LOD at baseline and at week 30. The data were, therefore, analyzed using the Friedman test, a nonparametric equivalent to the repeated measures analysis of variance. The data were first analyzed by group (Figures 8 and 9).

Table 4: Within-group comparisons of the proportion of plasma samples with detectable concentrations of unmetabolized folic acid.

	McNemar's S	df	P^a
1.1 mg group			
Week 0 versus week 6	7.00	1	0.008
Week 0 versus week 12	7.00	1	0.008
Week 0 versus week 30	1.00	1	0.32
5 mg group			
Week 0 versus week 6	6.00	1	0.014
Week 0 versus week 12	6.00	1	0.014
Week 0 versus week 30	1.00	1	0.32

[a]Critical P value = 0.0167 after Bonferroni correction for 3 pair-wise comparisons within each group ($0.05 \div 3 = 0.0167$).

At baseline, the median plasma concentration of unmetabolized folic acid was 4.8 nmol/L (undetectable to 41.9 nmol/L) in the 1.1 mg group compared to 3.7 nmol/L (undetectable to 22.7 nmol/L) in the 5 mg group ($z = 0.06$; $P = 0.95$). When analyzed by group, the change in plasma folic acid over 30 weeks of supplementation was not significant in the 1.1 mg group ($\chi^2 = 4.71$; df = 3; $P = 0.20$) or the 5 mg group ($\chi^2 = 6.3$; df = 3; $P = 0.10$).

When pooled data from both groups were analyzed, the change in plasma folic acid was found to be significant

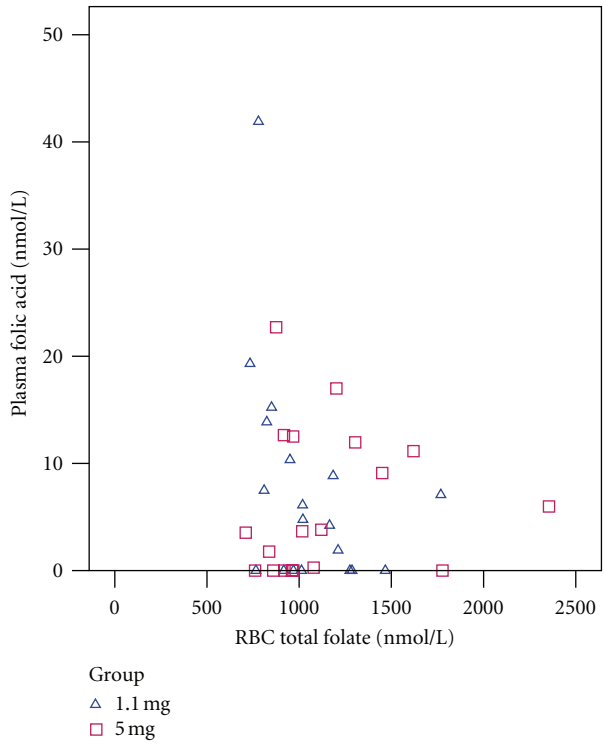

Figure 5: Relationship between plasma folic acid and RBC total folate. 1.1 mg group (triangles): Kendall's $\tau_b = -0.36$, $P = 0.04$. 5 mg group (squares): Kendall's $\tau_b = 0.15$, $P = 0.39$. Pooled data: Kendall's $\tau_b = -0.068$, $P = 0.56$.

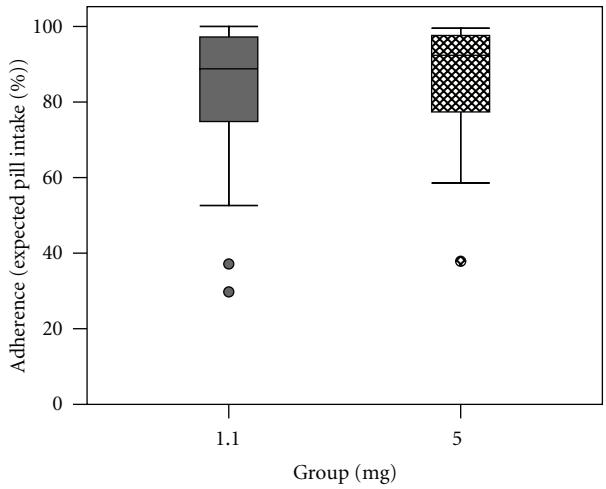

Figure 6: Rates of adherence to multivitamin supplementation.

($\chi^2 = 10.39$; df $= 3$; $P = 0.019$). Posthoc nonparametric multiple comparisons revealed a significant difference between plasma concentrations of unmetabolized folic acid at week 12 and week 30 ($Q = 4.04$; $P < 0.05$).

Comparing plasma folic acid between the two groups at each time point, there were no significant differences (Table 5)

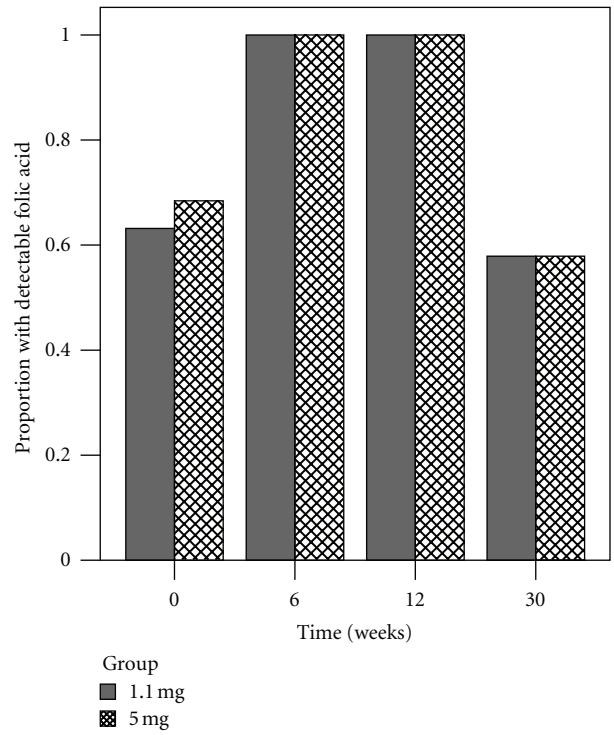

Figure 7: Proportion of plasma samples with detectable concentrations of unmetabolized folic acid. Detection rates at week 6 and week 12 were significantly higher compared to baseline (week 0) in both the 1.1 mg (#) and 5 mg (§) groups.

3.3.4. Estimated Dietary Folate Intake. The Block DFE Screener was administered twice during the study—at the baseline study visit to estimate usual folate intake in the six months preceding study participation and at the final study visit to estimate usual folate intake over the course of the study. Differences between groups and over time were evaluated by mixed-model analysis of variance. There was no significant difference between the two groups at baseline or week 30 in dietary folic acid or dietary total folate intake; similarly, there was no significant change in dietary folic acid or dietary total folate intake from baseline to week 30 (Tables 6 and 7). Thus observed changes in unmetabolized folic acid were most likely due to the intervention, as there was no significant change in dietary intake.

4. Discussion

The women participating in this study were recruited primarily through advertisements posted in The Hospital for Sick Children and through word-of-mouth. Consistent with other studies conducted through the Motherisk program, the women participating in this study tended to be highly educated and of higher socioeconomic status. All of the women were either enrolled in or had completed postsecondary education; the majority was employed full time. As several studies have shown socioeconomic status, which encompasses education, employment, and income, to be a predictor of folate intake and adequacy [28–31],

Table 5: Between-group comparisons of plasma concentrations of unmetabolized folic acid.

	Plasma folic acid (nmol/L)			
	1.1 mg	5 mg	z	P^a
Week 0	4.76 (ND–41.90)	3.67 (ND–22.71)	0.06	0.95
Week 6	7.23 (1.79–81.92)	6.05 (0.18–28.98)	1.26	0.21
Week 12	8.34 (2.42–86.43)	8.02 (0.97–24.31)	−0.11	0.91
Week 30	3.13 (ND–29.66)	4.35 (ND–16.45)	0.06	0.95

[a] P value, as determined by Wilcoxon-Mann-Whitney test.

Table 6: Estimated dietary folic acid intake (μg/day).

	Week 0	Week 30	P (week 0 versus week 30)
1.1 mg	221.5 ± 93.9	218.9 ± 93.4	>0.99
5 mg	194.3 ± 82.8	230.1 ± 116.3	0.22
P (1.1 mg versus 5 mg)	0.78	0.99	

[*] There was no significant effect of time ($F(1, 36) = 1.65$; $P = 0.21$), group ($F(1, 36) = 0.08$; $P = 0.78$), or time-group interaction ($F(1, 36) = 2.19$; $P = 0.15$).

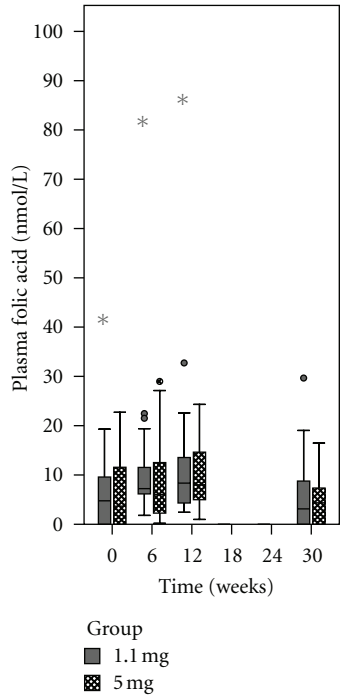

Figure 8: Plasma concentrations of unmetabolized folic acid among women who supplemented with 1.1 mg of folic acid (grey boxes) compared to 5 mg of folic acid (cross-hatched boxes). When analyzed by group, the change in plasma folic acid concentrations was not significant in either the 1.1 mg ($P = 0.20$) or 5 mg ($P = 0.10$) group.

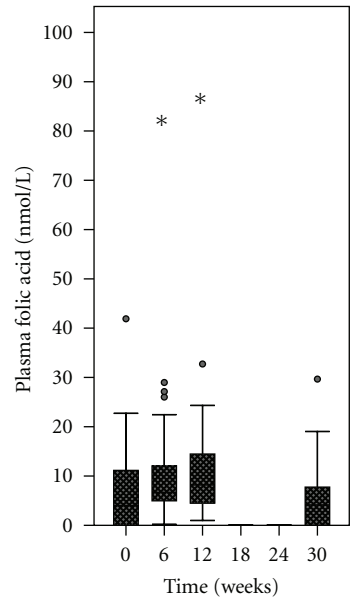

Figure 9: Plasma concentrations of unmetabolized folic acid among women who supplemented with either 1.1 mg or 5 mg of folic acid (all participants combined). When pooled data from both groups were analyzed, there was a significant change in plasma folic acid concentrations ($P = 0.019$). (∗) There was a significant decline from week 12 to week 30 ($P < 0.05$).

it was not surprising that most of the women (84%) had usual dietary folate intakes that met or exceeded the EAR for folate (320 μg/day DFE) from diet alone. Approximately three-quarters of the women met or exceeded the RDA of 400 μg/day DFE; none of the women exceeded the UL for folic acid. Estimated dietary total folate intakes (i.e., including natural food folates and folic acid-fortified foods) in our study group were similar to those reported previously among Canadian women of reproductive age [32–34]. Dietary folate intakes remained relatively stable over the course of the study.

None of the participants were found to be folate deficient (serum/plasma folate < 7 nmol/L or RBC folate < 360 nmol/L). Consistent with a recent report on folate status of women of reproductive age in Ontario, about two-thirds of the women had RBC folate concentrations that are associated with a very low risk for NTDs (>906 nmol/L); one-third of the women, therefore, would be at higher-than-baseline risk for NTDs, if they were to become pregnant.

Table 7: Estimated dietary total folate intake (μg DFE/day).

	Week 0	Week 30	P (week 0 versus week 30)
1.1 mg	525.6 ± 192.2	510.5 ± 191.5	0.97
5 mg	491.1 ± 185.6	541.2 ± 248.8	0.64
P (1.1 mg versus 5 mg)	0.94	0.97	

* There was no significant effect of time ($F(1, 36) = 0.43$; $P = 0.52$), group ($F(1, 36) = 0.00$; $P = 0.98$), or time-group interaction ($F(1, 36) = 1.47$; $P = 0.23$).

4.1. Baseline Concentrations of Unmetabolized Folic Acid. To date, there have been two large population-based studies that examined circulating folic acid concentrations in a country with mandatory folic acid fortification. One study measured unmetabolized folic acid concentrations in plasma samples collected during the sixth examination cycle of the Framingham Offspring Cohort study, which took place between January 1995 and August 1998 [35]; the second study measured folic acid in surplus serum samples collected from NHANES 2001-2002 participants' ≥60 years of age [36].

The prevalence of detectable levels of unmetabolized folic acid in our population at baseline was similar to the prevalence in non-B vitamin users in the Framingham Offspring Cohort examined *after fortification* (67%). In contrast, the median folic acid concentration in our study population was several times higher (3.76 nmol/L compared to 0.50 nmol/L). In the NHANES data set, both the detection rate (38%) and the mean folic acid concentration (1.7 nmol/L; the median was not reported) were lower compared to our population.

The underlying reasons for the apparent discrepancies between detection rates and plasma concentrations are unclear. We used an affinity-HPLC method with electrochemical detection based on the method described by Bagley and Selhub [24], as did the Framingham Offspring Cohort and NHANES studies. The reported detection limits were similar (0.18 nmol/L). However, as reviewed by Bailey and colleagues [36], available studies of unmetabolized folic acid do not demonstrate a relationship between detection rates and LODs, suggesting that the observed discrepancies are more likely due to real differences between the study populations rather than methodological issues. Both the Framingham Offspring Cohort and NHANES studies examined an older population consisting of both men and women, whereas our population consisted of women of reproductive age. The NHANES population is heterogeneous and nationally representative whereas the Framingham Offspring Cohort and our population are more homogenous and self-selected.

Kalmbach and colleagues identified four predictors of "high" folic acid concentrations: dietary folic acid intake, dietary total folate intake, use of B-vitamin supplements, and plasma total folate [35]. We excluded women who reported use of folic acid-containing supplements in the six months preceding study participation and the remaining three measures were not substantially higher in our study population compared to those reported for non-B vitamin users in the Framingham Offspring Cohort. Interestingly, these three measures also did not differ between participants with detectable and undetectable folic acid *within* our population, although the power of this comparison may have been limited by the smaller number of women who had undetectable folic acid ($n = 13$). Another study described a possible "threshold" effect for serum total folate such that the proportion of serum folate as folic acid in samples above 50 nmol/L was found to be significantly higher compared to those below 50 nmol/L [37]. Approximately one-third of the women in this study had a baseline plasma total folate concentration that was greater than 50 nmol/L; however, these thirteen women accounted for almost half of the plasma samples that did not have detectable levels of folic acid. Therefore the higher baseline folic acid concentrations in our population compared to the Framingham Offspring Cohort are not well explained by these factors.

4.2. Relationship between Plasma Folic Acid and Other Measures of Folate Status. The majority of studies describing adverse effects of folic acid and/or folate have evaluated exposures in terms of high folic acid intakes or high plasma or serum folate concentrations. Circulating unmetabolized folic acid has only recently gained the attention of researchers, as prior to the development of chromatographic methods for measuring folate in biological samples, available methods (e.g., microbiological assays, folate-binding assays) did not distinguish between folic acid and reduced folates. With the advent of these chromatographic methods, studies have been able to show that dietary folate intakes and blood folate concentrations are predictive of circulating folic acid. To date, however, these relationships have not been studied in a Canadian population.

The majority of the women (79%) did *not* have usual dietary folic acid intakes that exceeded the threshold dose for the appearance of unmetabolized folic acid in plasma; none consumed more than 400 μg/day, which has been shown to produce a sustained appearance of folic acid in plasma [38]. That folic acid was detectable in the majority of women in spite of low estimated folic acid intakes suggests that either (a) threshold doses are in fact lower than previously reported or (b) estimated folic acid intakes provided by the Block DFE Screener were not accurate.

The activity of DHFR, which is the rate-limiting step in the conversion of folic acid to 5-CH_3-H_4PteGlu, is highly variable. In a study using fresh human liver tissue, DHFR

activity was found to vary approximately fivefold among samples [39]. Presumably, individuals with lower levels of DHFR activity would have lower thresholds and individuals with higher levels of DHFR activity could consume and metabolize larger doses of folic acid. Such variation in the metabolism of folic acid could explain why, contrary to our hypothesis, we did not observe a significant correlation between plasma folic acid and dietary folic acid or total folate intake.

In the present study, dietary folic acid and dietary total folate intakes were estimated using the Block DFE Screener, a validated, folate-targeted, semiquantitative FFQ designed to measure usual and customary intake of dietary and supplemental folate. It was designed as an instrument that would rank subjects well according to folate intake and includes the 19 food groups that contributed to 60% of total folate intake in the United States in NHANES 1999-2000 [40]. However, dietary patterns of Canadians and Americans may be quite different and the quality of food composition tables has been called into question [41], which could reduce the validity of this questionnaire in our population and attenuate the correlation with plasma folic acid.

A recent study of pregnant and postpartum women in Canada found that, similar to NHANES 1999-2000 data, grain products were the greatest contributors to dietary folate intake, followed by fruits and vegetables [33]. These groups are well represented in the Block DFE Screener; however, there are items included in the questionnaire that are not major contributors to Canadian intakes, including meal replacement drinks and bars, hot cereals, tortillas, and beer. Conversely, there are major contributors to dietary folate intake among Canadian women that are not represented in the Block DFE Screener, including dairy products and fast foods. The omission of these food groups could result in inaccurate estimates of folic acid intake for women who consume them.

4.2.1. Relationship between Plasma Folic Acid and Blood Total Folate. The relationship between plasma concentration of unmetabolized folic acid and plasma total folate has been evaluated in several studies. Sweeney and colleagues measured plasma folic acid and plasma total folate in fasting plasma samples obtained from women undergoing elective Caesarean section and in nonfasting plasma samples obtained from a random sampling of individuals attending a blood donor clinic [42]. In both populations, plasma folic acid and plasma total folate were significantly correlated, although the strength of the correlation was stronger in fasting samples ($n = 20$; $r^2 = 0.300$) compared to nonfasting samples ($n = 50$; $r^2 = 0.110$).

In general, studies that found an association between plasma folic acid and plasma or serum total folate included both supplement users and nonusers. As a result, although dietary folic acid intakes were comparable to intakes in our population, mean or median *total* folic acid intakes (i.e., diet and supplements combined) were higher and the ranges of intakes were larger. The restricted range of dietary folic acid intakes in our population might explain the absence of correlation between plasma folic acid and plasma total folate. Because the median plasma total folate concentration in our study was comparable to, if not higher than, mean or median concentrations in previous studies, this further suggests that women in our study were achieving higher plasma folate concentrations as a result of higher intakes of naturally occurring food folates, and not folic acid.

4.3. Effect of Folic Acid Supplementation on Circulating Unmetabolized Folic Acid. Current guidelines advise all women who could become pregnant to consume a daily multivitamin containing 0.4 mg to 1 mg of folic acid [43–45]. Women who are at higher risk for having a baby with a NTD are advised to consume a daily multivitamin containing 4 to 5 mg of folic acid, beginning at least three months before conception. Some authorities also recommend the high-dose strategy for women who have a history of poor medication adherence in addition to lifestyle issues that may increase their risk for NTDs [43].

Until recently, however, there was limited data on the pharmacokinetics of the higher dose of folic acid. Nguyen and colleagues were the first to formally investigate the single-dose and steady-state pharmacokinetics of the 5 mg dose of folic acid in women of reproductive age [22, 46]. As the high-dose strategy provides more than ten-times the dosage that appears to saturate both hepatic metabolic capacity and plasma clearance mechanisms, we decided to expand on these findings by examining the effect of daily supplementation with 5 mg compared to 1.1 mg of folic acid on fasting plasma concentrations of unmetabolized folic acid. To the best of our knowledge, this was the first interventional study to evaluate the effects of long-term folic acid supplementation on plasma concentrations of unmetabolized folic acid among women of reproductive age who are also exposed to folic acid fortification.

4.3.1. Supplementation Increases Plasma Concentrations of Unmetabolized Folic Acid. We observed a significant increase in the proportion of women with detectable levels of unmetabolized folic acid over the first 12 weeks of supplementation; concentrations of unmetabolized folic acid also appeared to increase, however, although the overall effect of supplementation was significant, the differences between baseline and week 6 or week 12 were not statistically significant. This suggests that, although there is an effect of supplementation, it is small relative to the natural variation in circulating folic acid concentrations.

There is limited information on the effect of folic acid supplementation on plasma concentrations of unmetabolized folic acid. Bailey and colleagues have presented, in abstract form, preliminary data from a series of small trials evaluating the effects of 10 to 12 weeks of daily supplementation with 0.4 to 5 mg of folic acid in adults in the United States after fortification [47–49]. These studies included both men and women of varying ages and ethnicities. Plasma concentrations of unmetabolized folic acid at baseline were, on average, 0.5 to 0.7 nmol/L. At the lowest dose tested

(i.e., 0.4 mg/day), plasma folic acid increased approximately twofold over 12 weeks of supplementation. With higher doses (i.e., 1 mg/day, 2.5 mg/day, or 5 mg/day), plasma folic acid concentrations increased approximately threefold.

Similar to Bailey and colleagues' findings, we also found that the median plasma concentration of unmetabolized folic acid doubled (approximately) over the first 12 weeks of supplementation; this was true in spite of baseline values in our population that were, on average, five-times higher. The discrepancy in baseline values is likely due in part to their exclusion of not only individuals who consumed folic acid supplements in the three months preceding their participation in the study, but also those who reported "significant" consumption of folic acid from dietary sources (e.g., fortified breakfast cereals, energy bars, etc.) (J.E. Ayling, personal communication). There are likely other differences between the study populations with respect to characteristics such as age, sex, and ethnicity—some of which may be associated with differences in folic acid metabolism.

It has been suggested that individuals who have detectable levels of unmetabolized folic acid may represent a subpopulation that has altered folic acid metabolism and responds differently to ingested folic acid [36]. In our study, all of the women had detectable folic acid at some time over the course of supplementation; however, it is interesting to note that almost all of the women who had undetectable folic acid at baseline also had undetectable levels at week 30 and almost all of the women who had detectable folic acid at week 30 also had detectable levels at week 30. It is also interesting to note that, comparing the "detectable" and "undetectable" groups, there was no significant difference in dietary folic acid or total folate intake, suggesting that the women who had detectable folic acid at baseline and throughout the study may represent a "sensitive" group in our population. It would have been interesting to investigate the effects of folic acid supplementation among these women compared to the women who had detectable levels only during the interim study visits, however, our limited sample size precluded such analyses.

If such subpopulations do exist and were more highly represented in our study compared to Bailey and colleagues' studies, this might also explain the differences in baseline concentrations of unmetabolized folic acid and response to supplementation.

4.3.2. Plasma Concentrations of Unmetabolized Folic Acid Do Not Remain Elevated. An unexpected observation was a significant decline in concentrations of unmetabolized folic acid between week 12 and week 30, despite ongoing supplementation and sustained total folate concentrations. In fact, plasma concentrations of unmetabolized folic acid at week 30 were not significantly different from concentrations at baseline. Preliminary data from a study that examined folic acid concentrations before and after six months of folic acid supplementation among women of reproductive age observed only minimal changes in folic acid concentrations with doses up to 4 mg/day [37], which is similar to what we observed in our population. Unfortunately, data were not available (or not collected) at smaller intervals over the course of supplementation, thus it is not known whether unmetabolized folic acid concentrations were significantly higher during the interim, as they were in ours (compared to week 30).

We first considered the possibility that adherence decreased over the latter half of the study. In a recent study of prenatal multivitamin supplementation in a cohort of Motherisk callers who had either discontinued a previous multivitamin or had yet to start multivitamin supplementation in pregnancy, the most common reasons for discontinuing or not starting supplementation were nausea and vomiting of pregnancy (NVP), difficulty with taking multivitamins, and adverse gastrointestinal events. Women in the present study, however, did not experience NVP (as they were not pregnant) and although approximately one-third of the women reported adverse events, all were mild in nature and did not result in discontinuation of the intervention or withdrawal from the study. In fact, the median rate of adherence approached 90% in each group. We did not obtain week-by-week or month-by-month records of pill intake, thus we cannot exclude the possibility that adherence was higher in the initial weeks of the study before falling off towards the end; however, no decrease was observed in plasma or RBC total folate concentration. This suggests that pill intake occurred at relatively consistent rate over the course of the study and that the decrease in plasma folic acid was not the result of decreased adherence.

One possible mechanism for the observed decline in plasma concentrations of unmetabolized folic acid is upregulation of folic acid metabolism [9, 50]. Kamen and colleagues found that, as compared to human liver cells *in situ*, the expression and activity of DHFR was 100- to 200-times higher in human cell lines *in vitro* and fresh rat liver cells. It was postulated that exposure to high levels of folic acid in culture medium and laboratory rodent chow upregulated DHFR activity in cultured cells and in laboratory animals [51]. Theoretically, a similar process may occur in DHFR at the intestinal mucosa.

DHFR expression is partly controlled by a translational autoregulatory mechanism, where binding of DHFR to its cognate mRNA inhibits translation of the transcript [23]. Binding of H_2PteGlu to the DHFR-mRNA complex induces a conformational change that releases the mRNA transcript, resulting in resumption of translation and DHFR synthesis. As the first step in the metabolism of folic acid to coenzymatic forms is the reduction of folic acid to H_2PteGlu, cells exposed to high levels of folic acid would likely accumulate high levels of H_2PteGlu as well. Thus folic acid, via reduction to H_2PteGlu, could theoretically upregulate DHFR expression by translational derepression. Further studies are needed to determine whether or not induction of DHFR by folic acid occurs *in vivo* and, if so, to what clinical outcome.

4.3.3. Effect of Dose of Folic Acid Supplementation. Contrary to our original hypothesis, plasma concentrations of

unmetabolized folic acid were not significantly higher in the 5 mg group compared to the 1.1 mg group. This is consistent with preliminary data from the series of studies conducted by Bailey and colleagues that found no significant difference in folic acid concentrations achieved over 10 weeks of supplementation with daily doses up to 5 mg (compared to 1 mg) [47–49]. Although we cannot exclude the possibility that individuals consuming a supplement containing 5 mg of folic acid daily will temporarily be exposed to higher amounts of folic acid immediately after dosing, taken together, these data suggest saturation of folic acid uptake and/or retention and the existence of mechanisms that restore and maintain folate homeostasis following ingestion of pharmacological doses of folic acid. Nguyen and colleagues' analysis of plasma and RBC total folate concentrations achieved in this trial of folic acid supplementation were also suggestive of a limiting mechanism, as only a twofold difference in plasma and RBC total folate concentrations was observed despite a fivefold difference in dose [22].

At physiological doses, folic acid is absorbed via carrier-mediated transport involving the PCFT and RFC [7]. Pharmacological doses, however, saturate carrier-mediated transport systems and are likely absorbed primarily via passive diffusion [4]. As passive diffusion is a slower and less efficient means of absorption, this may explain the apparent nonlinearity in steady-state pharmacokinetics of pharmacological doses of folic acid.

Another mechanism may involve downregulation of the intestinal and/or renal transporters that are responsible for folate absorption and reabsorption, respectively. Using the Caco-2 cell line model of the intestinal epithelium and HK-2 cells (proximal renal tubule epithelial cells), Ashokkumar and colleagues observed that carrier-mediated uptake of tritiated folic acid by Caco-2 and HK-2 cells maintained in folate-oversupplemented media was significantly and specifically lower compared to cells maintained in folate-sufficient media [20, 23]. This was accompanied by significantly lower levels of RFC and PCFT protein in both intestinal and renal epithelial cells and of folate receptor protein in renal epithelial cells. This downregulation appeared to be mediated in part via a transcriptional mechanism, as mRNA transcript levels and promoter activity were lower in folate-oversupplemented cells. The reduction in folate receptor protein is of particular interest to this discussion because it is unique among the three proteins studied in that it has a higher affinity for folic acid than it does for reduced folates [52]. At least one-quarter of a 4 mg dose of folic acid is excreted unchanged as a result of exceeding the renal capacity for reabsorption, which is mediated by the folate receptor [53]. This would be exacerbated by a reduction in folate receptor expression and might offer a partial explanation for the absence of significantly higher levels of circulating folic acid in 5 mg group.

As the PCFT and folate receptor are also expressed in peripheral tissues, downregulation of these transporters would theoretically lead to decreased cellular uptake of folic acid. Although this would lead to *higher* concentrations of unmetabolized folic acid in plasma, it would also predict a larger proportion of the dose being available for renal excretion. This may be compounded by saturation of cellular folate pools under conditions of high folate intake; as cellular folate concentrations increase, there is increased competition for FPGS and the marginal formation of polyglutamates decreases [54]. Under these conditions, only a small proportion of folate that enters the cell is retained and the majority is released back into plasma.

In the primary analysis of this trial, Nguyen and colleagues found that women receiving the 5 mg dose of folic acid achieved significantly higher plasma and RBC *total* folate concentrations compared to women receiving the 1.1 mg dose [22]. This, together with our finding that unmetabolized folic acid concentrations were not significantly higher, suggests that the higher total folate concentrations achieved with the 5 mg dose of folic acid constitute reduced, coenzymatic folates. Therefore, upregulation of DHFR, as described in the previous section, may be another mechanism by which exposure to unmetabolized folic acid was regulated among women in the 5 mg group.

It is clear that folic acid supplementation is important for planning and pregnant women. What is not clear, however, is the optimal dose of folic acid needed for the prevention of NTDs and other folate-dependent congenital malformations. Current guidelines advise all women who "could become pregnant" to consume a daily multivitamin providing 0.4 mg to 1 mg of folic acid; a woman deemed to have personal characteristics or health conditions associated with an elevated risk of having a baby with an NTD may be advised to consume a higher dose of folic acid, depending on her contemporaneous folate status. However, there is a lack of research on the pharmacokinetics and safety of high-dose folic acid supplementation.

Folic acid is generally considered to be safe at doses up to 1 mg/day and there is little evidence to show that doses up to 5 mg/day are harmful to healthy adults. In recent years, however, there has been increasing concern that exposure to unmetabolized folic acid, which results from folic acid intakes that overwhelm the body's metabolic capacity, may be associated with adverse effects.

In Canada, legislation mandating fortification of enriched cereal grains with folic acid was introduced in 1998, resulting in universal increases in folic acid intakes and folate concentrations in the blood. In addition to consuming folic acid-fortified foods, many women also consume supplements containing folic acid, thus it is important to develop a better understanding of the relationship between unmetabolized folic acid and dietary and biochemical indicators of folate status and the effect of supplementation.

In this study, we evaluated plasma unmetabolized folic acid in relation to dietary folate intake, blood total folate concentration, and the effect of supplementation among healthy women of reproductive age using plasma samples collected from a randomized trial comparing 30 weeks of supplementation with 1.1 mg or 5 mg of folic acid per day. To the best of our knowledge, this was the first clinical trial that was conducted for the purpose of evaluating the pharmacokinetics of high-dose folic acid supplementation in this population and the data presented herein are the first to

describe the folic acid status of women of reproductive age in a folic acid-fortified population.

In this study, we found that unmetabolized folic acid is present at low levels in the majority of women who *do not* consume folic acid supplements but who *do* consume folic acid-fortified foods. Contrary to our original hypothesis, however, there was no significant correlation between plasma folic acid and dietary folic acid or total folate intake or between plasma folic acid and plasma or RBC total folate in samples collected at baseline (i.e., before supplementation). The former may reflect imprecision in our method of dietary assessment and the relatively restricted range of folic acid intakes in our population. On the other hand, the latter suggests that the ability to metabolize folic acid to reduced derivatives is highly variable and that *this* may be a more important determinant of systemic exposure to unmetabolized folic acid.

Upon initiation of supplementation, we observed a significant increase in the proportion of women who had detectable levels of unmetabolized folic acid in fasting plasma samples; however, the increase was not sustained. A similar rise and fall was observed in the concentrations of unmetabolized folic acid over the 30-week supplementation period; however, the increase in plasma folic acid over the first 12 weeks of supplementation did not reach statistical significance. After 30 weeks of supplementation, both the proportion of women with detectable folic acid and concentrations of folic acid returned to levels that were not significantly different compared to baseline. For both measures, there were no significant differences between the women receiving the 1.1 mg dose and those receiving the 5 mg dose. These data suggest that there are homeostatic mechanisms that limit systemic exposure to circulating folic acid, such as downregulation of carrier-mediated transport systems and upregulation of folic acid metabolism.

Taken together with data previously published by our group, it appears that women who supplement daily with 5 mg of folic acid achieve higher plasma and RBC total folate concentrations compared to women who supplement with 1.1 mg/day *without* an apparent increase in exposure to unmetabolized folic acid. This further suggests that the higher plasma and RBC total folate concentrations achieved with the 5 mg dose of folic acid represent reduced, coenzymatic folate; however, additional studies will be needed to confirm.

In summary, this work both corroborates and contradicts current and common views on folic acid metabolism. For instance, hepatic DHFR activity in humans is considered to be highly variable but universally low. The variation in unmetabolized folic acid concentrations before and during supplementation that we observed supports the notion that hepatic metabolic capacity is highly variable; however, for many women in the present study, plasma concentrations of unmetabolized folic acid remained low even though they were consuming 2.5- to 12.5-times the daily dose that was previously shown to produce a sustained appearance of folic acid in plasma. For these women, it would appear that concerns surrounding excessive exposure to unmetabolized folic acid with the 5 mg dose may be unwarranted; thus further consideration could be given to the high-dose folic acid strategy for the primary prevention of NTDs even in the absence of the standard risk factors. On the other hand, until more is known about the safety of exposure to unmetabolized folic acid, alternative approaches to achieving optimally protective folate concentrations could be considered for women who have a lower capacity to handle folic acid. One alternative could be supplementation with levomefolic acid (the calcium salt of 5-CH_3H_4PteGlu).

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Review Article

Opioid Dependent and Pregnant: What Are the Best Options for Mothers and Neonates?

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Pregnancy in opioid-dependent women is a major public health issue. Women who are afflicted by opioid addiction are a highly vulnerable group of patients frequently becoming pregnant unplanned and at risk of adverse pregnancy outcomes and perinatal complications. Opioid agonist maintenance treatment is the best option for the majority of women. Ideally, early and closely monitored treatment in an interdisciplinary team approach including social workers, nurses, psychologists, psychiatrists, gynecologists, anesthesiologists, and pediatricians should be provided. The treatment of comorbid psychiatric conditions, the resolution of financial, legal, and housing issues, and the psychosocial support provided have a significant effect on optimizing pregnancy outcomes. This paper aims to update health professionals in the field of gynecology and obstetrics on the latest optimal treatment approaches for mothers suffering from opioid dependence and their neonates.

1. Introduction

Illicit drug use among pregnant women is an international health issue that has become of increasing relevance in the past decades. In 2001, a national household survey reported 3.7% of pregnant women in the United States using illicit drugs [1]. In 2009 this number had increased to 4.5% [2]. The actual numbers are higher if estimated numbers of unreported cases are taken into account due to fear of stigmatism impairing self-report measures. In fact, a study of maternal urine samples at delivery of 715 women in Florida showed 13.3% were positive for an illicit drug such as marijuana, cocaine, or opiates. Although among illicit substances, the prevalence of substance abuse among pregnant women was highest for marijuana, followed by cocaine [3], the prevalence of opioid dependence was on the rise between 1970 and 1980 [4] and an estimated 8 million people worldwide were reported to abuse opioids in 2003 [5]. Though men still outnumber women, the proportion of women continues to increase, and more than 70% of opioid-dependent women are of child-bearing age. Unplanned pregnancies are common due to effects of opioids on the female reproductive system, frequently leading to irregular menstruation or amenorrhea [6]. Additionally, chaotic lifestyles associated with drug abuse often foster insufficient birth control measures and consequently unexpected pregnancies. In fact, the rate of unintended pregnancies has been found to range between 80% and 90% among opioid-dependent women [7].

2. Opioid Dependence and Pregnancy

Opioid-dependent women commonly face numerous socioeconomic problems such as unemployment, coaddicted partners, and partner violence [8]. Prostitution as a means of attaining drugs often leads to health problems such as infectious disease or these occur as a consequence of syringe sharing and are poorly attended to [9]. The majority of opioid-dependent women suffer cooccurring psychiatric disorders with prevalence numbers ranging between 56 and 73%, mainly affective disorders, PTSD, or personality disorders [9–11] (see Table 1).

The failure to recognize mental disorders is a major risk to the health of mother and neonate as comorbid depression, anxiety disorders, and psychosis are associated with a variety

Table 1: Psychiatric *comorbidity* in substance abuse treatment and matched controls*.

	SA	Controls
Depression	36.3%	4.2%
Anxiety disorder	16.3%	2.3%
ADHD	17.2%	3.0%
Conduct disorder	19.3%	1.2%
Conduct disorder (w/ODD)	27.3%	2.3%
Any psychiatric diagnosis	55.5%	9.0%

*All $P < .001$ [12].

of negative pregnancy outcomes [13]. Examples of these are preterm labor and poor fetal growth [14, 15], a heightened risk for perinatal complications and dysfunctional mother-child bonding [16]. Ideally, comorbid psychiatric conditions should be adequately treated, and the use of antidepressant drugs such as SSRI medication, which has been shown to be safe during pregnancy, may be indicated. However, a careful risk-benefit evaluation of pharmacological treatment by a psychiatric professional experienced in treating pregnant women is warranted [17]. It should be part of a multiprofessional team approach comprising psychiatrists, psychologists, gynecologists, midwifes, nurses, social workers, and anesthesiologists. (see Figure 1).

3. Medical Treatment of Opioid-Dependent Pregnant Women

Though ultimately, abstinence from opioids might seem the best option during pregnancy, few opioid-addicted women can handle abstaining from opioids at such a time in their lives filled with changes and stress. Additionally, rapid detoxification during pregnancy cannot be recommended from a medical standpoint, as withdrawal has been linked to intrauterine stress for the fetus associated with poor fetal growth, preterm delivery, and fetal death [18]. Though gradual detoxification in the second or third trimesters has been achieved in a selected group of women, the majority of women have a high risk of relapse. The best option for most opioid-addicted pregnant women is opioid maintenance treatment with a long-acting synthetic opioid such as methadone or buprenorphine [19–24]. Methadone has for a long time been the established maintenance medication for pregnancy [25, 26], however, in recent years, buprenorphine has been increasingly subject of studies as a valuable alternative to methadone with beneficial effects on the neonatal abstinence syndrome of the newborn.

Pioneer work with standardized prospective evaluation on the use of buprenorphine in pregnant women has been conducted in the late 1990s by Fischer et al. at the Addiction Clinic in Vienna, who was first to publish a study demonstrating maternal and fetal safety of women maintained on buprenorphine during pregnancy and consecutively during conception [22, 27]. The pilot study published in 2000 was followed by a double-blind, double dummy comparison study of 14 women published in 2006, forming a first basis for larger follow-up studies and showing higher retention rates in the buprenorphine group. So far, the largest double-blind, double dummy study comparing the safety and efficacy of buprenorphine versus methadone in pregnant opioid-dependent women was the "MOTHER study" (Maternal Opioid Treatment: Human Experimental Research). It was conducted between 2005 and 2008 as a multisite randomized controlled trial encompassing 6 US American sites and one European site at the Addiction Clinic, University Hospital of Vienna, Austria. The main outcome of this trial of 131 completers and their neonates was recently published in the New England Journal of Medicine [28], finding that neonates prenatally exposed to buprenorphine had a significantly shorter duration of treatment and required significantly lower amounts of morphine medication compared to methadone-exposed neonates. The shorter duration of hospitalization of buprenorphine-exposed neonates should also be seen in the light of health service costs, as large numbers of neonates are affected by NAS every year. However, treatment with methadone still has its place as 28 of 86 women in the buprenorphine group (33%) discontinued treatment compared to 16 of 89 women (18%) maintained on methadone [28]. Buprenorphine can be seen as an important treatment option for this target group, but methadone continues to be the medication for those women who do not positively respond to buprenorphine.

Another important aspect affecting pregnant opioid-maintained women that deserves mention is the need for dose adjustment in the majority of women, usually around the beginning of the third trimester, due to changes in metabolic rates, increased estrogen levels, and enzyme induction [29, 30]. After delivery, most women will request dose decreases due to changes in hormonal status. The same principle applies to the use of psychotropic medications during pregnancy, such as SSRIs, where frequently dose adjustment is necessary, and psychiatric symptoms can worsen temporarily.

Recent reports have shown that not only the dose but also the duration of maintenance treatment during pregnancy plays a role in improvement of pregnancy outcomes, as in a recent study women who had been on methadone maintenance treatment (MMT) for the full pregnancy had higher birth weights and a higher likelihood of abstinence from concomitant medication associated with higher gestational age at delivery compared to women who had only been on MMT for part of their pregnancy [31]. Results from studies like this emphasize the responsibility of gynecologists to seek close cooperation with addiction specialists as soon as pregnancy is ascertained.

4. Perinatal Pain Management of Opioid-Dependent Women

Opioid dependence is associated with heightened sensitivity to pain, chronic hyperalgesia, and tolerance to opioid pain medication [32], making peripartum pain management of opioid-dependent women particularly challenging. There is a

Figure 1: The multiprofessional team approach at the Addiction Clinic, University hospital of Vienna, Department of Psychiatry.

persistent lack of standardized treatment recommendations, stigma, and overcaution due to fear of "drug-seeking" behavior, resulting in undertreatment of peripartum pain in the majority of cases. Additional factors such as nicotine addiction also contribute to heightened pain sensitivity [33, 34]. This is significant given that more than 90% of opioid-dependent women are smokers [35]. Due to abrupt nicotine deprivation in the hospital, they often require higher doses of pain medication [36]. Furthermore, the high prevalence of other psychiatric diagnoses, such as affective disorders, represent an additional independent predictor of intensified pain experience [32, 37]. Prior recommendations on pain treatment of opioid-dependent patients have stressed the importance of continuous, adequately dosed maintenance treatment as a basis [38]. Recent findings support this recommendation and, additionally, the use of NSAIDs (NonSteroidal Anti-Inflammatory Drugs) to supplement, and the use of opioids, other than the ones used for maintenance treatment, for sufficient pain control during delivery and postpartum [32, 39]. The use of NSAIDs cannot be recommended during pregnancy, particularly during the third trimester due to the risk of early closure of the ductus arteriosus. In early pregnancy the use of NSAIDs has been linked to increased risk of miscarriage and premature birth [40].

5. The Neonatal Abstinence Syndrome of the Newborn

The neonatal abstinence syndrome of the newborn is a condition which becomes manifest in the first few days after delivery affecting more than half of newborns born to opioid-dependent mothers [41]. It is characterized by symptoms affecting primarily the central nervous system, the respiratory system, and the digestive tract. The first scale for measurement of neonatal abstinence syndrome was developed by Loretta Finnegan et al. in the early 1970s [42]. It consists of symptoms such as increased sneezing, watery eyes, frequent yawning, poor sucking, reduced sleep duration after feeding, and increased (hyper) reflexes. Management of this condition is best handled in a multiprofessional team approach in specially trained centers, where symptoms of neonates are rated at regular intervals and, if needed, treatment is initiated using morphine hydrochloride drops given to infants. In 2007, Fischer and colleagues at the Vienna addiction clinic published a study comparing phenobarbital to morphine hydrochloride as NAS treatment medication, showing that the majority of neonates had a significantly shorter duration of NAS under morphine hydrochloride drops which has become the established form of treatment [43]. However, prolonged use of morphine in the postnatal period should be avoided as recent studies have demonstrated a number of negative consequences of opioids on neural cells of the growing brain [44].

A recently updated Cochrane review by Osborn referring to treatment options in 645 infants confirmed that opiate (morphine) treatment is superior to supportive care only. The analysis of prior studies also showed that opiate treatment was also superior to phenobarbitone and to diazepam in terms of rates of treatment failure and in reducing the likelihood of seizures [41]. The basis for effective medical treatment of NAS is the standardized rating of symptoms in neonates and supportive nonpharmacological interventions [45].

6. Individual Predisposition to NAS

A question which has not been resolved despite numerous hypotheses is why some neonates will develop symptoms of neonatal abstinence syndrome, and others will not. The

majority of studies that have examined the association between maternal maintenance dose and NAS have found no association [21, 23, 27, 46–50]. A most recent review and meta-analysis of 67 studies on maternal methadone dose and NAS, and another encompassing 10 studies with various medications, support prior findings, also not reporting any correlation [51, 52]. Factors that do have an impact on NAS and neonatal outcomes are concomitant consumption of opioids, cocaine, or other substances. In particular, benzodiazepine consumption has been associated with prolonged neonatal abstinence syndromes [53]. Another factor, which has been shown to play an important role during pregnancy, is the use of nicotine, as over 90% of opioid-dependent pregnant women are strongly dependent on nicotine [35, 54]. The prescription use of SSRIs and other psychotropic medications also has a negative impact on NAS [55]. The role of neonatal gender in NAS occurrence has been addressed in two prior studies which found inconclusive results. One study of a population of 64 neonates exposed to methadone found that male neonates exhibited a higher NAS intensity in the first four days postpartum, however, no sex-specific differences in rates of NAS treatment were found [55]. The second study reported no significant sex-related differences in a retrospective chart review of 308 methadone-exposed neonates [56].

Though some factors have been determined that can be seen as predictors of NAS, a lot of questions around this topic remain unresolved. There is a good chance that answers may actually rather be found on a more complex level such as biochemical processes in the placenta. Genetic variations of certain placental transporter genes could explain levels of maternal opioids in the fetal circulation during pregnancy, which in turn could explain severity and incidence of NAS [57, 58]. However, further research is needed to clarify these findings, and it is also questionable how such genetic findings can contribute to therapeutic options.

7. Breastfeeding and Maintenance Treatment

Breastfeeding under oral opioid agonist treatment is recommendable for women if they are not comorbidly suffering from active forms of infectious disease such as hepatitis C with high blood viral loads; HIV is a definite contraindication. For methadone, breastfeeding can reduce the severity and duration of NAS and delay the onset of symptoms [59–61]. One reason for this can be the comfort obtained through mother/child bonding, another, the oral bioavailability of methadone. As a result of breast feeding under methadone maintenance, the need for medical treatment of NAS may be decreased [61]. If women want to breastfeed and no contraindication such as either infectious disease or continued illicit drug use exists, physicians should support their needs [62–64]. The safety of buprenorphine in breastfeeding has not been well-investigated. So far, data available show low concentrations in breast milk [65] so that a similar recommendation might be valid as for methadone. Nonetheless, though findings so far are supportive, they are restricted by shorter periods of observation and smaller numbers of investigated cases [66].

8. Conclusion

Opioid-dependent pregnant women are a highly vulnerable group of patients who frequently have unplanned pregnancy [7] and are at risk of unfavorable outcome and perinatal complications. They often suffer comorbid psychiatric disorders that need to be recognized and treated adequately in order to avoid complications during pregnancy and ensure a chance for healthy mother-child interaction. The majority of women benefits most from opioid agonist maintenance therapy with a long-acting synthetic opioid such as methadone or buprenorphine. The management of pain during delivery and thereafter is often challenging due to opioid tolerance and heightened pain sensitivity. Opioid-dependent pregnant women are in need of early and closely monitored treatment in a multiprofessional team approach including social workers, nurses, psychologists, psychiatrists, gynecologists, anesthesiologists, and pediatricians. The resolution of financial, legal, and housing issues, and the psychosocial support provided through treatment have a significant effect on optimizing pregnancy outcomes.

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Research Article

Effect of Domperidone on Insufficient Lactation in Puerperal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background. There is a controversy within the medical community regarding the role of domperidone as a galactagogue and the drug has been removed from the US market owing to safety concerns. *Objective*. To perform a systematic review and meta-analysis of the available data assessing the effect of domperidone on breast milk production in women experiencing insufficient lactation. *Study Selection*. Randomized controlled trials (RCTs) examining the effect of domperidone on breast milk production of puerperal women were eligible for inclusion. *Data Analysis*. Absolute and relative changes from baseline were calculated for individual studies and pooled using a random effects model. *Results*. Three RCTs including 78 participants met the inclusion criteria. All showed a statistically significant increase in breast milk production following treatment with domperidone. The analysis of pooled data demonstrated a statistically significant relative increase of 74.72% (95% CI = 54.57; 94.86, $P < 0.00001$) in daily milk production with domperidone treatment compared to placebo. No maternal or neonatal adverse events were observed in any of the trials. *Conclusions*. Evidence from a few small RCTs of moderate to high quality suggests that domperidone produces a greater increase in breast milk supply than placebo.

1. Introduction

The benefits of breastfeeding are well recognized for both the mother and baby; thus, efforts should be made to promote initiation, duration, and exclusivity of breastfeeding [1]. The recently published survey of Canadian women who gave birth and were residing with their infants at the time of the interview has found that breastfeeding intention and initiating rates were fairly high, 90% and 90.3%, respectively, among women of this representative sample [2]. However, reported exclusive breastfeeding rates at three and six months fell substantially—51.7% and 14.4%. While factors that affect breastfeeding success are multiple and nonmodifiable at times, the early recognition and timely management of modifiable risk factors is warranted to improve lactation performance [3]. Various nonpharmacological interventions have been shown to be effective and hence are incorporated in the current clinical recommendations for promoting breastfeeding [1]. Among them are individual and group breastfeeding education provided by lactation specialists, peer counseling, in-person, or telephone support. Pharmacological interventions to improve lactation, mainly dopamine antagonists, are usually recommended only after nonpharmacological modalities have failed, and this is largely due to scarcity of available evidence and potential safety issues with pharmaceutical galactagogues [4, 5].

Domperidone, a peripheral dopamine receptor antagonist, is believed to enhance breast milk production by increasing prolactin secretion [6–8]. It has a favorable safety profile when compared to metoclopramide, another dopamine receptor antagonist, with only rare extrapyramidal side effects owing likely to poor blood-brain barrier penetration of domperidone [9–11]. The drug is well tolerated with relatively few side effects reported including headache, dry mouth, and abdominal cramps [10, 12]. While domperidone is not available for any indication in the United States due to arrhythmia concerns, it is approved in Canada and other countries as a prokinetic agent. Moreover, there is

a worldwide experience with domperidone in treating nausea and vomiting. The use of domperidone as a galactagogue, hence, represents an "off-label" indication.

In 2004, the United States Food and Drug Administration (FDA) issued an advisory against the use of domperidone as a milk enhancer due to safety concerns [13]. There have been a few reports of cardiac arrhythmia and sudden death in cancer patients treated with intravenous domperidone which are often cited in the literature [14]. Rapid intravenous administration or high doses of domperidone as well as concurrent hypokalemia might be significant contributors to these adverse outcomes leading to discontinuation of the intravenous route of administration. A single case report of reversible QT prolongation associated with oral domperidone administration has been published [15]. In neonates, oral administration of domperidone was associated with QT prolongation [16]. Whereas the potential pro-arrhythmic effect of domperidone should not be ignored, the FDA concern over the use of domperidone for promoting lactation has been regarded by lactation experts as a gross overestimation. Available pharmacokinetic data, although limited, indicates minimal excretion of domperidone into breast milk with extremely low (less than 0.01% of the maternal weight-adjusted dose) infant exposure via breast milk [6–8, 12]. No side effects have been reported in exposed infants. The American Academy of Pediatrics lists domperidone as compatible with breastfeeding [17].

Nevertheless, there is a controversy regarding the role of domperidone as a galactagogue: some authors claim no or little effectiveness, largely due to limitations of available data [18] while other researchers suggested that domperidone is a galactagogue of choice based on evidence available [4]. This situation might be a source of confusion in the medical community and, therefore, may compromise clinical management decisions.

The objective of our study was to perform a systematic review and meta-analysis of the available data assessing the effect of domperidone on breast milk supply in women experiencing insufficient breast milk production.

2. Methods

2.1. Eligibility Criteria. Randomized controlled trials (RCTs) examining the effect of domperidone on breast milk production were considered for inclusion. We utilized the PICO format (population, intervention, comparison, and outcome) to develop our clinical question, guide the literature search, and assess eligibility of potentially relevant studies. The population of interest was puerperal women who had experienced insufficient lactation after delivery. We accepted any definition of insufficient lactation, with the most common definition being milk supply below the infant's daily oral feeding requirements. The intervention considered for this paper was domperidone treatment to augment lactation; the comparator considered was placebo or no treatment. The outcome of interest was percent change in daily breast milk volume after domperidone treatment.

2.2. Search Strategy. The following electronic databases were searched: Ovid MEDLINE(R) (1948 to May 2011), EMBASE (1947 to May 2011), and Cochrane Library, with no restrictions on language or year of publication. The last search was run on May 31 2011. Our search strategy included the following National Library of Medicine Medical Subject Headings (MeSH) terms: "domperidone" combined with "lactation" OR "milk production" OR "galactagogue" OR "breastfeeding." The search was limited further to human data and clinical trials. Reference lists of relevant review papers and all selected articles were hand searched to identify additional trials.

2.3. Study Selection and Quality Assessment. Literature search and eligibility assessment was performed independently by two reviewers. One reviewer extracted the data and performed quality assessment of included trials. The second reviewer checked the extracted data and quality assessment. Disagreements in judgment between reviewers were resolved by discussion. The following data was extracted: characteristics of trial participants (number, inclusion criteria), type of intervention (dose and duration of domperidone or placebo treatment), outcome measure (type and assessment tool), and maternal and neonatal adverse effects reported.

Study quality was assessed using the GRADE (grading of recommendations, assessment, development, and evaluation) system [21]. The GRADE system was developed by a widely representative group of scientists and adopted by the Cochrane Collaboration to assess the quality of evidence for outcomes reported in systematic reviews. Each individual study was rated as that of high, moderate, low, or very low quality. The Cochrane Collaboration's tool has been applied to assess risk of bias across studies. The following domains were evaluated—sequence generation, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Randomized controlled trials are generally rated as a high quality but might be downgraded. Factors that may decrease the quality of evidence include serious limitations in design, imprecision of results, unexplained heterogeneity, and indirectness of evidence and high probability of publication bias.

2.4. Statistical Analysis. The primary effect measure for this paper was the change in daily breast milk volume from baseline to the end of the treatment presented as a mean difference and standard deviation. Absolute and relative changes from baseline were recorded for individual studies. Absolute mean differences in daily breast milk volumes before and after treatment were extracted from individual studies. Relative mean differences were calculated as percentage change from baseline.

When the standard deviations of the absolute changes from baseline were not available from individual studies, we imputed them as described in detail in the Cochrane Handbook [22–24]. In brief, we calculated correlation coefficients from one available study which reported the means and standard deviations for change in breast milk volume from baseline [8]. Using the imputed correlation coefficients values, we thereafter calculated a change from

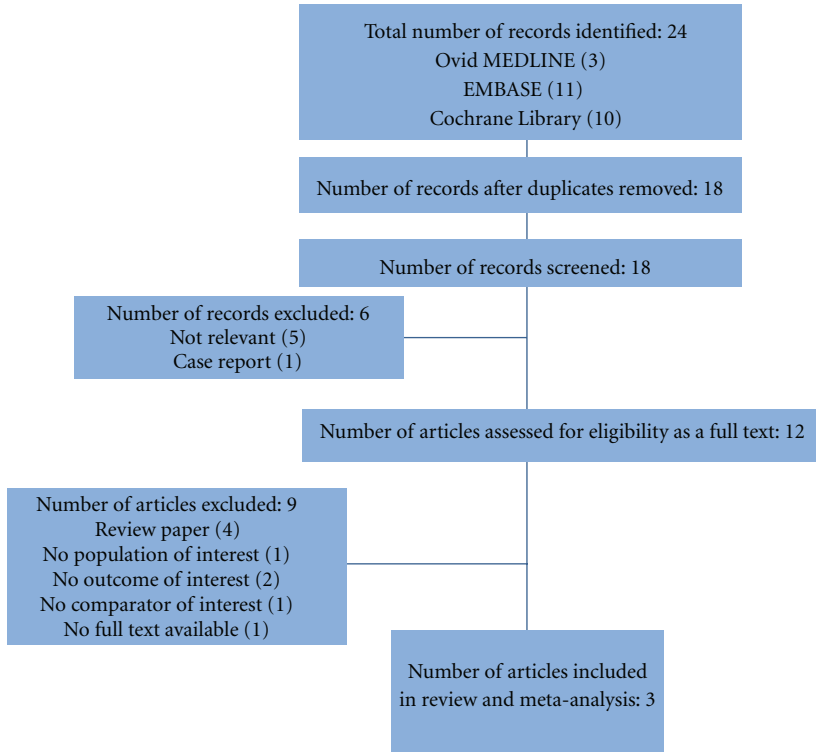

Figure 1: Flow chart of selected studies.

baseline standard deviations for the other studies with missing standard deviations [19, 20]. A sensitivity analysis was performed utilizing the lowest and highest values of the correlation coefficient to determine the robustness of the results.

The standard deviations of relative change (%) were calculated as $SD_{\text{relative change}} = SD_{\text{absolutechange}}/\text{breast milk volume}_{\text{baseline}}$. Pooled estimates of the weighted mean differences and 95% CI were calculated using a random effects model. The I^2 statistic was used to assess the extent of heterogeneity among studies. A priori subgroup analyses were not planned. Due to insufficient number of studies, a formal assessment of reporting bias by visual inspection of a funnel plot was not possible.

3. Results

3.1. Study Selection. The literature search retrieved a total of 24 citations (Figure 1). After duplicate publications were eliminated, 18 remaining abstracts were screened for eligibility. Of these, six were excluded (five were deemed not relevant and one was a case report). The full text of the remaining 12 citations was analyzed further in detail. Nine papers were excluded due to various reasons. Three studies met the inclusion criteria and were included in the systematic review and meta-analysis [8, 19, 20].

3.2. Study Characteristics. All three studies selected for this review were randomized, placebo-controlled trials with a total of 78 patients enrolled (37 in domperidone group and 41 in placebo group) [8, 19, 20]. Table 1 summarizes characteristics of included studies. All participants have experienced inadequate breast milk production postpartum and, therefore, were randomized to domperidone or placebo. Of note, all mothers were enrolled after a few weeks postpartum allowing time to establish lactation and/or receive appropriate lactation support. However, only one study mentioned extensive lactation counseling prior to enrolment [8].

The dose of domperidone used across the studies was 30 mg/d (10 mg orally 3 times daily). The length of the treatment ranged from 7 to 14 days. All studies reported the change in daily milk production from baseline to the end of the treatment. In Petraglia et al. [19], the mothers breastfed their full-term infants, and thus daily milk volumes were assessed by weighing the babies before and after breastfeeding. In two other studies [8, 20], the mothers pumped breast milk to feed their preterm babies and the amount of milk expressed was recorded.

3.3. Methodological Quality of Included Studies. Table 2 displays the summary of risk of bias for individual studies included in the meta-analysis. Two of the studies, by Da Silva et al. [8] and Campbell-Yeo et al. [20], were ranked as having low risk of bias. The description of randomization, allocation concealment, blinding, and reporting in these two papers was judged as adequate. Da Silva et al. [8], however, reported incomplete or nonreturned records for three out of 11 participants in the domperidone group which represents missing data for >25% of participants. Overall, both studies

Table 1: Characteristics of trials included in analysis.

Reference	N of participant, Intervention/placebo groups	Inclusion criteria	Domperidone dose	Domperidone duration of treatment	Outcome	Outcome assessment
Petraglia et al. [19] (1985)	9/8	Premiparous mothers of term infants with insufficient lactation[a] 2 weeks post partum	30 mg/day	10 days	Daily breast milk yield, before and after treatment, mL/day	By weighing the infants before and after breastfeeding using an electronic integrating scale and summarizing the single milk yields for the day
Da Silva et al. [8] (2001)	7/9	Mothers of preterm infants with low milk production[b]	30 mg/day	7 days	Daily breast milk volume, before and after treatment, mL/day	Mechanically expressed breast milk by using a double collecting pump
Campbell-Yeo et al. [20] (2010)	21/24	Mothers of preterm infants (<31 weeks gestation) with lactation failure[c] ≥3 wks after delivery	30 mg/day	14 days	Daily breast milk volume, before and after treatment, mL/day	Mechanically expressed breast milk by using a double collecting system

[a] insufficient lactation defined as milk yields at least 30% lower than those reported as normal
[b] low milk production defined as not meeting the infant's daily oral feeding requirements
[c] lactation failure defined as not of the following: a decreasing milk supply by >30% from peak volume based on maternal count or inability to meet the daily nutritional intake of the infant.

Table 2: Methodological quality of RCTs included in the meta-analysis.

Studies, year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Petraglia et al. [19] (1985)	Insufficient information/unclear risk of bias	Insufficient information/unclear risk of bias	Insufficient information/unclear risk of bias	Insufficient information/unclear risk of bias	Insufficient information/unclear risk of bias	Insufficient information/unclear risk of bias	No/low risk of bias
Da Silva et al. [8] (2001)	Yes/low risk of bias	Yes/low risk of bias	Yes/low risk of bias	Yes/low risk of bias	Insufficient information/unclear risk of bias	No/low risk of bias	No/low risk of bias
Campbell-Yeo et al. [20] (2011)	Yes/low risk of bias	Yes/low risk of bias	Yes/low risk of bias	Yes/low risk of bias	No/low risk of bias	No/low risk of bias	No/low risk of bias

were judged as free of serious limitations and were graded as high-quality evidence.

The study done by Petraglia et al. [19], to the contrary, did not provide sufficient information on sequence generation and allocation concealment. Furthermore, the study is described as a double-blind trial; however, there is no information whether placebo and active drug were of similar appearance and taste. It is also unclear from the paper whether all women randomized initially completed the trial. Given the above-mentioned limitations in the study design and implementation, Petraglia et al. was downgraded from high- to moderate-quality evidence.

3.4. Results of Individual Studies. Three included RCTs evaluated the effect of domperidone on a daily breast milk volume in the women with insufficient lactation in comparison to placebo.

Da Silva et al. reported that after 7-day treatment, the mean daily milk volume had increased by 49.5 (SD = 29.4) mL/day in the domperidone group compared to 8.0 (SD = 39.5) mL/day in the placebo group [8]. Similarly, Petraglia et al. demonstrated that, following 10-day treatment, daily milk yield was significantly higher in a small group of domperidone-treated mothers than that of the placebo-treated group [19]. The mean increase in daily milk yield was 326 (imputed SD = 21.4) mL/day after domperidone versus 63 (imputed SD = 23.7) mL/day after placebo treatment.

Finally, a significant increase in daily breast milk production was found in Campbell-Yeo et al. [20]: mean increase of 195.8 (imputed SD = 98.1) mL/day after a 14-day course of domperidone compared to 33.1 (imputed SD = 83.2) mL/day in a placebo-treated group [20].

Overall, in absolute values, all three studies had shown a statistically significant increase from baseline in breast milk production following treatment with domperidone.

Due to substantial differences in baseline milk volumes across the studies, the relative changes from baseline were

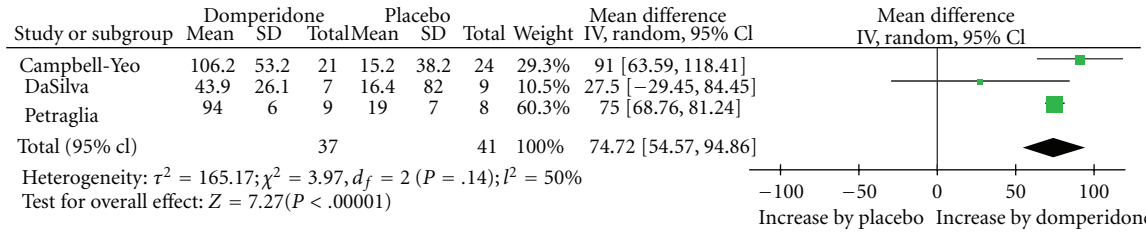

Figure 2: Percent change in milk volume with domperidone treatment.

calculated and used to estimate the pooled effect of domperidone (Figure 2).

3.5. Pooled Analysis. The analysis of pooled data demonstrated a statistically significant increase, of 74.7% (95% CI = 54.6; 94.9, $P < 0.00001$) in daily milk production following treatment with domperidone while comparing to placebo. We observed a moderate statistical heterogeneity among the studies ($I^2 = 50\%$).

4. Discussion

Our findings indicate that domperidone increases inadequate breast milk production in nursing mothers more effectively than placebo. A statistically significant increase in the mean change in daily breast milk volume from baseline was observed in all three studies comparing domperidone and placebo. This consistency of the domperidone effect across the studies enhances the confidence of its beneficial effect as a galactagogue. Importantly, no maternal or neonatal adverse events were observed in any of the three trials. Although not included in this analysis, the study by Wan and colleagues demonstrated a dose-response increase in milk production, further supporting our findings [12].

Another strength of the current meta-analysis lies in the fact that, despite the paucity of published reports on effectiveness of domperidone to promote lactation, we attempted to identify and include only randomized placebo-controlled studies which are regarded as higher quality evidence. Two out of the three included trials fulfilled the GRADE criteria for high-quality evidence [8, 20], while the third study [19] was downgraded to moderate-quality evidence due to insufficient details on study design and execution and, therefore, as having a potential risk of bias.

Based on the moderate-high quality of evidence from three RCTs, the pooled effect of a 75% increase from baseline in daily milk production following treatment with domperidone is deemed to be clinically meaningful.

Our study has several limitations. Only three eligible studies were found with small sample sizes (17, 16, and 45 participants in each trial, resp.). It has been suggested that small trials with an insufficient number of participants and events may produce spurious treatment effects due to random error [25]. Furthermore, there have been reports showing that some meta-analyses become inconclusive when adjusted for random error risk [26, 27]. Hence, the calculation of optimal information size (similar to the concept of sample size calculation for individual studies) and the use of appropriate statistical tools (i.e., trial sequential analysis) have been advocated to judge results of meta-analysis as reliable and conclusive.

On the other hand, it is unclear how many studies are needed to be included in meta-analysis to render results trustworthy. Moreover, some researchers have demonstrated that meta-analysis with a fewer trials do produce robust results consistent with long-run findings [28]. However, it is difficult to foresee which results might be changed by subsequent large-scale trials. Nonetheless, owing to the above-mentioned limitations, our findings must be interpreted with caution, and generalizable recommendations might be still premature.

Additionally, a moderate statistical heterogeneity was found to exist across the studies' results. While all three trials have utilized the same doses of domperidone (or placebo) and reasonably similar duration of treatment, the differences in study populations (mothers of preterm versus full-term infants, breastfeeding or pumping their milk) and outcome measurement instruments (increase in milk supply versus infant weight gain) are likely to explain the observed heterogeneity. We have used a random effects model for the pooled estimate to deal with statistical heterogeneity. However, too few studies available precluded subgroup analyses to further explore the observed heterogeneity. We believe, though, that the selected trials were methodologically sound to combine in the present meta-analysis. The clinical relevance of this modest heterogeneity is probably not meaningful as there is a considerable consistency in domperidone effect across individual studies and no biological reason to suspect that the opposite direction effect might be true. Still, it is sensible to investigate potential sources of heterogeneity as more research on this topic becomes available.

One methodological challenge we encountered in the present meta-analysis is not uncommon and thus deserves special mention. The issue is related to handling missing variance estimates data in primary studies included in meta-analysis. Two out of three RCTs selected for our review failed to provide standard deviations (SDs) for changes from baseline which we selected as a primary effect measure. There have been several methods proposed to impute missing variance estimates for continuous outcomes [22–24]. Since Da Silva et al. [8] reported SDs, we were able to calculate the correlation coefficient, a measurement of similarity between the baseline and final measurements across participants from this study, and then apply the calculated value to impute a change-from-baseline standard deviation for two

other studies included in our meta-analysis. In general, a correlation coefficient of zero indicates no correlation which is unusual for clinical outcomes as we expect certain degree of association between measurements within an individual. Similarly, a correlation coefficient of one is unlikely due to certain variability present within an individual. The calculated correlations obtained from Da Silva et al. were reasonably similar and close to 1 for the domperidone and placebo groups (0.97 and 0.78, resp.). We used an average correlation coefficient of 0.875 to impute the missing change-from-baseline standard deviations for the remaining studies. A sensitivity analysis was performed utilizing the lowest and highest values of the correlation coefficient and repeating the analysis. This did not change our overall conclusion as the pooled estimates and confidence intervals were not significantly changed in terms of magnitude or directionality (data not shown). Although a certain degree of uncertainty exists regarding the accuracy of the results derived from this approach, there is a growing body of the literature indicating the validity of results from meta-analyses utilizing various imputation methods [29, 30].

5. Conclusions

Currently available data from a few small randomized controlled trials suggest that domperidone produces greater increase in breast milk supply than that found with placebo in some puerperal women with insufficient milk production. These results, however, should be interpreted in the context of the limitations of available data. Additional randomized clinical trials of adequate sample size are desirable and might have an impact on our confidence in the estimate of domperidone effect as a galactagogue. In the realm of clinical practice, however, while the balance between desirable and undesirable effects often guides treatment decisions, the current analysis supports consideration that domperidone might be an effective treatment option for selected women with inadequate lactation. It appears to be prudent though to try nonpharmacological interventions, for example, maternal lactation education, first [1, 5].

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Research Article

The Effects of Maternal Supplementation of Polyunsaturated Fatty Acids on Visual, Neurobehavioural, and Developmental Outcomes of the Child: A Systematic Review of the Randomized Trials

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Polyunsaturated fatty acid (PUFA) use in pregnancy has been promoted as beneficial for visual and neurobehavioural development in the fetus. However, no systematic review of the randomized trials has been conducted. The objective of this review was to evaluate potential advantages of this regiment by reviewing all randomized trials in pregnancy. *Methods*. Systematic review of randomized controlled studies comparing cognitive and visual achievements among infants whose mothers were treated and untreated with PUFA during gestation. *Results*. Nine studies met the inclusion criteria, three focusing on visual and six on neurobehavioural development. Due to differing outcome measurements in the infants, the studies could not be combined into a formal meta-analysis. Synthesizing the existing data, for both visual and neurobehavioural development, most studies could not show sustained benefits to infant cognition or visual development. *Conclusion*. At the present time a recommendation to change practice and supplement all expecting mothers with PUFA to improve offspring vision or neurobehavioural function is not supported by existing evidence.

1. Introduction

Polyunsaturated fatty acids (PUFAs) of the ω-3 and ω-6 families cannot be synthesized by the human body [1], making the parent fatty acids of these families—alpha-linolenic acid (ALA) and linoleic acid (LA)—essential fatty acids that must be obtained from the diet [2]. ALA is converted into eicosapentaenoic acid (EPA) and then to docosahexaenoic acid (DHA), a critical component of cell membranes especially in the brain and retina. LA is converted into arachidonic acid (AA), a membrane component and a precursor to signaling molecules [2]. The ratio of the ω-3 to ω-6 families of PUFAs is critical because both families are metabolized by the same enzymes, and increasing the amount of ω-3 fatty acids (FAs) in the diet, for example, may decrease the availability of the ω-6 products. Therefore, there is a potential risk of reducing AA levels in the fetus with maternal supplementation of ω-3 FAs [1].

Because the PUFAs required by the fetus are supplied by preferential placental transfer of preformed long-chain PUFA (LC-PUFA) rather than the precursors ALA and LA, it has been proposed that additional maternal supply of DHA and AA during pregnancy may improve early cognitive and visual development [3]. The limited available data on LC-PUFA in the developing human brain indicates that fetal accumulation of LC-PUFA is slow in the earlier weeks of gestation and rapidly increases in the third trimester [4].

Among the ω-3 FAs subtypes, DHA is the only one that accumulates to an appreciable extent in the developing brain

and eye [5]. DHA is actively and preferentially transferred to the fetus by specific fatty acid placental transfer and membrane binding proteins. Of all cells, the highest content of DHA is found in retinal photoreceptors, the cells responsible for phototransduction [6]. As well, the visual cortex of the brain has high levels of DHA. Brain and visual development is most sensitive to malnutrition in the third trimester and in the first 18 weeks of postnatal life. In Rhesus monkeys and rats fed diets limited in LCPUFA during pregnancy, there are reduced levels of PUFAs in pups in both the retina and the visual cortex [7–9]. Pregnant Rhesus monkeys and their pups fed diets low in n-3 fatty acids exhibit below normal visual acuity scores at 4–12 weeks compared to mother and infant monkey pairs fed diets with "ample" n-3 fatty acids [9].

In animal studies, severe restriction of ω-3 fatty acids results in lower concentrations of DHA in the brain and poorer cognitive and behavioural capacities [10]. Several human studies have suggested that maternal diet rich in seafood correlates with higher scores on tests of cognitive function. Observational studies have suggested that prenatal AA status correlates positively with neurodevelopmental outcome during early infancy, but not at older ages [4].

In Health Canada "Prenatal Nutrition Guidelines for Health Professionals," women are advised to consume at least 150 g of cooked fish weekly, preferably those with lower levels of contaminants such as methyl mercury and polychlorinated biphenyls (PCBs), suggesting that fish intake during pregnancy may be linked to better infant and child development [11]. With respect to LC-PUFA supplementation, it is advised that fish oil supplements should not be considered equivalent to eating fish, and though they provide ω-3 fatty acids, there is insufficient evidence to draw conclusions on the effects of fish oil supplementation on infant development [12]. Observational studies correlating PUFA with fetal development suffer from numerous confounders that may affect outcome, such as socioeconomic status, maternal education, and other nutrients status.

The objective of this systemic review was to evaluate the potential effects of interventional supplementation of ω-3 FAs during the pregnancy period only on infant neurobehavioral and visual development, without the potential effects of breastfeeding or dietary supplementation.

2. Material and Methods

2.1. Inclusion and Exclusion Criteria. Studies included in this review were randomized control trials (RCTs) comparing LC-PUFA supplementation with placebo or no supplementation in pregnant women. Trials that used supplementation only during breastfeeding and/or infant dietary supplementation were excluded. In contrast, trials that started in pregnancy but continued during breastfeeding were included. Trials reporting only biochemical outcomes or using animals were not included and only original research articles were considered. Trials in which precursors of essential FAs (ALA and LA) were used in intervention group were not included because the preferential placental transfer for LC-PUFAs precursors is far less effective. Abstracts for which a published full paper could not be located were excluded for this review.

To ensure a high quality of evidence, we restricted the review to RCTs with Jadad scores of 3 or greater on the 5-point scale [13].

2.2. Search Strategy. We completed a computerized literature search of MEDLINE (1950–June 2010), EMBASE (2010), the Cumulative Index to Nursing and Allied Health (CINALH) (from inception to June 2010), and the Cochrane Library (2010). We supplemented this search by investigating relevant references from published reviews [2–4, 14, 15]. There was no limit on the language of publication.

Search terms used were "omega or n-6 or n-3 or eicosapentaenoic acid or EPA or docosahexaenoic acid or DHA or arachidonic acid or LC-PUFA or long-chain fatty acid or essential fatty acid or fish oil or fatty acid" and "supplementation" and "pregnancy or maternal."

2.3. Methods of Review

Trial Selection. Two researchers independently applied the inclusion criteria to each potential relevant trial and differences with regards to their eligibility were resolved by consensus.

2.4. Quality Assessment. Two researchers independently assessed the quality of the studies that met the inclusion criteria using the Jadad method [13], and articles included had to score between 3 and 5 on the 5-point scale.

3. Results

All 9 identified randomized trials met our inclusion criteria, and all of them achieved at least 3 on the Jadad score (Figure 1). Three trials were focused on retinal development [16–18] while six studied neurodevelopment [16, 19–23]. Though trials with all LC-PUFA (ω-3 and ω-6) supplementation were considered for this review, none of the trials used ω-6 in the intervention group. The characteristics of the included trials are summarized in Table 1. The duration, sources, and amounts of ω-3 LC-PUFA, DHA, and EPA supplied varied among trials. The doses ranged from 2×100 mg DHA/week [17, 18] to 1.1 g EPA, 2.2 g DHA/day, which were used in the study by Dunstan et al. [19]. The trials differed in the starting point of intervention, ranging from the 15th [17, 18] to the 25th weeks of gestation [23]. All trials ended supplementation at delivery, with the exception of the studies by Helland et al. [20–22], which continued supplementation until 3 months after delivery. Because these studies did not change the practice of breastfeeding between control and treatment groups, we still included them in our review. Because the methods of measuring visual and neurodevelopmental outcomes varied widely among studies, the combination of the results into a formal meta-analysis was deemed inappropriate.

3.1. Effectiveness of PUFA for Visual Development. To allow readers who are not specialists in measuring visual development to follow the results, the description of the study results

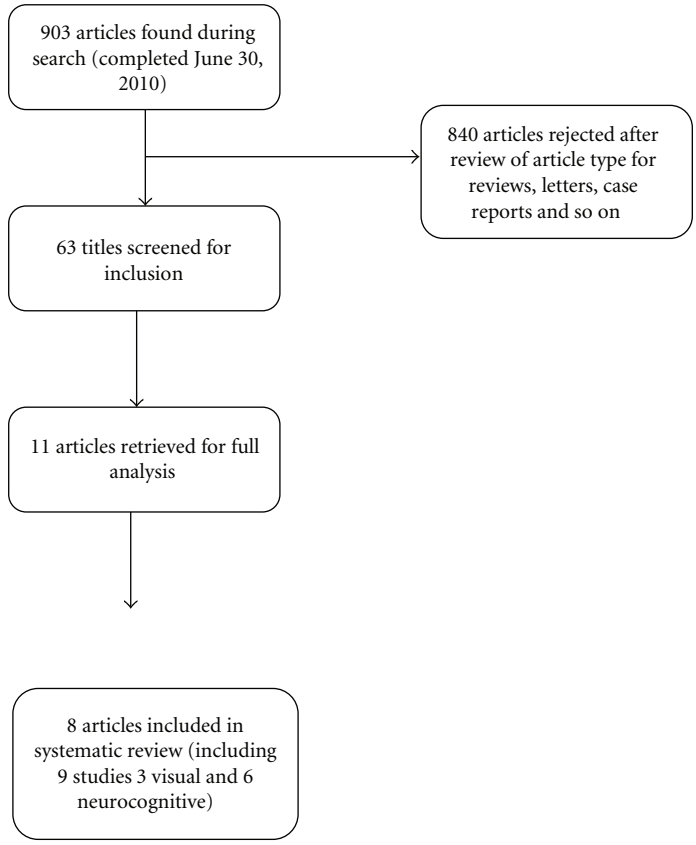

Figure 1: Search strategy flow chart.

is preceded by description of the methods used by the different groups. There are various ways to assess vision in humans; however, not all of these methods can be used as diagnostic tools in children, let alone in infants. Both visual function (the ability to see) and visual acuity (a quantifiable measure of vision function) can be tested. There are several aspects of visual acuity (the spatial limit of visual discrimination): detection, resolution, identification, and hyperacuity. A commonly used test, Teller Acuity Cards [25], tests resolution, or the smallest angular separation between two objects side by side [26].

Visual function may also be assessed using objective electrophysiological measures such as the visual evoked potentials (VEPs) (steady state and transient). Retinal function can be assessed using the electroretinogram (ERG). The International Society of the Clinical Electrophysiology of Vision (ISCEV) provides standards for both VEP and ERG testing [27, 28]. VEPs are recorded with electrodes placed on the back of the scalp to measure the responses generated by the visual cortex in response to a change in visual stimulus. Responses to this test indicate the function of the visual pathway: retina, optic nerve, and brain (specifically the occipital cortex) and are dependent on unobstructed ocular media such as the cornea and lens. When used to assess visual function, the VEP does not localize where in the visual pathway damage exists. ERGs are measured using electrodes placed on the cornea of the eye and forehead. Subjects are presented with flashes of light of different intensities and the resulting responses generate characteristic outputs. The positive and negative peaks of different outputs are known to originate in specific areas of the retina which localize damage to a specific layer of the retina. Both VEPs and ERGs can be described in terms of amplitude and implicit time or latency of the response.

Judge et al. conducted a longitudinal, double-blinded RCT of thirty nonsmoking women supplemented with either DHA-rich (mean = 214 mg/d) cereal bars or placebo bars starting at 24 weeks of gestation [24]. Infants were assessed at 4 and 6 months of age by Teller Acuity Cards Procedure (ACP) which is a type of preferential looking test for resolution. This technique assumes that children would rather look at a pattern than a blank stimulus [29]. It consists of a series of gray cards with one circle with a black and white grating (of different frequencies) and another card of equal luminance to the grating. An observer must identify that the child has preferentially looked at the grated stimulus (but are themselves blinded to which side the grated stimulus is on). The test is repeated, switching the side of the grated stimulus, until the observer feels they can reliably decipher whether the child is in fact preferentially looking at the grated card. That grating frequency, referred to as a spatial frequency, is then said to be above the child's acuity threshold. After adjusting for potential confounding factors, including infant feeding type, there was a significant difference in visual acuity between groups at 4 months, but not at 6 months postnatally. Both supplemented and nonsupplemented groups showed

Table 1: Description of included studies.

Study (year)	Jadad score	Treatments—maternal diet supplementation	Outcome	*N*	Test results
Treatments and outcomes for studies considered—retinal development					
Malcolm [17]	3	*Controls* (C): 2 placebo capsules (323 mg sunflower oil)/day *Treatment*: 2 fish oil capsules (blended fish oil, Marinol D40: 100 mg DHA)/day From wk 15 of pregnancy until delivery	Age: 50 and 66 wks after conceptional age—*visual evoked potential* (transient VEP P100 peak latencies (ms))	DHA: $n = 31$ C: $n = 29$	No effect of group at any time
Judge [16, 24]	4	*Controls*: 3,5, or 7 placebo cereal bars (corn oil)/wk *Treatment*: 3, 5, or 7 cereal bars (300 mg DHA)/wk (average was 5 bars/wk: 214 mg/d of DHA) From wk 24 of pregnancy until delivery	Age: 4 and 6 mo *Teller Acuity Cards*	DHA: $n = 16$ C: $n = 14$	4 months DHA: 3.7 ± 1.3 c/d C: 3.2 ± 1.3 c/d $P = 0.018$ No difference at 6 months
Malcolm [18]	4	*Controls*: 2 placebo capsules (sunflower oil)/day *Treatment*: 2 fish oil capsules (Marinol D40: 100 mg DHA)/day, total 200 mg/d from wk 15 of pregnancy until delivery	Age: within 1 wk of birth *Scotopic electroretinogram*	DHA: $n = 31$ C: $n = 29$	No effect of group on VEP maturity
Treatments and outcomes for studies considered—neurodevelopment					
Tofail [23]	4	*Controls*: 4 placebo capsules (soybean oil: total 2.25 g LA and 0.27 g LNA)/day *Treatment*: 4 fish oil capsules (total 1.2 g DHA and 1.8 g EPA)/day From wk 25 of pregnancy until delivery	Age: 10 mo *Bayley Scales of Infant Development II, Mental Developmental Index (MDI)* *Psychomotor Developmental Index (PDI)*	Fish oil $n = 125$ Soy oil $n = 124$	Mental developmental index: Fish 102.5 (8.0) Soy 101.5 (7.8) 95% CI of difference between means: −0.98, 3.0 Psychomotor developmental index Fish 101.7 (10.9) Soy 100.5 (10.1) 95% CI of difference between means: −1.3, 3.8
Judge [16, 24]	3	*Controls*: 3, 5, or 7 placebo cereal bars (corn oil)/wk *Treatment*: 3,5, or 7 cereal bars (300 mg DHA)/wk (overall average of 214 mg/d of DHA) From wk 24 of pregnancy until delivery	Age: 9 mo *Infant planning test (IPT)* *Fagan test of infant intelligence (FTII)*	IPT DHA: $n = 14$ C: $n = 15$ FTII DHA: $n = 15$ C: $n = 15$	Infant planning test (1) Intention score DHA = 8 (2.3), C = 6.7 (3) $P^2 = 0.017$ (2) Intentional solutions DHA = 2.5 (1.3), C = 1.7 (1.5) $P^2 = 0.011$ Fagan test Scores for 5 different variables, no significant difference in any
Helland [20–22]	4	*Controls*: 10 ml corn oil (4747 mg LA, 92 mg alpha LA)/day *Treatment*: 10 ml cod liver oil (1183 mg DHA, 803 mg EPA)/day From wk 17–19 of pregnancy until *3 months after* delivery	Age: 2nd day and 3 mo *EEG* Age: 6 mo and 9 mo: *Fagan test*	2nd day EEG T: $n = 66$ C: $n = 83$ 3 mo T: $n = 61$ C: $n = 61$ Fagan 6 mo T: $n = 144$ C: $n = 118$ 9 mo: T: $n = 130$ C: $n = 115$	EEG: no difference b/w groups at both ages. Fagan: no difference at either time.

Table 1: Continued.

Study (year)	Jadad score	Treatments—maternal diet supplementation	Outcome	N	Test results
Helland [20–22]	4	*Controls*: 10 ml corn oil (4747 mg LA, 92 mg alpha LA)/day *Treatment*: 10 ml cod liver oil (1183 mg DHA, 803 mg EPA)/day From wk 18 of pregnancy until *3 months* after delivery	Age: 4 yrs *Kaufman Assessment Battery for Children (K-ABC)*	Cod oil: $n = 48$ Corn oil: $n = 36$	K-ABC mental processing composite 4 yrs: 106.4 (7.4) versus 102.3 (11.3) for control $P = 0.049$
Helland [20–22]	3	*Controls*: 10 ml corn oil (4747 mg LA, 92 mg alpha LA)/day *Treatment*: 10 ml cod liver oil (1183 mg DHA, 803 mg EPA)/day From wk 18 of pregnancy until *3 months after* delivery	Age: 7 yrs *Kaufman Assessment Battery for Children (K-ABC)*	Cod: $n = 82$ Corn: $n = 61$	K-ABC mental processing composite—no difference
Dunstan [19]	3	*Controls*: 4–1 g olive oil capsules (total 2.7 g n9 oleic acid)/day *Treatment*: 4–1g fish oil capsules (total 1.1 g EPA, 2.2 g DHA)/day (3.7 g of ω-3 PUFA/d) From wk 20 of pregnancy until delivery	Age: 2.5 yr *Griffiths Mental Development Scales (GMDS)* *Peabody picture vocabulary test IIIA Child Behavior checklist 1.5–5 y*	T: $n = 52$ C: $n = 46$	Hand and eye coordination T ($n = 33$): 114 (10.2) C ($n = 39$): 108 (11.3) $P = 0.008$ No significant difference on other tests

an increase in ACP score over time but the change in score over time was not significantly different between the two groups and the authors suggested that DHA supplementation aided in visual system maturation [24].

Malcolm et al. conducted a prospective placebo controlled, randomized double-blind trial investigating electroretinogram (ERGs) in infants born to 100 woman supplemented with 200 mg DHA or 200 mg sunflower oil placebo from week 15 of pregnancy until birth [17]. This study was well designed and used the bipolar Burien Allen electrodes and a Ganzfeld dome, known to elicit repeatable valid responses [28]. These tests were administered to the children without sedation which can be problematic based on the child's level of cooperation. The authors reported that infant DHA status, and ERG implicit times, amplitude, and stimulus response functions at birth, did not differ between groups for 60 infants tested within one week of birth [17]. However, infants in the highest quartile for cord blood DHA had significantly higher retinal sensitivity ($\log \sigma$) as compared with those in the lowest quartile, and those in the highest quartile for plasma DHA were born at significantly later gestational age than those in the lower quartile, regardless of maternal supplementation type. The authors concluded that, although maternal supplementation had no effect on infant DHA status or retinal development, those infants with higher DHA status had increased retinal sensitivity and longer gestational age [17].

Malcolm et al. also tested this cohort using VEPs [18]. After supplementation, red blood cell (RBC) DHA concentration and the percentage of total fatty acids (%TFA) in pregnant women ($n = 54$) were higher in the fish oil group than in the placebo group from 28 wks to delivery ($P < 0.05$). As before, DHA supplementation did not significantly elevate levels of DHA measured as RBC concentration of %TFA in umbilical cord blood. Fifty-five infants tested showed no significant group differences in mean peak latencies of major components of flash VEP waveform or in the peak latency of the P100 component of the pattern-reversal VEP, and no significant correlation was detected between flash VEP peak latencies and RBC/plasma DHA levels in cord blood at any time (birth, 50 weeks after conceptional age (PCA), and 66 weeks PCA). Similarly, no differences were found in the threshold check size of the pattern-reversal VEP at 50 or 66 weeks PCA between supplementation groups. Pattern-reversal VEP maturity, measured as shorter peak latency, correlated at 50 weeks and 66 weeks PCA with cord DHA status, but not with maternal supplementation group. Here, infants in the top quartile of RBC DHA status (median −5.46%) did not differ significantly in VEP maturity from those in the lowest quartile (median −3.45%).

3.2. Neurodevelopment. Six trials met the inclusion criteria, achieving Jadad scores of at least 3. Of these six trials, three were published by Helland et al. based on followup of one RCT [20–22]. Therefore, there was a total of four independent RCTs included in this part of the systemic review.

Various methods of measuring neurodevelopment were used in the six papers accepted for this review, and these will be described to allow the reader to evaluate the results. The Bayley Scales of Infant Development Second Edition (BSID-II) is a standardized test used to assess motor and cognitive development of children between the ages of zero and three years. Raw scores are compared with age-based normative data to determine individual standard scores. The BSID-II includes two subscales: the mental development index (MDI) and psychomotor development index (PDI) [30, 31]. Using this method, Tofail et al. found no significant difference between the MDI and PDI scores of 10-month-old children of mothers supplemented with fish oil or soy oil during the last trimester of pregnancy [23]. This study took place in Bangladesh, and 28% of the mothers in the test population suffered from undernutrition. The authors speculated that because there was attrition of 38% from the original randomized

sample and the attrition sample was at greater risk for neurodevelopmental problems due to clinical difficulties during pregnancy, the lack of treatment effect may be attributed to the attrition of those that likely would have benefited most from treatment. In addition, the authors commented on the lack of validation or standardization of the Bayley-II in Bangladesh, which may have limited the sensitivity to detect minor differences between groups [23].

Judge et al. used the infant planning test and Fagan tests to compare the neurodevelopment of 9-month-old infants of mothers supplemented with DHA or placebo during pregnancy [16]. The Fagan test is used to estimate infants' recognition memory, as a proxy of intellectual ability, by presenting them with novel and familiar facial pictures [32]. Those children who spend more time fixating on novel stimuli are given higher scores. This test is thought to represent the speed with which infants acquire new knowledge and has been shown to moderately correlate with IQ at 2 years of life [33]. This task assesses a single aspect of development, namely, facial (visual) recognition.

Other standardized infant developmental tests (e.g., Bayley Scales of Infant Development, Mullen Scales of Early Learning) use a variety of tasks to estimate infant IQ and, based on their assessment of other functions (e.g., motor, language, and other problem-solving tasks), may act as a better estimate of later cognitive functioning. The infant planning test requires infants to execute a series of steps to retrieve a toy as a measure of their problem solving ability [33–37]. This test, as well as its method for scoring and assessing performance, is unpublished and has no available reliability or validity information, limiting the interpretation of the findings. The women from both study groups were instructed to consume 3, 5, or 7 cereal bars/wk from week 24 to delivery. The average was 5 bars a week, averaging 214 mg/d of DHA consumption. Significantly higher problem-solving scores (i.e., better performance) were associated with maternal PUFA supplementation as measured by the infant planning test. However, there was no difference detected in facial recognition by the Fagan test. The authors stated that the lack of significant differences may not be surprising, as the Fagan test is more sensitive at 4 and 6 months of age [38]. Another possibility is that PUFA supplementation may not impact this specific skill of development as it is thought to be a measure of selective visual attention and facial recognition.

Helland et al.'s three studies examined infants of mothers supplemented daily with 10 mL cod liver oil (1183 mg DHA, 803 mgEPA) or 10 mL corn oil placebo, from wk 18 of pregnancy until 3 months after delivery, to measure effects on infant neurodevelopment [20–22]. 242 of the 251 infants were breastfed at least until 3 months of age, and a subset (n = 130) were started on supplement of cod liver oil (5 mL daily from 4 wks of age). No differences were found between the infant diet in the supplemented groups in terms of PUFA content, and for the sake of the present systematic review we were interested only in groups that differed with respect to maternal supplementation. Helland et al. measured neurodevelopment at ages day 2 and 3 months using EEG (n = 149) [20], 6 and 9 months using the Fagan test (n = 245) [21], and 4 years (n = 84) and 7 years (n = 143) using the Kaufman Assessment Battery for Children (K-ABC) [22], in which sequential processing, simultaneous processing, achievement, and nonverbal abilities are scored in a multisubtest battery. The raw scores for each category were converted to standard scores according to the American norms since the Norwegian version has not been standardized. There were no differences found in the test scores at any of the ages [20–22], except at 4 yrs, when children of cod-oil-supplemented mothers scored higher on the mental processing composite of K-ABC [22].

Dunstan et al. studied the effects of fish oil (3.7 g of ω-3 PUFA/d) supplementation during pregnancy from wk 20 to delivery on several scales of cognitive assessment of the child at age 2.5 yrs [19]. The Griffiths Mental Development Scales (GMDS) used by the group have six subscales of development (locomotor, personal, social, speech and hearing, eye and hand coordination, and performance and practical reasoning) and a general score is derived from the averages of the subscale scores [39]. The Peabody Picture Vocabulary Test (PPVT) III is a test of English receptive vocabulary [40]. Finally, the Child Behaviour Checklist (CBCL) measures parental perception of child competencies, behaviours, and language development [41]. The study used all three measures at age 2.5−3 yrs and found that the infants of the supplemented group had significantly higher scores on the eye and hand coordination subtest of the GMDS than those of the control group ($P = 0.02$). However, there were no significant differences in the scores for any other sections of the GMDS, the PPVT-III, or the CBCL. The relatively high doses of ω-3 PUFA supplementation in this study were not associated with any deleterious effects on neurodevelopment or growth [19].

4. Discussion

The 8 randomized trials reviewed by us focusing on the effects of maternal PUFA supplementation on the neurocognitive and retinal development in the child have found very limited, if any, benefits to supplementation. Even in the studies that found statistically significant differences between treatment and control groups, the differences were small and of little potential clinical importance. These trials have found that even high doses of supplementation of ω-3 PUFA (up to 3.7 g/d) were not associated with any detrimental effects [19].

These studies did not detect a relationship between the doses of supplementation and measured effects [18, 19] and found that, although there was an association between infant DHA status and retinal/VEP maturity, there was no correlation between maternal supplementation of PUFAs and infant DHA status [18, 19]. In contrast, Dunstan et al., using the highest doses of 4 × 1g fish oil/day (3.7 g DHA/d), found improved scores only in the hand and eye coordination subtest in the K-ABC for infants in the treatment group [19]. Although the study by Judge and colleagues was well designed, the sample size was small and the vehicle of DHA administration (DHA-rich cereal bars) differed from the other studies on visual development which used fish oil capsules.

Measurements of maternal or infant DHA status were not reported. The study did not report whether acuity was tested monocularly or binocularly. As effects were found at

4 months but not 6 months, it is possible that maternal supplementation provides an initial advantage which disappears with time. One would only expect a continued difference if prenatal supplementation predisposed infants to have better vision. Two different and inconsistent values for visual acuity scores were presented in the abstract versus the text. Contact with the authors clarified that the value in the abstract was based on using the GLM model (a statistical method of using least squares to fit general linear models), whereas the value in the text was calculated using group means.

The detected difference of 0.5 cycles/degree (c/d) (see Table 1), although statistically significant, falls within the normal range for age (binocular acuity) at four months (6.8–1.7 c/d) and six months (9.1–2.2 c/d) [25]. The authors noted that a limitation of this study was in the use of ACP, which, although shown to be repeatable [30, 31], has inherent subjectivity.

As in the ERG study by Malcolm [17], maternal supplementation did not correlate with infant DHA status [17]. This is interesting especially because the mothers in each group did have significantly different levels of DHA and %TFA at delivery. This study used solid methodology to test VEP responses, with the authors conducting both flash and transient pattern-reversal VEPs. The flash VEP is only able to give an indication of whether the visual cortex responds to light stimulation, whereas the pattern-reversal VEP yields information on the quality of the response. This may explain why significant differences were found in pattern-reversal VEPs and not in flash VEPs. Sweep VEPs are likely the best way to test cortical responses in infants, because they take the shortest time to elicit and there would be less chance of a child loosing attention to the stimulus [42–44]. The authors reported VEP results using latencies which are less variable than amplitudes [44]. The authors of this study reported averaging their trials over 30–50 epochs, which is certainly sufficient to minimize the signal-to-noise ratio.

The results of both studies conducted by Malcolm et al. suggest that infant DHA status, but not maternal supplementation, is correlated with infant visual development. Synthesizing these three studies, at the present time a recommendation to change practice and supplement all expecting mothers with PUFA to improve offspring vision is supported by the existing evidence.

The data of the studies included in this systematic review could not be combined into a formal meta-analysis because the measures used in the studies varied greatly with regard to dosage, length of supplementation, age of testing, and the measures of effect. Even without quantitatively combining the results, it is evident that any beneficial effect from ω-3 PUFA supplementation, if it exists, is very small and therefore likely not clinically significant. Cohen et al. conducted an analysis on prenatal intake of n-3 PUFAs and cognitive development, in which they estimated that increasing maternal DHA intake by 1 g/d may increase child IQ by about 1.3 points.

In explaining the results of the neurocognitive interventions, Helland and colleagues suggested that the lack of measured effect may be because the effects of the ω-3 PUFAs are diluted by several other factors such as other nutrients, drugs, social stimulation, and diseases. Other possible explanations were lack of effect of ω-3 PUFAs or that their methods of cognitive testing were not sufficiently sensitive to detect differences at these ages. Alternately, performance on the specific visual task used in the Fagan test was not impacted [20], as found in the Judge et al. study [16]. In contrast, early neurodevelopment, when assessed with a measure inclusive of a broader range of skills (K-ABC), was sensitive to these changes. Even when group differences in mental processing scores were detected at four years of age, these were not of a magnitude to make a significant clinical impact (4 IQ points, or about one-quarter of a standard deviation).

In synthesizing the existing neurocognitive studies, the papers included in this systematic review have yielded variable results in terms of whether PUFA supplementation during pregnancy was of benefit to infant neurocognitive development. In the longitudinal study by Helland et al., the limited effects evident at four years of age were nullified three years later [20–22]. In Dunstan et al.'s study, a single positive effect was contrasted by mostly negative results [19]. When comparing numerous endpoints, a single positive result may arise by chance only, as $P < 0.05$ means a 1 in 20 chance of "no difference" becoming "significant," especially since multiple comparison correction for the large number of comparisons was not performed in Dunstan et al.'s study [19]. Similarly, Judge et al. found one significantly positive effect in a large number of negative tests [16]. If there was a genuine favorable effect, it was of small magnitude and may not persist in later years [21]. Thus, in considering the results of these six studies, at the present time a recommendation to change practice and supplement all expecting mothers with PUFA to improve infant neurodevelopment is not strongly supported by the existing research results.

Several limitations exist in the body of knowledge analyzed by us. First, studies that examined the effects of LC-PUFAs in preterm infants were not included in this review. However, developmental benefit to PUFA supplementation may be more consistent in infants born prematurely. It may be argued that as preterm infants are denied the full gestation period to accumulate an adequate amount of DHA, they may benefit the most from increased maternal DHA levels during pregnancy, achieved with DHA supplementation.

Preterm infants fed with DHA-supplemented formula have shown better visual resolution acuity at 2 and 4 months [45] and higher Bayley mental and psychomotor development scores at 118 weeks [46].

Second, the included studies have employed a variety of tests in order to measure neurocognitive and retinal development. Because these measures assess different components of brain development and aspects of cognition, it may not be surprising that there are inconsistent results among different studies.

5. Conclusions

Our systematic review of RCTs suggests that the research available to date regarding the maternal supplementation of PUFAs in retinal and neurocognitive development of

the infant is not consistent in showing a benefit to supplementation. However, there is evidence that dietary deficiency in LC-PUFAs can adversely affect retinal and neurocognitive development outcomes in animals, and these data are corroborated in nutritionally impaired women in Bangladesh thus, it is important to maintain a healthy diet that contains sufficient sources of PUFAs, such as eggs and fish.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Adherence with Drug Therapy in Pregnancy

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Available information suggests that nonadherence with medication is a common problem in pregnant women. Not taking prescribed drugs may have potentially negative consequences as patients may not achieve their therapeutic goal. In addition to the many factors that may influence medication-taking behaviour in the general population, unique challenges are encountered in pregnant women as both maternal health and fetal well-being must be considered. On the one hand, pregnant women may be motivated to keep their underlying disease under control, while, on the other hand, fear and anxiety regarding the potential harmful effects of their medication on their unborn child may result in poor adherence with needed medication. Providing evidence-based information, ideally preconceptually, regarding the effects of their medication during pregnancy may be important in avoiding misperceptions that lead to nonadherence.

1. Introduction

Advances in drug therapy have resulted in efficacious treatments being available for many acute and chronic medical conditions; however, it is well recognized that "Drugs don't work in patients who don't take them" [1]. The WHO defines adherence, a term which is often used interchangeably with compliance, as the extent to which a person's behaviour-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider [2]. Unfortunately, nonadherence with medication regimens is not uncommon with the potential negative consequences of failure to achieve the desired treatment goal. Many factors may play a role in whether patients comply with their therapy and pregnancy may present unique challenges as fetal well-being must also be considered in addition to maternal health. This paper will provide a brief overview of medication adherence in general and then will focus on some of the issues related to medication-taking behaviour during pregnancy.

2. Overview of Medication Adherence

Nonadherence with drug therapy may take many forms with delayed or omitted doses being the most common errors. Discontinuation of medication administration prior to completion of the course is also common. Adherence is generally measured over a specified period of time and often reported as the percentage of the prescribed doses of medication actually taken by the patient [3]. In a meta-analysis of 569 studies, reported adherence to medical treatment ranged from 4.6% to 100% with a median of 76% and an overall average of 75.2% [4]. Drug compliance may be of particular concern with chronic conditions as therapy is often long term and patients without symptoms may be required to take medication to prevent later complications without any immediate benefits noted. Contrary to what one might think seriousness of the underlying medical condition does not ensure compliance, as has been shown with both cancer and organ transplant therapy [5–9]. Not taking one's medication is not without clinical implications given the relationship between inadequate adherence and unfavourable disease outcome. In a meta-analysis of 21 studies, good adherence with drug therapy was associated with lower mortality compared with poor adherence (odds ratio 0.56, 95% CI 0.50–0.63) [10]. Other consequences of nonadherence may include inappropriate alteration in treatment regimens or dosage adjustments with subsequent toxicity, unnecessary investigations, and increased costs.

Nonadherence with medical therapy is a complex multifaceted problem involving patient and family factors, disease factors, physician factors, and regimen factors [11]. Unfortunately, none of these factors have been found to reliably predict which patients will or will not take their prescribed medication. Various methods are available to assess adherence; however, all have advantages and disadvantages and no universally accepted gold standard exists. The accuracy of self-reporting is often questioned, in particular when the suggestion is that compliance is good. Pill counts may also underestimate adherence as patients "dump" their pills prior to their clinic visit. Measurement of drug levels, available for a limited number of medications, only reflects recent ingestion. Electronic monitors that provide continuous "real-time" measurement can provide information on temporal dosing patterns and allow correlation with breakthrough clinical events.

It is important to have a high index of suspicion in order to identify early those noncompliant patients who have failed to attain their treatment goal and who may benefit from more targeted support and adherence-enhancing strategies that may include educational and behavioural approaches. Potential barriers to adherence should be identified. No single intervention has been shown to be effective across all patients, conditions, and settings [12]. In a review of interventions for enhancing medication adherence less than one-half of the interventions tested were associated with statistically significant increases in medication adherence and only 29 of 93 interventions reported statistically significant improvements in treatment outcomes. The common theme was more frequent interaction with patients with attention to adherence [13].

3. Medication Adherence in Pregnancy

Despite the ample evidence in the literature of the important role of adherence with drug therapy in influencing treatment outcome in the general medical population, there is a relative paucity of studies that have focused specifically on whether pregnant women do or do not take their medication. Much of the research addressing medication compliance during pregnancy has been undertaken in women with HIV infection although there are scattered reports in other medical conditions.

The information available suggests that nonadherence with prescribed drugs is also a problem in the pregnant population. 39% of women who received one or more prescriptions reported noncompliance during pregnancy when interviewed within two weeks after delivery. Reasons included doubts about the use of the drug during pregnancy, expected side effects, disappearance of the complaints for which the drugs were prescribed, or the complaint persisted notwithstanding drug therapy. Approximately 40% of women had had one or more questions about drugs during their pregnancy with safety being the issue that raised most questions [14].

Similarly, using data from the North Jutland Prescription Database and from the Danish National Birth Cohort survey, the overall compliance rate with prescription drugs in pregnant women was estimated to be 43% [15]. In the outpatient clinics of an Australian hospital, medication nonadherence was reported by 59.1% of pregnant participants with a chronic health condition. Nonadherence was mainly nonintentional, with forgetting to take medication being the most common reason. In this study, the majority of participants had some concerns about using any medication during pregnancy [16].

3.1. Adherence with HIV Medications. Poor adherence with HIV treatment regimens may be a determinant of virologic failure, emergence of drug resistant virus, and disease progression [17]. In addition to treating the mother's underlying disease, antiretroviral treatment in pregnant women also aims to prevent vertical perinatal HIV transmission to the child [18, 19]. Highly active antiretroviral therapy (HAART) has reduced mother-to-child transmission rates to around 1 to 2% in resource-rich countries [20]. Lack of medication adherence in pregnant women with HIV infection may interfere with these goals. Medication nonadherence was a significant factor associated with suboptimal viral suppression at the time of delivery (defined by HIV viral load ≥ 1000 copies) in addition to baseline viral load $\geq 10{,}000$ copies per milliliter [21].

Studies have shown that HIV-infected pregnant women have greater adherence with antiretroviral drugs than nonpregnant women [22–24]. However, adherence rates during pregnancy are still not optimal and have been reported to be between 43.1% and 80% using various methods of compliance assessment [22–28]. Better compliance with prescribed medications during pregnancy may be related to concern for the baby's health [24, 29]. In the Women and Infant Transmission Study, 90% of women who reported improved adherence with their HIV medications during pregnancy stated that their baby's health was the primary reason [24]. Dosing regimen has also been shown to be important as less than 6 pills per day and up to two doses per day were associated with better adherence [22]. Similarly, pregnant women who were prescribed zidovudine only once or twice daily demonstrated significantly higher adherence than those prescribed this medication three to five times per day [23]. Social support, especially from family members, has a positive influence on medication-taking behaviour [25].

Barriers to good adherence with antiretroviral therapy include being preoccupied with other issues and hectic lifestyles [29] as well as illicit drug use [27, 28]. Untreated depression during pregnancy is also associated with nonadherence to HIV treatment regimens and treatment of depression may improve medication adherence [30]. As poor adherence with antiretroviral drugs during pregnancy may predict nonattendance at infant followup [31], identifying women who are having trouble taking their medication is important.

3.2. Adherence with Medications Prescribed for Other Conditions. As in the general population less than perfect adherence with medication taking has been demonstrated in patients with other medical conditions, examples of which will be discussed.

3.2.1. Epilepsy. Incomplete compliance with anticonvulsant medication was reported by 62.3% (157/252) of pregnant women with epilepsy [32]. Hair analysis was undertaken in 26 pregnant women taking carbamazepine or lamotrigine with four patients (15%) showing declines in drug concentration in the more proximal segments suggesting a change in drug-taking behaviour. Results were interpreted to suggest that these women had discontinued their medication during pregnancy [33].

3.2.2. Asthma. For three categories of asthma severity before pregnancy (intermittent, mild persistent, and moderate/severe), mothers whose medication use fell below the recommended guideline experienced more severe asthma during pregnancy than women using their recommended medication [34]. In an online survey, 39% of women who have been pregnant reported that they had discontinued or reduced their asthma medication during pregnancy, a third having done so without discussion with a physician. Of potential significance in managing these patients, 40% of women indicated that they would be more likely to continue taking their asthma medication during pregnancy if their obstetrician alone recommended it [35]. 40% of pregnant asthmatic subjects reported nonadherence to inhaled corticosteroid medication (ICS). However, after asthma education nonadherence to ICS decreased to 21% [36] which is important to note as lack of appropriate treatment with inhaled corticosteroids is associated with exacerbations of asthma during pregnancy [37].

3.2.3. Inflammatory Bowel Disease. Although studies have suggested that exacerbations of inflammatory bowel disease (IBD) during pregnancy may worsen pregnancy outcomes, 84% of female patients with IBD reported concerns that their IBD medications would harm their pregnancy while only 19% reported concerns about the effect of active IBD on pregnancy [38]. In Crohn's disease 67% (37/55) of women reported adherence to medical treatment during pregnancy [39] while in ulcerative colitis 60% (37/62) of women reported adherence [40]. With both conditions, reasons stated for nonadherence included quiescent disease and fear of negative effects on the fetus [39, 40].

3.2.4. Nicotine Replacement Therapy. Adherence to nicotine replacement therapy (NRT) is low among pregnant smokers. Fish et al. found that overall only 29% of 104 women used NRT for the recommended 6 weeks and 41% used NRT as directed in the first 48 hours after a quit attempt [41].

4. Factors Affecting Medication Adherence in Pregnancy: Perception of Risk

In addition to the multiple factors that may affect medication adherence in the nonpregnant population, there are unique influences that may play a role in pregnant women. On the one hand, pregnant women may be motivated to take their medication for the well-being of their baby, mindful of the potential negative fetal consequences of untreated maternal disease. On the other hand, it has been demonstrated that women may not take their medication due to concerns regarding potential adverse fetal effects [14, 39, 40, 42]. In some cases this fear may be justified based on known teratogenic effects; however, in many cases medications have not been demonstrated to be harmful. It has been shown that pregnant women tend to overestimate the risks associated with drug use during pregnancy. Most women who completed an internet survey were able to correctly identify that the general risk of malformation is $\leq$5%; however, they overestimated the teratogenic risk associated with many drugs during pregnancy [43].

5. Improvement in Medication Adherence in Pregnancy

If women with inadequately controlled disease due to inadequate adherence with drug therapy are identified, they may be targeted for evidence-based counselling to correct their misperceptions, allay their fears, and hopefully improve medication-taking behaviour [43]. In addition, it may be possible to avoid medication nonadherence before it happens by proactively addressing the pregnant woman's concerns about the safety of medications. Ideally, with chronic drug therapy this counselling may occur as part of prepregnancy planning. Survey studies have shown that pregnant women feel they need information about the use of drugs during pregnancy [14, 42]. Media and other sources may provide misleading information provoking anxiety amongst pregnant women [43]. Given the overestimation of risk, the discussion should include, if available, evidence-based information on the effects of the medication's use during pregnancy allowing the pregnant women to make an informed decision as to whether to continue their prescribed therapy. Education should focus on the important role of good medication adherence for the health of both the mother and fetus.

Counselling by teratogen information services may play a role in influencing medication-taking behaviour [43]. After counselling by Motherisk, a Canadian teratogen information service, 61.1% (22/36) of pregnant women who had discontinued their antidepressant or benzodiazepine medication restarted their medication within a few days [44]. Health care workers, such as obstetricians and family physicians, are uniquely positioned to not only monitor adherence but to encourage consultation with drug information services to dispel misconceptions about the risks of medications to the fetus.

A meta-analysis of studies of directly observed therapy of highly active antiretroviral therapy (DOT-HAART) found that DOT-HAART recipients were more likely to achieve undetectable viral load and HAART adherence of greater than or equal to 95% [45]. A similar approach has been suggested for pregnant women. The third trimester of pregnancy may present an opportunity for the use of directly observed HAART to achieve virologic suppression for prevention of mother-to-child transmission of HIV [46]. Using a simulation model, use of DOT in women receiving HAART in 3rd trimester was associated with a relative risk of mother-to-child HIV transmission of 0.39 relative to conventional

HAART. It was projected to be highly cost-effective, averting the downstream medical costs associated with pediatric HIV infection [46]. All but one of 17 Latina pregnant and postpartum women positively evaluated a proposed hypothetical modified DOT program [29] suggesting that at least some women would be accepting of this approach.

6. Summary

Surprisingly, although it is generally accepted that the maintenance of good health of the pregnant women through the treatment of underlying maternal medical conditions is of potential benefit to the unborn fetus, medication nonadherence is a commonly encountered problem in this population. As in the nonpregnant patient the problem is complex with many factors playing a role; however, additional issues such as the potential effects of the medication on the baby may affect the mother's decision-making process. Ideally, poor compliance with therapy can be avoided through appropriate education of the mother although it is unlikely that this approach will be effective in all cases and solve all problems. More research to provide the evidence-based information regarding the effects of drugs during pregnancy, in order to avoid misperceptions, as well as better knowledge translation is needed. Identification and evaluation of other effective strategies to improve medication adherence in pregnant women who are already not taking their medication will also be important.

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Research Article

Breastfeeding Self-Efficacy and the Use of Prescription Medication: A Pilot Study

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Objective. To examine the association of self-efficacy, perception of milk production, and lactating women's use of medication prescribed to increase breast milk in a cohort of 18–40-year-old mothers over six months. *Methods*. Mothers ($n = 76$) attending community clinics completed the Breastfeeding Self-Efficacy Scale and the Humenick/Hill Lactation Scale, a measure of perceived milk production, three times. *Results*. Domperidone, a dopamine antagonist, was used by 28% of participants. On average, those using domperidone had lower self-efficacy scores than those not using it ($P < 0.05$) and were more likely to have used formula (Pearson chi-square test statistic = 6.87, df = 1, $P < 0.05$). Breastfeeding self efficacy and perception of milk production were positively correlated. *Conclusion*. Breastfeeding assessment conducted prior to prescription of galactogogues is recommended for mothers and healthy term babies. Following Baby-Friendly hospital protocols and increasing self-efficacy for lactating women may be most effective in sustaining breastfeeding. Risks and benefits of various galactogogues are discussed.

1. Introduction

Breastfeeding is the optimal form of nutrition for term and preterm infants [1–3]. Short- and long-term benefits are associated with reduced sudden infant death syndrome; positive immunological effects; reductions in the risks of otitis media, nonspecific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, obesity, type 1 and 2 diabetes, and childhood leukemia [1, 4]. However, exclusive breastfeeding, defined by the Public Health Agency of Canada [5] as "breastfeeding with no other liquid or solid given to the infant," is short-lived among lactating mothers everywhere. In a study comparing results from the Listening to Mothers II (LTM2; $n = 1563$) and the Maternal Experience Survey (MES; $n = 6421$) conducted in the United States 2005 and Canada 2006, respectively, rates of exclusive breastfeeding in hospital postpartum were reported as 61.2% and 75.4% [6]. At three months this rate dropped to 42.5% for the LTM2 and 51.7% for the MES. At six months both surveys reported exclusive breastfeeding rates of less than 20% [6]. Maintenance of breastfeeding seems challenging for many women. Perception of insufficient breastmilk production may contribute to cessation rates [7, 8].

Galactogogues are substances that increase milk volume by enhancing the rate of milk production and include both medications such as domperidone, metoclopramide, and herbs such as fenugreek, blessed thistle, and fennel (Tables 1 and 2). Common indications for galactogogues usually occur where lactation is nonexistent or threatened by known causes. This includes induction of lactation for adoptive mothers, relactation after weaning, maternal hypothyroidism, stimulate lactation in women with neonates in the neonatal intensive care unit, and for mothers who express milk by hand or pump [7, 9, 12, 13].

Anecdotally, there appears to be a trend for health care professionals to recommend pharmacological measures for mothers in the community who present with reported low milk supply issues. Reported low milk supply may be alleviated by modifying maternal self-efficacy through skill improvement and knowledge development [2]. The efficacy of galactogogues on the maintenance of breastfeeding for

Table 1: Prescription drugs used to increase breastmilk production.

Drug (trade name)	Intended use	Mechanism	Potential side effects
Domperidone (*Motilium*)	Antiemetic treatment of reflux disease	Peripheral dopamine antagonist	(i) Maternal cardiac arrhythmia (ii) Possible neurological side effects in infants (iii) Dry mouth, abdominal cramps, and headache (iv) Not approved in the United States
Metoclopramide (*Maxeran*)	Antiemetic	Dopamine antagonist	Drowsiness, restlessness, fatigue, anxiety, insomnia, depression, sedation, and pseudo-Parkinsonism Pediatric: prolonged clearance in infants which can result in high serum levels and a risk for methemoglobinemia. Side effects are more common in children
Sulpiride (*Eglonyl*)	Schizophrenia Antipsychotic Antidepressant	Selective dopamine antagonist	Extrapyramidal reactions and sedation in adults as well as suspected potential neonatal endocrinological effects Excreted in breastmilk
Chlorpromazine (*Thorazine*)	Antipsychotic	Increases prolactin	Sedation, lethargy, and risk of apnea Pediatric: SIDS
HGH human growth hormone (Somatotropin)	Hormone purified polypeptide of recombinant DNA	Stimulates milk production	Hypoglycemia Pediatric: absorption from breastmilk is unlikely
THR thyrotrophin releasing hormone	Treatment of hypothyroidism	Affects prolactin release	Theoretically may cause hyperthyroid condition in infants
Oxytocin (*Pitocin Syntocinon*)	Endogenous nonapeptide hormone	Stimulates milk ejection reflex	Hypotension, hypertension, water intoxication and excessive uterine contractions, bradycardia, and arrhythmias Pediatric: neonatal jaundice

Metoclopramide [9], Domperidone [10], Motilium [9, 10], and Sulpiride [11].

healthy term newborns and their mothers is unknown. Galactogogues are more commonly used for re-lactation and lactogenesis for adoptive mothers and mothers of babies in neonatal intensive care [13, 14].

High intention and initiation rates of breastfeeding, exclusive or otherwise, are rarely maintained beyond six months [15]. There are a multitude of reasons women stop breastfeeding including a lack of self-confidence in breastfeeding skills, lack of functional support, low spousal support, desire to smoke, sore nipples, postpartum depression, and maternal nutritional concerns [15–17]. Women who have experienced breast surgery, most commonly breast reduction and augmentation, may not be able to produce enough milk [18]. Maternal obesity has been implicated in delayed lactogenesis [19].

The use of formula in hospitals has been linked with low breastfeeding success rates [20]. The Baby-Friendly Hospital Initiative (BFHI) was introduced by the World Health Organization and UNICEF to increase breastfeeding rates and recommends the reduction of formula use in hospitals to promote breastfeeding [21]. In 1996, in Belarus, Kramer et al. conducted a randomized trial using the model of the Baby-Friendly Hospital initiative as an intervention and found that exclusive breastfeeding and duration increased for the first year of infants' lives given exposure to BFHI compared with standard of care received in control hospitals [22]. In 2005, it was also found that following BFHI steps, duration of breastfeeding increased. Of note, their sample consisted of women who may have been interested in exclusive breastfeeding and selected hospitals with BFHI [23]. At the same time, there was high media coverage on BFHI in Sweden where the study took place so awareness might have been heightened as breastfeeding rates in non-BFHI hospitals also rose [23].

The use of formula in hospital and at home has long been considered a detriment to exclusive breastfeeding and breastmilk production. However, formula is available in all hospitals as there are women who do not breastfeed. A national survey conducted in the United States reported that women choose not to breastfed because of personal preference (66.3%), they face current medical/physical problems (14.9%), feeding multiples or failed breastfeeding [24–26].

Maintenance of exclusive and partial breastfeeding is challenging for many women. Worldwide, the most common reason reported by mothers for early cessation of breastfeeding is maternal perception of insufficient milk production [8, 13, 24–32]. Insufficient milk production, often referred to as insufficient milk syndrome (IMS) was initially described by Gussler and Briesmeister in 1980 and was quickly recognized by the World Health Organization as the world's largest threat to the continuation of breastfeeding [8]. The prevalence of perceived insufficient milk production by mothers is not precisely known but has been reported between 30% and 80% [32]. This reason is associated with the highest discontinuation of breastfeeding occurring as early as 1–4 weeks postpartum [33]. Maternal perception of insufficient milk production is almost never validated by measured milk volume but is a prime influence in maternal

Table 2: Herbs commonly associated with galactogogue properties and known interactions.

Herbals	Intended use (main effect)	Potential side effects	Potential interactions	Contraindications
Alfalfa* (*Medicago sativa)*	Tonic Rejuvenative Diuretic	Diarrhea Reversible pancytopenia Reactivates-systemic Lupus	Immune modulators	Pregnancy Allergies
Anise* (Pimpinella anisum)	Expectorant Antispasmodic Antiseptic Antiflatulence	Seizures	Anticoagulants MAO inhibitors oral contraceptives	Pregnancy: abortifacient
Black seed caraway (*Carum carvi*)	Dyspepsia, antinausea, antiflatulent incontinence galactogogue	Contact dermatitis Weak antispasmodic activity	Disulfiram	Pregnant, breastfeeding due to antispasmodic effects
Blessed thistle* (*Cnicus benedictus*)	Stimulates menstruation, antidiarrheal, antibacterial, expectorant galactogogue	Nausea, vomiting diarrhea, contact dermatitis	Antacids, H2 antagonists, proton pump inhibitors, sucralfate, insulin	Pregnant and breastfeeding
Fennel* (*Foeniculum vulgare)*	Expectorant Antispasmodic URTI	Seizures Nausea, pulmonary edema	Anticonvulsant Sun exposure	Unknown
Fenugreek* (Trigonella foenum-graecum)	GI complaints URT congestion Antidiarrheal	Uterine stimulant Hepatotoxicity Maple-syrup Urine diarrhea	Anticoagulants Antidiabetics	Pregnancy (uterine stimulant) breastfeeding
Goat's rue (Galega officinalis)	Diuretic Galactogogue Antihyperglycemic	Headache weakness nervousness	None reported	Caution for children, pregnant, and breastfeeding patients
Milk thistle* (Silybum marianum)	Dyspepsia, liver damage from chemicals	Nausea, vomiting diarrhea	Aspirin, cisplatin, disulfiram, hepatotoxic drugs	Pregnant or breastfeeding patients

Nursing Herbal Medicine Handbook, Nursing Drug Handbook Series, Springhouse Pennsylvania.
*Often herbs are used in combination, such as mother's milk tea, various combinations of fenugreek, blessed thistle, anise, coriander, fennel, marshmallow and other herbs.

decision making to supplement with formula, discontinue breastfeeding, or use of products that stimulate milk supply.

Galactogogues include prescription and over-the-counter (OTC) drugs, or complementary and alternative medications (herbal supplements). In the United States, it is estimated that 15% of breastfeeding women have used herbal galactogogues but the extent of galactogogue use is unknown for Canadians [34]. The use of herbal galactogogues is cause for concern because users do not confide in their health care providers and may mix prescription, OTC, and herbal medications with potential for adverse effects [35, 36].

A number of herbal supplements are purported to have galactogogue properties (Table 2). In Canada, Koren et al. of the Motherisk Program, estimate that between 7 and 55% of pregnant women use herbal supplements even though the safety and efficacy of these during pregnancy and lactation are unknown [37]. A recent American study surveyed herbal supplement use in pregnant women and reported the 14% of users did not consider herbal remedies as medications but natural and therefore benign [38, 39]. However, herbal supplements often lack standard dosing and preparation, and known composition [40]. Published research is scant supporting herbs' effectiveness in increasing milk production and more importantly their safety to mother and infant. Additionally, use of herbal medications may not be disclosed to conventional health care personnel and clients may use both prescriptions and herbal supplements courting potential adverse reactions. While there is some evidence to support the safety and efficacy of select prescription drugs, much less exists for herbal supplements, and little is known regarding drug/herbal supplements interactions [41].

Women consulting health care professionals for the perception of insufficient milk production may receive a recommendation to supplement with formula and/or to use a prescription medicine. Prescribing drugs for insufficient milk has recently gained popularity among physicians and nurse practitioners, although a lack of consensus persists regarding the efficacy of prescription galactogogues and their safety for infants [28, 30, 31]. "Some providers may inappropriately recommend galactogogues prior to emphasizing the primary means of increasing the overall rate of milk synthesis (i.e., frequent feeding and complete milk removal at regular intervals)." [7, page 42].

The most commonly prescribed drugs are the gastrokinetic agent, domperidone, and the antiemetic, metoclopramide. Until 2010, increased milk production was an off-label use for domperidone in Canada but the Federal Drug Administration in the United States does not recommend it due to reports of arrhythmias in users and the possibility of adverse effects for infants [8, 42]. The side effects of domperidone, a dopamine antagonist, include an increase in prolactin levels, dry mouth, abdominal cramps, and headache [4, 33, 34]. Domperidone is thought not to cross the blood-brain barrier but is excreted in breast milk in low amounts [35]. Although infant exposure to domperidone is considered insignificant, evidence is scant [36]. Other drugs that have been used include antipsychotics such as sulpiride, chlorpromazine, and hormones including human growth hormone, thyrotropin releasing hormone (TRH), and oxytocin nasal spray (Table 1).

In preparation for submission of a national grant we conducted a pilot study in 2009 using a prospective cohort design with a convenience sample of mothers. The purpose of the pilot was to examine self-efficacy, perceived milk production, and lactating women's use of medication prescribed to increase breastmilk in a cohort of 18–40-year-old mothers over six months. The pilot allowed testing of the recruitment strategy and the demographic questionnaire. This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary. Permission to access the community clinics was granted by the Director, Community Health Centres, Partnerships and Services, Alberta Health Services.

2. Material and Methods

A convenience sample of seventy-six mothers was recruited from parent drop-in clinics at six community health centres in Calgary, Alberta, during a three-month period. Women attended the clinics for breastfeeding support and well baby checkups. Participants were literate in English, and were breastfeeding or had attempted to breastfeed a singleton infant within the previous two months. Exclusion criteria included mothers with gestational diabetes, previous breast reductions or augmentations, illnesses such as breast cancer requiring mastectomy or extended breast lump biopsies, and those who did not have a telephone. Term, healthy babies were included in the study. Excluded from the study were babies less than 37 weeks gestation, those physically compromised, or those born with abnormalities that would affect breastfeeding such as cleft lip or palate. Participants identified by public health nurses and approached by research assistants were given a package of questionnaires assessing breastfeeding self efficacy, maternal perception of insufficient milk production, and use of galactogogues. They were surveyed again by telephone at 3 and 6 months after entry. If a woman weaned within the follow-up contact time, she was asked to complete the last set of questionnaires.

The Breastfeeding Self-Efficacy Scale, short-form (BSES) [43], measures a mother's perceived ability to breastfeed her baby. Breastfeeding self-efficacy (BSE) is defined as a mother's confidence in her perceived ability to breastfeed the baby [44]. Decreased self-efficacy is known to be involved in cessation of breast-feeding [27, 45]. It has been shown to be associated with perceived insufficient milk production [30]. The Hill and Humenick Lactation Scale (HHLS) is a direct measure of the perception women have of their own milk production [46]. A demographic information sheet designed for this study collected data on variables known to affect breastfeeding, for example, type of delivery, family support, previous breastfeeding experience, preparation for breastfeeding, and formula use at hospital and at home.

The BSES short form is a 14-item self-report instrument where items are preceded by the phrase "I can always" and anchored with a 5-point Likert scale where 1 = not at all confident and 5 = very confident. Items are summed to produce a score ranging from 14 to 70 with higher scores indicating higher levels of breastfeeding self-efficacy [47]. The BSES has been used extensively for a decade with a variety of populations and is widely published. The short-form scale has established validity and reliability in English and three other languages [43, 44, 47]. The Cronbach's alpha coefficient for the English short form is 0.94 [43, 47].

Perceived milk production was measured using the HHLS. It examines maternal commitment, satisfaction, and perceived infant satiety [46]. The HHLS is a 20-item self-report instrument where all items are anchored with a 7-point Likert scale where 1 = strongly disagree and 7 = strongly agree and can be used for subscale analysis. The three subscales show moderate to high internal consistency, Cronbach's alpha coefficients: 0.75 to 0.98 [48]. Items are summed to produce a score ranging from 20 to 140 with higher scores indicating higher levels of commitment and perceived infant satiety. It has been used with diverse populations over the last fifteen years and is widely published [49, 50].

Information was entered into PAWS version 17 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to characterize the sample and describe sociodemographic characteristics. A correlation matrix was calculated to determine if any socio-demographic characteristics were significantly correlated with each of the dependent variables. Potential covariates included age, parity, education, marital status, prior experience breastfeeding, reported support for breastfeeding, use of formula in hospital, prenatal class attendance, type of delivery, level of education, support, and preparation for breastfeeding (i.e., prenatal classes). Chi square test was used to explore the relationships between categorical demographic variables. The generalized estimating equation (GEE) was used to estimate multiple predictors for BSES and HHLS. This is considered an appropriate method to identify predictors in repeated measures studies. Known predictors of breastfeeding continuation such as delivery experience, prenatal classes, access to breastfeeding information, and support for partner and family were controlled for in the model. All comparisons were calculated with statistical significance set at a $P < 0.05$.

Table 3: Sample characteristics $N = 76$.

Variable	Number of women	n%
Marital status		
Married	60	79
Other	16	21
Education years		
High school	14	18
Trade school	4	5
Postsecondary	55	72
Type of delivery		
Vaginal	51	67
Cesarean section	25	33
Prenatal classes		
Have you ever attended prenatal classes? Yes	58	76
Did you attend prenatal classes for this pregnancy? Yes	40	53
Did you find prenatal information useful? Yes	67	88
Previous breastfeeding experience		
Yes	32	42
Formula received in hospital		
Yes	32	42
When the decision to breastfeed was made?		
When I became pregnant	26	34
I was always going to breastfeed	44	58
After prenatal classes	2	3
My partner and I discussed it	4	5

Totals may not add to 100% given missing data.

3. Results

On average the participants were 30 years old (range 19–40 years), initiation of exclusive breastfeeding was reported by 57%. At Time 1, entry into the study, 83% reported breastfeeding and formula feeding and their babies were between 1 and 20 weeks old. Seventeen per cent were exclusively breastfeeding. Forty-seven per cent were still breastfeeding at Time 2 but also using formula. At the end of Time 3, almost one-third of participants reported use of domperidone during breastfeeding to increase milk production (Table 3).

Table 4 shows the parameter results for predicting BSES scores and independent variables. Women who used formula at any time had lower breastfeeding self efficacy than those who did not use formula ($P < 0.05$). Women reporting lower breastfeeding confidence used both formula and domperidone, two interventions undertaken to ensure their babies were fed but which may be reflective of the lack of confidence in the ability to exclusively breastfeed. Women who had confidence in their ability to breastfeed (high BSES scores) also had high perceived milk production scores (high HHLS scores).

Women ($n = 32$) who used formula had lower BSES scores than those who did not ($n = 43$, $P < 0.001$, 95% CI = -11.66, -3.66). Domperidone was reported by 28% of the participants. Those who used domperidone had lower BSES scores than those who did not ($P < 0.05$, 95% CI = -10.13, -1.15).

Women reporting lower breastfeeding confidence as measured by BSES used both formula and domperidone (Table 4). The GEE results showed that there was no significant association found between education, marital status, and formula use and HHLS scores.

A positive association between those who used domperidone and formula was found (Pearson chi square, test statistic = 6.87, df = 1, $P < 0.05$). As years of education increased, BSES scores increased (95% CI = 0.628, 3.251, $P < 0.05$). Also, prenatal classes specific in breastfeeding information increased BSES at Time 1 only ($P < 0.05$, 95% CI = 1.455, 14.5).

4. Discussion

The rate of exclusive breastfeeding was low in our study—a finding similar in many other international studies. Breastfeeding combined with formula feeding was the most commonly reported method of feeding over time. Domperidone was prescribed to one third of breastfeeding women in our study. We were unaware of the particular circumstances precluding prescription but our inclusion criteria removed preterm babies, re-lactating women and those with known health situations that would have knowingly affected breastfeeding or breast milk yield. There are reports of increasing domperidone prescription for mothers of preterm babies (<31 weeks) [51], but the healthy well educated mothers in our study were from the community and their babies were term (≥37 weeks) so we found the rate of prescription use in our small study high.

We have reported a 33% rate of surgical delivery and there may be some justification in using dopamine antagonists to raise serum prolactin levels in some women who have had a cesarean section as they may lack a significant rise in prolactin levels [52]. Substances that increase prolactin levels may be effective for those women with known low serum prolactin but this test is seldom, if ever, done. There may be women who are responders and nonresponders to dopamine antagonists but this would have to be determined by challenge.

We found that confidence in breastfeeding skills and perceived breastmilk production were positively correlated but we also report high use of domperidone. We were unable to determine if use of domperidone contributed to perceived breastmilk production. This likely had to do with our inability to access a sample of women earlier in the postpartum period and prior to use of domperidone. Women reported that prenatal classes specifically addressing breastfeeding had an important influence on self-efficacy early in the postpartum period, a finding supported earlier in

Table 4: Parameter results for predicting BSES and independent variables.

Parameter(s) applied with BSES	95% Wald confidence interval		Hypothesis test		
	Lower	Upper	Wald chi-square	df	Sig.
Education	.628	3.251	8.399	1	0.004
Formula use	−12.801	−2.313	7.977	1	0.005
Formula use over time	.135	4.550	4.327	1	0.038
Specific prenatal breastfeeding classes	1.455	14.513	5.745	1	0.017

Level of significance $P < 0.05$.

a Canadian sample of breastfeeding women [53]. We support consistency of breastfeeding information offered throughout the reproductive period, beginning in prenatal classes and extending into the postpartum period or as long as the woman continues breastfeeding.

Formula use was also associated with the use of domperidone. We found that the HHLS did not discern between combination feeding mothers and exclusively breastfeeding mother. Women can feel satisfied and confident while combining breastfeeding and formula to feed their babies; however this combination may decrease duration of breastfeeding [20].

4.1. Limitations. A limitation of this study is the small urban convenience sample of women from one region in Canada. Our sample recruitment was curtailed by the H1N1 pandemic at which time Canadian federal, provincial, and local health agencies recommended isolation for infants under 6 months who could not receive H1N1 immunization [54]. Women stopped attending the drop-in clinics and community clinic nurses were redeployed to H1N1 immunization clinics and our study ceased prematurely.

Nurses selecting women in the clinic may knowingly have suggested those women already using a galactagogue or those women who were motivated to participate in a breastfeeding study may have more readily self-selected to participate in this study, thereby creating selection bias.

In our study only one woman reported using a herb (fenugreek) to increase milk production, and this does not reflect the range of herbal use reported elsewhere [34]. We found higher education associated with higher breastfeeding self efficacy but this may be a reflection of our participants. Our study sample consisted of well-educated, socially-advantaged women with excellent medical access, attributes not shared by all breastfeeding women. Also, participants entered the study at various times postpartum and recall bias may have affected responses. The hospitals where our sample delivered were not Baby-Friendly accredited, which may have skewed the results of this pilot study as formula is readily available on the units. Mothers may have received the recommendation to supplement with formula in hospital which can decrease a mothers overall breastfeeding duration [20].

4.2. Implications for Practice. We recommend that for healthy term infants born to healthy mothers, prescription medication should not be a first-line response to maternal perceived insufficient milk production, a recommendation also held by the Academy of Breastfeeding Medicine [7]. The increase in prescription medications may indicate the acceptance of a "ready fix" subsequent to short assessment visits with physicians by anxious mothers [55]. Best practice indicates a physical examination, an assessment of a breastfeeding session, and an interview prior to suggesting a prescription medication to address perceived insufficient milk production [10, 55]. By following best-practice guidelines, those women who are experiencing a physiological decrease in milk production will be appropriately identified as needing the pharmacological support to maintain adequate milk production. Our results concur with others: women with increased confidence in their breastfeeding ability are more likely to persist and are less likely to question their milk production [24–26, 56]. Combating perceived insufficient milk remains an ongoing challenge for all health care professionals working with breastfeeding mothers. Improving information to postpartum mothers directly related to milk supply (fullness, timing of feeds), measures of infant satiation (satiation cues, output), and growth spurts in infants may help some mothers address breastfeeding concerns. Stressing the importance of nighttime breastfeeding in the first eight weeks postpartum, when prolactin levels are the highest may also help to decrease mothers' perception of insufficient milk [55].

5. Conclusion

In 2011, Protocol 9 published by the Academy of Breastfeeding Medicine Protocol Committee stated that caution should be exercised when recommending drugs to assist initiation, maintenance, or augmentation of human milk synthesis. Stronger ties in hospital to Baby-Friendly standards, increased availability of education for health care professionals, and standard practice guidelines for breastfeeding assessment prior to medication introduction into the breastfeeding dyad may promote breastfeeding self-efficacy and increased satisfaction of mothers and healthier babies.

Abbreviations

BSE: Breastfeeding self-efficacy
BSES: Breastfeeding Self Efficacy Scale
FDA: Federal Drug Administration
HHLS: Hill and Humenick Lactation Scale
H1N1: Influenza A virus subtype
LTM2: Listening to Mothers II
MES: Maternal Experience Survey
TRH: Thyrotropin releasing hormone.

Conflict of Interests

There are no competing interest. The authors are responsible for the content and writing of this paper.

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Research Article

The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

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Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are known to cause fetal renal damage in pregnancy. Due to conflicting reports in the literature, their safety after first trimester exposure has been debated. Our aim was to determine whether the use of ACE inhibitors or ARBs in the first trimester of pregnancy is associated with an increased risk for major malformations or other adverse outcomes. All subjects were prospectively enrolled from among women contacting a teratogen information service. At initial contact, details of maternal medical history and exposures were collected and follow-up interviews were conducted to ascertain pregnancy outcomes. Two comparator groups, women with hypertension treated with other antihypertensives, and healthy controls were also recruited. Baseline maternal characteristics were not different among the three groups. There were no differences in rates of major malformations. Both the ACE-ARBs and disease-matched groups exhibited significantly lower birth weight and gestational ages than the healthy controls ($P < 0.001$ for both variables). There was a significantly higher rate of miscarriage noted in the ACE/ARB group ($P < 0.001$). These results suggest that ACE inhibitors/ARBs are not major human teratogens; however, they may be associated with an increased risk for miscarriage.

1. Background

Hypertension is a fairly common condition, estimated to affect between 6% and 8% of pregnancies [1]. It can occur as one of four conditions: chronic hypertension, preeclampsia-eclampsia, chronic hypertension with superimposed preeclampsia, and gestational hypertension [2]. Hypertension is associated with an increased risk of adverse effects in both the mother and the fetus, and treatment is warranted. Perinatal and infant complications may include prematurity, neonatal death, placental abruptions, and small-for-gestational age babies [3–7]. Maternal complications include pulmonary edema, hypertensive encephalopathy, retinopathy, cerebral hemorrhage, and acute renal failure [2], which are worse in untreated patients.

Data on the safety of antihypertensive drugs in pregnancy are relatively sparse [8]. Based on the existing data, methyldopa, nifedipine, labetolol, and other beta-blockers have been considered the drugs of choice in the treatment of hypertensive disorders in pregnancy [9].

Angiotensin converting enzyme inhibitors (ACE) are now widely used as first-line medications in nonpregnant hypertensive patients. A more recent class of agents, the angiotensin II receptor blockers (ARBs) are also gaining in popularity. Unfortunately, both of these classes of drugs have been contraindicated in pregnancy because of their association with characteristic adverse fetal effects [9] when used beyond the first trimester of pregnancy, including fetal hypocalvaria and renal insufficiency. The etiology of these defects appears to be related to fetal hypotension and reduced renal blood flow in the fetus.

Intrauterine growth restriction, prematurity, patent ductus arteriosus, severe neonatal hypotension, neonatal anuria, and neonatal or fetal death have also been observed with these drugs [10]. Anuria associated with oligohydramnios may produce fetal limb contractures, craniofacial deformities, and pulmonary hypoplasia. Based on their similar pharmacologic effects, it is generally assumed that the ARBs will behave in much the same manner although published

data on large numbers of exposed pregnancies do not exist [11–19]. To date, most human cohort studies or case series have failed to find teratogenic effects of ACE inhibitors after first trimester exposure [11, 20–24]. Recently, based on a relatively small cohort study, Cooper et al. suggested an increased risk of cardiovascular effects with first trimester use of these agents [25]. These findings, if real, are of major concern, because ACE and ARBs continue to be used in women of reproductive age, many of whom may use inadequate contraception [26, 27]. Moreover, since half of all pregnancies are unplanned [28, 29], inadvertent exposures to ACE and ARBs in pregnancy will continue to occur.

The primary objective of this study was to determine the risk for major congenital malformations following maternal exposure to ACE inhibitors and ARBs during the first trimester of pregnancy.

2. Methods

This was a prospective, observational, controlled cohort study. Eligible women were identified among callers to the Motherisk Program at the Hospital for Sick Children in Toronto. The Motherisk Program is a counseling service for women, their families, and health professionals on the safety or risk of drugs, chemicals, radiation, and infection during pregnancy. The study groups consisted of women who contacted the Motherisk Program concerning exposure to ACE-ARBs during the first trimester, other antihypertensives in pregnancy and healthy comparators not exposed to any known teratogen or medications for chronic conditions. Any patient reporting use of ACE/ARBs into pregnancy was eligible for inclusion. We controlled for potential effects of hypertension by comparing this group to two other groups of subjects, women exposed to other antihypertensive agents (including methyldopa or calcium channel blockers), and a healthy group without hypertension. The comparator groups were matched to the study groups by gestational age at recruitment, maternal age, and alcohol and cigarette use. The healthy comparator group was also selected from among callers to the Motherisk program. These women had no chronic medical conditions. Subjects were excluded if they were unwilling or unable to complete the follow-up interviews in English.

At initial contact with the patient before or during the early weeks of pregnancy, standardized questionnaires were used to document maternal medical history and exposures. Information about current and past pregnancies was obtained as was details about concurrent medical conditions. After the expected date of delivery, patients were followed up; the information collected at intake was complimented with additional details on medical conditions or exposures occurring since the initial contact. Details about delivery and infant outcomes were also recorded at follow-up.

The primary outcome measure was the rates of major malformations, which was compared among the 3 groups. Secondary endpoints included live birth rates, birth weight, gestational age, rates of perinatal, and neonatal complications as well as rates of miscarriage. Possible confounding factors, such as the presence of diabetes, were also considered in the analysis.

The rates of major malformations among the 3 groups were compared using the chi-square test or Fisher's exact test as appropriate. Continuous data were compared using the Kruskal-Wallis analysis of variance for three group comparisons. An alpha level of 0.05 was considered statistically significant and two-tailed tests were used for all analyses. Statistical analysis was performed with SigmaStat software (version 3.0).

This study was approved by the Research Ethics Board of the Hospital for Sick Children.

3. Results

We were able to successfully collect and follow 138 pregnancies exposed to ACE inhibitors or ARB's, 112 pregnancies exposed to "other" antihypertensives and 138 healthy pregnancies. There were no significant differences among the three groups in terms of maternal characteristics (Table 1), as the ACE/ARB group was matched with the healthy comparator group on most of these parameters. In the ACE/ARB group, the majority of women were exposed to these drugs exclusively in the first trimester (114 women—90%). A total of 8 (6.3%) women were exposed to these drugs in the first and second trimester, while only 6 (4.7%) continued the drugs for all three trimesters. The ACE/ARB group included 38 (27.5%) women exposed to ramipril, 25 (18.1%) exposed to lisinopril, and 15 (10.9%) women exposed to enalapril (Table 2). In the ACE/ARB group, there were 18 diabetics (13%), 6 with Type 1 diabetes mellitus and 12 with Type II diabetes mellitus.

When comparing pregnancy outcomes (Table 3), there were no differences in sex of offspring or rates of fetal distress. There were significant differences in birth weight and gestational age at delivery with both the hypertensive patient groups exhibiting lower birth weights (3225 g ACE/ARB group, 3063 g other antihypertensives, and 3511 g healthy controls, $P < 0.001$) and earlier gestational ages at delivery (37.6 weeks ACE/ARB group, 37.8 weeks other antihypertensives, and 39.6 weeks healthy controls, $P < 0.001$) compared to the healthy controls. There was a significantly higher rate of miscarriages in the ACE/ARB group, as compared to the "other" antihypertensive and healthy control groups (18.0%, 8.9%, and 11.8%, resp., $P < 0.001$).

There were 2 cases of major malformations in each of the three groups (Table 2), with no statistical differences among them ($P = 0.99$). As there was not a higher rate of malformations in the exposed group, we did not perform detailed analysis with diabetes as a covariate; however, one malformed case in the treatment group was from a diabetic mother. In addition, among the ACE/ARB group two of the spontaneous abortions occurred in diabetic mothers. Analyzing the pregnancy outcomes excluding these two cases did not change the significance in the rate of spontaneous abortions.

Table 1: Characteristics of included subjects.

Characteristic	ACE/ARB exposed ($n = 138$)	Other antihypertensives ($n = 110$)	Healthy nonexposed ($n = 138$)	P value
Age (yrs ± SD)*	34.9 ± 4.9	34.3 ± 4.2	33.9 ± 4.5	0.18
Gravidity (%)†				
1	41 (29.7)	31 (28.2)	41 (29.7)	
2	39 (28.3)	41 (37.3)	41 (29.7)	0.60
≥3	58 (42.0)	38 (34.5)	56 (40.6)	
Parity (%)†				
0	59 (42.7)	44 (40.0)	57 (41.3)	
1	38 (27.5)	46 (41.8)	47 (34.1)	0.13
≥2	41 (29.7)	20 (18.2)	34 (24.6)	
Previous miscarriage (%)†				
0	110 (79.7)	81 (73.6)	105 (76.1)	
1	17 (12.3)	22 (20.0)	21 (15.2)	0.54
≥2	11 (8.0)	7 (6.4)	12 (8.7)	
Previous elective abortions (%)†				
0	119 (86.2)	103 (93.6)	123 (89.1)	0.27
≥1	19 (13.8)	7 (6.4)	15 (10.9)	
Gestational age at call (wks ± SD)‡	7.0 ± 3.4	10.5 ± 8.3	7.4 ± 3.4	0.09
Alcohol†				
No	114 (85.1)	100 (90.1)	125 (90.6)	0.30
Light	20 (14.9)	11 (9.9)	13 (9.4)	
Smoking†				
No	117 (88.0)	102 (93.6)	129 (93.5)	0.18
Yes	16 (12.0)	7 (6.4)	9 (6.5)	

*One-way Anova, †chi-square test, ‡one-way Anova on ranks.

Table 2: Specific ACE/ARB's used by expose subjects.

	Count (%)
Ramipril	38 (27.5%)
Lisinopril	25 (18.1%)
Enalapril	15 (10.9%)
Monopril	8 (5.8%)
Valsartan	8 (5.8%)
Perindopril	7 (5.1%)
Candesartan	6 (4.3%)
Irbesartan	6 (4.3%)
Losartan	5 (3.6%)
Quinapril	5 (3.6%)
Cilazapril	3 (2.2%)
Fosinopril	3 (2.2%)
Telmisartan	3 (2.2%)
Captopril	2 (1.4%)
Prinivil	1 (0.7%)
Trandolapril	1 (0.7%)
Polytherapy	2 (1.4%)

4. Discussion

Establishing the safety of ACE inhibitors and ARBs after first trimester exposure is important for a number of reasons. Most notably is that women continue to need effective treatment for their existing chronic hypertension and that a large number of pregnancies will be exposed inadvertently to these agents. Accurate information on the safety of these agents will assist women and their health care practitioners in making rational choices about appropriate treatment. While there is a consensus that ACE inhibitor/ARBs should be discontinued when pregnancy is diagnosed to prevent fetal renal damage and associated complications, women often do not plan pregnancy, and fetal exposure in the first trimester is inevitable.

Our results are reassuring and consistent with a growing body of evidence that did not find an apparent increased risk for malformations among liveborns following exposure to ACE inhibitor/ARBs in early pregnancy [11]. In fact, the rates of malformations were comparable to our healthy comparator group. Given that the ACE/ARBs are known to affect the fetal renin-angiotensin axis which becomes active in the second trimester, it is not surprising that to date, adverse fetal effects of these agents have been shown only after exposures which continued into the second half of pregnancy. Our findings support the current hypothesis that teratogenic effects are likely mediated through disruptions in the renin-angiotensin axis and, therefore, not observed with such early exposures.

There were significantly more spontaneous abortions in the ACE/ARB group as compared to the other antihypertensive or healthy groups. Some animal data support this finding

Table 3: Pregnancy outcomes following exposure to ACE/ARBs or other antihypertensives as compared to a healthy comparator group.

Characteristic	ACE/ARB exposed ($n = 139$[a])	Other antihypertensives ($n = 112$[b])	Healthy nonexposed ($n = 138$)	P value
Fetal outcome				
Livebirth	108 (77.7%)	105 (93.7%)	120 (88.2%)	<0.001
Spontaneous abortion	25 (18.0%)	4 (8.9%)	16 (11.8%)	
Elective abortion	6 (4.3%)	0	0	
Fetal death	0	3 (2.7%)	0	
Gestational age at birth (wks ± SD)	37.6 ± 3.1	37.8 ± 2.8	39.6 ± 1.6	<0.001
Delivery				
Vaginal	62/108 (57.4%)	57/106 (53.8%)	83/120 (69.1%)	0.045
Cesarean section	46/108 (42.6%)	49/106 (46.2%)	37/120 (30.8%)	
Preterm delivery				
No	81/108 (75%)	79/105 (75.2%)	117/120 (97.5%)	<0.001
Yes	27/108 (25%)	26/105 (24.8%)	3/120 (2.5%)	
Birth weight (grams ± SD)	3225 ± 862	3063 ± 839	3511 ± 471	<0.001
Sex				
Male	59 (54.6%)	49 (46.6%)	57 (47.5%)	0.43
Fetal malformations[†]				
Yes	2/108 (1.8%)	2/105 (1.9%)	2/120 (1.6%)	0.99

[a]Including 1 twin pregnancy.
[b]Including 2 twin pregnancies.
[†]Fetal malformations are reported as a proportion of liveborn (in the ACE/ARB group-1 choanal atresia and 1 hypospadias, in the other antihypertensives group-1 unspecified heart murmur and 1 undescended testicle, in the health unexposed group-1 Down's syndrome and 1 inguinal hernia).

showing an increase in mortality among fetuses exposed during organogenesis [30]. This may also be the result of confounding effects of underlying maternal conditions, including higher incidence of diabetes mellitus among women receiving ACE/ARBs [31], but the possibility of spontaneous abortions as a result of fetal malformation cannot be excluded. In addition, while the number of diabetics with spontaneous abortion was small, precluding our ability to perform a regression analysis, excluding these two cases for a subgroup analysis did not change the significant findings of the spontaneous abortion outcome.

In the three-way comparison, there was a significant difference in mean gestational age at birth as well as birth weight, with babies born either to mothers exposed ACE/ARBs or to other antihypertensive drugs exhibiting a lower mean gestational ages at birth as well as a lower birth weights. The decrease in gestational age at birth as well as birth weight is consistent with the findings in women with chronic hypertension [32], attributable to placental dysfunction and decreased placental blood flow [30]. Including a disease-matched comparison group, our data suggest that the decrease in gestational age at birth and the lower birth weight are likely related to disease effects similar to all previous studies. Our ability to detect small increases in the risk of major malformations is limited by the available sample size. Though this cohort has an 80% power (with $\alpha = 0.05$) to detect only a 2.5-fold increased risk, however, our data are in agreement with several recent published cohort studies and series [11, 20–24, 33], which failed to show increased malformation rates after first trimester exposure to ACE inhibitors/ARBs. In addition, we were unable to provide analysis on any particular ACE/ARB, to determine if there are differential effects of the two classes of drugs, or to assess for dose effects as the numbers in any particular drug-dose combination were small.

Our study may be limited by population selection bias. Namely, subjects were recruited following contact with a teratogen information service and may not represent the general antihypertensive using population. These are patients who have sought out additional information about their risks may be more diligent about seeking out prenatal or medical care in general.

The positive study by Cooper et al. [25] has been heavily criticized for inappropriately addressing potential confounders such as diabetes [31], some of which may not have been diagnosed. A large study by Malm et al. suggest that the apparent increased risk of ACE inhibitor is the result of maternal diabetes, as exposure to ACE inhibitors without diabetes was not associated with a higher teratogenic risk [33]. While we had insufficient cases to rule out a possible confounding effect of diabetes in our cohort, we had a substantial proportion of subjects with underlying diabetes, and it is apparent that subjects on ACE/ARBs are more likely to be diabetics than those on other antihypertensives.

Our findings suggest that inadvertent exposure to ACE inhibitors/ARBs in the first trimester of pregnancy may not present significant risks for malformations in live births but may be associated with higher rates of spontaneous abortion. However, given the strong evidence for teratogenicity beyond the first trimester and the availability of other safer effective antihypertensives in pregnancy, it is imperative that women on such agents receive prompt attention in the early part of pregnancy so that their antihypertensive medications can be appropriately adjusted.

Conflict of Interests

The authors have no conflict of interests to declare.

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Review Article

Selective Serotonin Reuptake Inhibitors in Human Pregnancy: To Treat or Not to Treat?

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Selective serotonin reuptake inhibitors (SSRIs) are increasingly prescribed during pregnancy. The purpose of the present paper is to summarize and evaluate the current evidence for the risk/benefit analysis of SSRI use in human pregnancy. The literature has been inconsistent. Although most studies have not shown an increase in the overall risk of major malformations, several studies have suggested that SSRIs may be associated with a small increased risk for cardiovascular malformations. Others have noted associations between SSRIs and specific types of rare major malformations. In some studies, there appears to be a small increased risk for miscarriages, which may be associated with the underlying maternal condition. Neonatal effects have been described in up to 30% of neonates exposed to SSRIs late in pregnancy. Persistent pulmonary hypertension of the newborn has also been described with an absolute risk of < 1%. The risk associated with treatment discontinuation, for example, higher frequency of relapse and increased risk of preterm delivery, should also be considered. The overall benefit of treatment seems to outweigh the potential risks.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of depression, anxiety, and other disorders. Estimates suggest that the lifetime risk for depression ranges between 10 and 25% with a peak prevalence occurring at childbearing age [1]. According to Evans et al., 9–14% of all pregnant women display signs of depression and/or have illnesses that fulfil research diagnostic criteria for depression [2]. The prevalence rates of depression during pregnancy are 7.4%, 12.8%, and 12.0%, for the first, second, and third trimesters, respectively [3]. A number of SSRIs were introduced since the 1980s, including fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. They have better efficacy, tolerability, and safety compared to first-generation antidepressants, for example, tricyclic antidepressants, and are safer in overdose. They exert their effects by inhibiting the presynaptic plasma membrane serotonin transporter. The serotonin transporter mediates the reuptake of serotonin into the presynaptic terminal; neuronal uptake is the primary process by which neurotransmission via 5-hydroxytryptamine (neuronal serotonin) is terminated. Thus, treatment with an SSRI initially blocks reuptake and results in enhanced and prolonged serotonergic neurotransmission. All SSRIs share a similar mechanism of action despite having different chemical structures. The use of antidepressants and anxiolytics has shifted from the domain of psychiatry to primary care, with the discovery of more selective and safer drugs. SSRI use in pregnancy has increased over the years [4–7]. In recent years the proportion of pregnancies with SSRI exposure in the USA is 6% [6, 7]. SSRIs readily cross the human placenta [8, 9]. In spite of the widespread use of SSRIs during pregnancy and the relative extensive literature available, there are conflicting views on the safety of these drugs during pregnancy. The purpose of the present traditional literature review is to summarize and evaluate the current evidence for the risk benefit analysis of SSRI use in human pregnancy.

2. Human Studies on SSRIs in Pregnancy

2.1. Congenital Anomalies (see Table 1). A summary of studies on the use of SSRIs in human pregnancy is presented in

Table 1. Many studies on the use of SSRIs during pregnancy have not shown an increase in the overall risk of major malformations [10–28]. Several studies have suggested that the use of SSRIs, particularly paroxetine, may be associated with a small increased risk for cardiovascular malformations [29–38]. Other studies have noted associations between SSRIs in pregnancy and specific types of relatively rare major malformations (neural tube defects, craniosynostosis, omphalocele, or right ventricular outflow tract defects) [39–41]. Some of these studies are retrospective and burdened with recall and selection bias. The largest dataset with prospective exposure information available to date is from the Swedish Medical Birth Registry. Their initial report has been negative [16]. Later, increased risk of cardiovascular defects was observed with paroxetine, predominantly of septal defects [30, 31]. Recently, new associations were noted, for cystic kidney with SSRIs, for relatively severe malformations with fluoxetine, and for any cardiovascular defect and hypospadias with paroxetine [38]. Three recently published meta-analyses on paroxetine exposure in pregnancy and cardiovascular malformations have not been consistent [42–44]. In the meta-analysis published by Bar-Oz et al. [42], first trimester paroxetine exposure was associated with a significant increase in the risk of cardiac anomalies. Women using antidepressants in pregnancy were more likely to utilize ultrasound in pregnancy and postnatal echocardiograms compared with women who did not. In this study, significantly more women receiving paroxetine used the medication for anxiety or panic disorders compared to women using other SSRIs. Detection bias was suggested as a contributing factor to the observed risk of cardiovascular malformations with paroxetine. In the meta-analysis published by O'Brien et al. [43], no increased risk of congenital malformations was associated with paroxetine. Cardiac malformation rates were similar and within population norms. In the meta-analysis published by Wurst et al. [44], there was an increased risk for combined cardiac defects and aggregated congenital defects with first trimester paroxetine use. Two opposing commentaries on this topic were recently published [45, 46]. The definition of cardiovascular malformations varied among studies, some including small septal defects, while others excluded them. The inconsistency across these studies may be explained by differences in study design, by confounding factors, for example, maternal underlying psychiatric disorder, coadministered medications, lifestyle factors (smoking, drinking), maternal BMI, and diabetes, or they may be spurious. Overall, there are over 33,000 reported pregnancy outcomes after prenatal exposure to various SSRIs.

We have calculated the overall rate of major congenital anomalies and of cardiovascular anomalies in the published prospective studies after prenatal exposure to SSRIs, where rates were available [10–15, 20, 25, 32, 33] and found 3.8% (189/4920) and 0.9% (53/6094), respectively, both well within their baseline risk in the general population. It can be summarized that the majority of the prospective studies have not shown an increase in the overall risk of major malformations. The studies which have suggested that SSRIs may be associated with a small increased risk for malformations were particularly with paroxetine.

2.2. Judging the Evidence for SSRIs as Possible Causes of Major Malformations. Seven criteria for proof of human teratogenicity have been amalgamated by Shepard [51] and are presented in Table 2 and discussed as follows.

(1) Many of the studies with positive findings on SSRIs in pregnancy are prescription studies, and women may not have actually taken the drugs. Exact timing of exposure during sensitive periods is often problematic, although exposure preceded the outcome.

(2) There are several isolated studies with inconsistent findings of statistically significant associations. Confounding factors are often insufficiently controlled for. Many of the prospective studies are underpowered for associations between exposure and specific malformations. Many of the retrospective studies are burdened with potential biases. All studies considered here are observational. The relative risk even in positive studies is below six and the lower bound of the 95% confidence interval often close to one. The findings in regard to the type of malformations are inconsistent in the underlying studies and even in studies from the same database published at different time points.

(3) In the positive studies, there was some dominance of cardiovascular malformations, septal defects in some studies, and right ventricular outflow tract obstruction defects in others. In the case of SSRIs, particularly paroxetine; however, they were non-specific. In many of the large studies, diagnosis of malformations uses classification codes and lacks careful delineation of clinical cases.

(4) The fourth criterion is not relevant in the context of SSRIs. SSRIs are common exposures in pregnancy, and most of the described defects are also relatively common.

(5) Animal reproductive studies in rats and rabbits administered paroxetine [52], fluoxetine [53], or sertraline [54] during organogenesis did not show a teratogenic effect.

(6) There is evidence based on mouse whole-embryo studies to suggest that serotonin plays a role in cardiovascular and craniofacial development [55–58]. Paroxetine 1 μM was shown to decrease serotonin-mediated proliferation of dissociated rat embryonic cardiac myocytes [59]. Rat whole-embryo culture results showed an increase in branchial bar fusion, but not cardiac malformations, after exposure to paroxetine at concentrations much higher than those achieved clinically [60]. It has been speculated that the observed malformations in vitro may be early ontogenetic indicators for infrequent cardiovascular anomalies observed in vivo. Fluoxetine was found to adversely affect cell viability and differentiation to cardiomyocytes at higher concentrations than those achieved clinically in a dose-dependent manner using mouse embryonic stem cell system [61]. SSRIs inhibit

Table 1: SSRIs in human pregnancy.

Study	Design	Sample size	SSRI	Results	Comments
Pastuszak et al., [10]	Prospective comparative multicentre cohort study	$n = 128$	Fluoxetine	No increase in the rate of major malformations	Small numbers
Chambers et al., [11]	Prospective comparative cohort study	$n = 228$, $n = 101$ (with physical examination)	Fluoxetine	No increase in the risk of major anomalies, higher incidence of 3 or more minor anomalies 15.5% versus 6.5%, $P = 0.03$	Physical examination by a single dysmorphologist
McElhatton et al., [12]	Prospective comparative collaborative ENTIS study	$n = 689$ antidepressants	Fluoxetine $n = 96$ Fluvoxamine $n = 66$ Paroxetine $n = 3$	No increase in the rate of congenital anomalies	Small numbers
Goldstein et al., [13]	Prospective registry, historic controls	$n = 769$	Fluoxetine	No increase in the rate of congenital anomalies	Manufacturer's data, spontaneous reports
Wilton et al., [14]	Postmarketing survey	SSRIs 187	Paroxetine $n = 63$ Fluoxetine $n = 52$ Sertraline $n = 51$ Fluvoxamine $n = 21$	No increase in the rate of congenital anomalies	Small numbers
Kulin et al., [15]	Prospective comparative multicentre cohort study	"New" SSRIs 267	Sertraline $n = 147$ Paroxetine $n = 97$ Fluvoxamine $n = 26$	No increase in the risk of major congenital anomalies	
Ericson et al.,[a] [16]	Swedish Medical Birth Registry, initial report	SSRIs: $n = 531$	Citalopram $n = 375$ Paroxetine $n = 122$ Sertraline $n = 34$ Fluoxetine $n = 16$	No increase in the rate of congenital anomalies	Incomplete drug reporting
Unfred et al., [47]	Prospective comparative cohort study	$n = 101$	Paroxetine	Increased risk of congenital anomalies (4/96 (4.2%) 1/195 (0.5%) $P = 0.04$) no pattern	Rate of anomalies in comparison group low, is, unpublished data
Simon et al., [17]	Retrospective cohort	SSRIs: $n = 185$	Fluoxetine $n = 129$ Sertraline $n = 32$ Paroxetine $n = 28$ > 1 SSRI: some	No increase in the rate of congenital anomalies; however, the rate of cardiac malformations was 2.2% in the exposed group versus 0% in unexposed	Prescription study, reliance on routinely collected clinical data, sample of live births rather than pregnancies, large number of comparisons
Hendrick et al., [18]	Review of obstetric and neonatal records	SSRIs: $n = 138$	Fluoxetine $n = 73$ Sertraline $n = 36$ Paroxetine $n = 19$ Citalopram $n = 7$ Fluvoxamine $n = 3$	No increase in the rate of congenital anomalies	Uncontrolled design, small numbers
Malm et al.,[c] [19]	Population-based cohort study, Finnish registries	SSRI: $n = 1398$	Citalopram $n = 554$ Fluoxetine $n = 525$ Paroxetine $n = 152$ Sertraline $n = 118$ Fluvoxamine $n = 65$	No increase in the rate of congenital anomalies	Prescription study, data on dose not provided

Table 1: Continued.

Study	Design	Sample size	SSRI	Results	Comments
Sivojelezova et al., [20]	Prospective comparative cohort study	$n = 125$	Citalopram	No increase in the rate of major malformations	
Wogelius et al.,[b] [29]	Population-based cohort study, Danish registries	SSRIs $n = 1051$	NA	Increased risk for overall anomalies (Ad RR 1.34 (95% CI 1.00–1.79) early, 1.84 (95% CI 1.25–2.71 2nd-3rd m) cardiovascular 29%	Data on specific SSRIs not provided, prescription study
Wen et al., [21]	Retrospective cohort study	SSRIs: $n = 972$	Paroxetine by 1/3	No increase in the risk of birth defects	Prescription study
Schloemp et al., [22]	Prospective comparative cohort	$n = 119$	Paroxetine	No increase in the risk of birth defects	Unpublished data
Vial et al., [23]	Prospective comparative cohort	$n = 683$	Paroxetine	No increase in the risk of birth defects	Unpublished data
Källén and Otterblad-Olausson,[a] [30], [a] [31]	Swedish Medical Birth Register, updated	SSRIs: $n = 6555$	Fluoxetine $n = 926$ Citalopram $n = 2701$ Paroxetine $n = 959$ Sertraline $n = 1906$ Fluvoxamine $n = 38$ Escitalopram $n = 72$	Increased risk of cardiovascular defects with paroxetine OR 1.63 95% CI 1.05–2.53 mostly septal defects 13/20	Incomplete drug reporting, potential detection bias, multiple comparisons
Davis et al., [24]	Retrospective case control study	SSRIs: $n = 805$	Paroxetine $n = 182$	No increase in the risk of birth defects	Prescription study
Bérard et al., [48]	Retrospective nested case-control study	$n = 1403$ antidepressants	Paroxetine $n = 542$ n (>25 mg/d) = 143 other SSRIs $n = 443$	No increase in the rate of congenital anomalies, increased risk for overall and cardiac malformations in the high-dose (>25 mg/d) group (Ad OR 3.07 (95% CI 1.00–9.42))	Prescription study, calculation of average daily dose affected by duration in the first trimester
Alwan et al., [39]	Retrospective case-control study	Cases:$n = 9622$ Control:s $n = 4092$	SSRIs 2.4% of cases 2.1% of controls, (sertraline 0.8%, fluoxetine 0.7%, paroxetine 0.5% citalopram 0.2%)	Associations between any SSRI and craniosynostosis, paroxetine/sertraline and anencephaly, paroxetine and right ventricular outflow tract obstruction defects, omphalocele and gastroschisis—small absolute risks	Small numbers of exposed infants for individual anomalies, multiple comparisons, data on dosage unavailable, potential recall and selection biases

Table 1: Continued.

Study	Design	Sample size	SSRI	Results	Comments
GSK/Cole et al., [49, 50]	Retrospective epidemiologic study	$n = 4936$ antidepressants	Paroxetine $n = 1020$	Increased risk for overall congenital anomalies for paroxetine (Ad OR 1.89 (95% CI 1.20–2.98))	Manufacturers' data from a large US insurer using data originally for a study on bupropion in pregnancy
Louik et al., [40]	Retrospective case-control study	9849 infants with defects and 5860 without	SSRIs: 2.7% of infants without malformations, 1.6–4.8% of infants with various malformations	Association between paroxetine and right ventricular outflow tract obstruction defects, clubfoot, undescended testes and NTDs, sertraline and omphalocele and septal defects—small absolute risks	Small number of exposed infants for individual anomalies, multiple comparisons, data on dosage unavailable, potential recall and selection biases
Einarson et al., [25]	Prospective comparative cohort study 8 TISes	$n = 1174$	Paroxetine	No increase in the risk of cardiac defects in the paroxetine group (0.7%) compared to controls	Spontaneously resolved cardiovascular defects not included
Diav-Citrin et al., [32]	Prospective comparative cohort study 3 TISes	SSRI: $n = 809$ 1467 controls	Paroxetine $n = 348$ Fluoxetine $n = 253$	Increased Cr OR for cardiovascular anomalies after paroxetine 3.47 (95% CI 1.13–10.58) Ad OR 2.66 (95% CI 0.80–8.90), Cr OR 4.81 (95% CI 1.56–14.71) Ad OR 4.47 (95% CI 1.31–15.27) after fluoxetine	After adjustment for potential confounders OR significant only for fluoxetine and cigarette smoking of 10 or more/day, septal defects considered major anomalies even when spontaneously closed, large confidence intervals
Oberlander et al., [33]	Population-based cohort study, Canada, BC	SRIs: $n = 2625$ SRIs+BZ: $n = 968$ Controls: $n = 107,320$	SRIs: $n = 2625$ SRIs+BZ: $n = 968$ controls: $n = 107,320$	Increased risk of cardiovascular (CV) defects after combined exposure to SRI and BZ, increased risk for an ASD after SRI monotherapy, major anomalies after fluoxetine and BZ	Clinical significance of the anomaly not verified, many septal defects minor and spontaneously resolve, attempt to control for confounders
Pedersen et al.,[b] [34]	Population-based cohort study, Danish registries	SSRIs: $n = 1370$ 493,113 controls	Fluoxetine $n = 348$ Citalopram $n = 460$ Paroxetine $n = 299$ Sertraline $n = 259$ >1 SSRI $n = 193$	Increased prevalence of septal defects with sertraline (OR 3.25 (95% CI 1.21–8.75)) and citalopram (OR 2.52 (95% CI 1.04–6.10))	Prescription study, potential selection bias, underlying condition potential confounder, information on malformation from hospital registry (more sensitive to severe and visible malformations)
Wichman et al., [26]	Retrospective controlled review of medical records at the Mayo Clinic	SSRIs: $n = 808$ 24,406 controls	Citalopram $n = 122$ Venlafaxine $n = 53$ Escitalopram $n = 8$ Paroxetine $n = 134$ Fluoxetine $n = 184$ Sertraline $n = 296$ > 1 SSRI $n = 11$	3/808 (0.4%) had congenital heart disease after exposure to SSRIs compared with 2.05/24,406 (0.8%) without exposure to SSRIs ($P = 0.23$)	No review of SSRI exposure timing, of demographic or clinical information including use of other drugs, smoking, or alcohol use, data from physician prescription records. Small VSDs may be undetected soon after birth.

Table 1: Continued.

Study	Design	Sample size	SSRI	Results	Comments
Merlob et al., [35]	Prospective comparative hospital-based study	SSRIs: $n = 235$ 67,636 controls	Paroxetine $n = 92$ Fluoxetine $n = 66$ Citalopram $n = 43$ Escitalopram $n = 13$ Sertraline $n = 8$ Fluvoxamine $n = 4$ Venlafaxine $n = 9$	Non syndromic heart defects (mild) identified by echocardiography among infants with murmur on 2nd-3rd day of life RR 2.17 (95% CI 1.07–4.39)	Small sample size of exposed group, lack of data on potential confounders, ascertainment of SSRI use based on maternal report, no detection bias; all newborns with murmur examined by a pediatric cardiologist including echocardiography.
Klieger-Grossmann et al., [27]	Prospective comparative cohort study	$n = 213$	Escitalopram	No increased risk for anomalies	Unpublished data
Kornum et al.,[b] [36]	Population-based cohort study, Danish registries, updated	SSRIs: $n = 2064$ 213,712 controls	Citalopram $n = 658$ Fluoxetine $n = 472$ Sertraline $n = 352$ Paroxetine $n = 297$ Escitalopram $n = 88$ > 1 SSRI $n = 195$	SSRI use associated with increased risk of overall malformations (Ad OR 1.3 (95% CI 1.1–1.6)) and cardiac (Ad OR 1.7 (95% CI 1.1–2.5)), for specific SSRIs increased risk for septal defects with sertraline (Ad OR 3.3 (95% CI 1.5–7.5))	Prescription study, potential selection bias, underlying condition potential confounder, information on malformation from hospital registry (more sensitive to severe and visible malformations)
Bakker et al., [37]	Population-based case-control study, the Netherlands	$n = 678$ with heart defects 615 controls	Paroxetine	No significantly increased risk for heart defects overall (AOR 1.5 (95% CI 0.5–4.0)) increased risk for ASD with paroxetine in T1 (AOR 5.7 (95% CI 1.4–23.7))	Small number of exposed infants for individual anomalies
Reis and Källén,[a] [38]	Swedish Medical Birth Register, updated	SSRIs: $n = 10,170$ 1,062,190 controls	Fluoxetine $n = 1522$ Citalopram $n = 3950$ Escitalopram $n = 153$ Paroxetine $n = 1208$ Sertraline $n = 3297$ Fluvoxamine $n = 42$ Unspecified $n = 86$	Increased risk for cystic kidney ($n = 9$) with SSRIs (OR 2.39 (95% CI 1.09–4.54)), for relatively severe malformation (OR 1.29 (95% CI 1.00–1.67)) with fluoxetine, for any cardiovascular defect (OR 1.66 (95% CI 1.09–2.53) 12/24 septal defects) and for hypospadias ($n = 9$) (OR 2.45 (1.12–4.64)) with paroxetine	Prospective exposure information, largest dataset available. Incomplete drug reporting, potential detection bias, multiple comparisons, possible confounding by the underlying psychiatric condition, smoking, obesity, alcohol, folic acid, association with preexisting diabetes and hypertension
Shechtman et al., [28]	Prospective comparative cohort study	$n = 241$	Citalopram or escitalopram	No increased risk for anomalies	Unpublished data
Malm et al.,[c] [41]	Retrospective cohort, based on Finnish population-based registries	SSRIs: $n = 6,976$	Citalopram $n = 2,799$ Fluoxetine $n = 1,818$ Paroxetine $n = 968$ Sertraline $n = 869$ Escitalopram $n = 441$ Fluvoxamine $n = 240$	Increased risk for isolated VSDs with fluoxetine ($n = 19$) (Adj OR 2.03 (95% CI 1.28–3.21)) (0.5% absolute risk increase), for right ventricular outflow tract defects with paroxetine ($n = 3$) (Adj OR 4.68 (95% CI 1.48–14.74)) (0.2% absolute risk increase), for NTDs with citalopram ($n = 8$) (Adj OR 2.46 (95% CI 1.20–5.07))	Large dataset, attempt to control for confounders (i.e., maternal age, parity, year of pregnancy, marital status, smoking, purchase of other psychiatric drugs, maternal prepregnancy diabetes). Large number of comparisons, some associations based on small numbers, drug compliance and timing of exposure in pregnancy not confirmed, septal defects considered major anomalies even when spontaneously closed

[a] From the same database of the Swedish Medical Birth Register, [b] from the same database of the Finnish registries, [c] from the same database of the Danish registries.

Table 2: Shepard's amalgamation of criteria for proof of human teratogenicity (Source: shepard, 1994 [51]) applied to SSRIs.

Criterion	Fulfillment by SSRIs
(1) Proven exposure to agent at critical time(s) in prenatal development.	No
(2) Consistent findings by two or more epidemiologic studies of high quality: (a) Control of confounding factors (b) Sufficient numbers (c) Exclusion of positive or negative bias factors (d) Prospective studies, if possible (e) Relative risk of six or more (?)	No
(3) Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful	No
(4) Rare environmental exposure associated with rare defect	Not applicable
(5) Teratogenicity in experimental animals	No
(6) The association should make biological sense	No
(7) Proof in an experimental system that the agent acts in an unaltered state	Evidence of placental transfer

Note: items (1), (2), and (3) or (1), (3), and (4) are essential criteria. Items (5), (6), and (7) are helpful but not essential.

the serotonin transporter. However, developmental defects were not observed in mutant serotonin transporter knockout mice [62]. In another study, gross morphologic abnormalities were not seen in serotonin transporter knockout mice, but association was found with sudden death of the newborn mice in the first week after delivery [63]. Histologic analysis of heart sections of these mice showed that they develop cardiac fibrosis. In terms of biological plausibility, in vitro studies have been helpful in suggesting mechanistic information that adds to the plausibility of the suspected association, though in concentrations much higher than plasma concentrations in humans in clinical settings. However, as stated earlier, in vivo animal studies to date have not supported an association between in utero exposure to SSRIs and major anomalies.

(7) There is evidence for placental transfer of SSRIs.

In summary, despite some troubling associations between SSRIs and major malformations, especially cardiovascular, the overall current scientific evidence has not fulfilled the criteria for proof of human teratogenicity of SSRIs. Despite having over 33,000 reported pregnancy outcomes after prenatal exposure to various SSRIs, the differences in the design of these studies and their conflicting results are confusing. One, therefore, wonders whether further well-designed epidemiologic studies, with sufficient power and good control of potential confounders will be helpful in verifying whether SSRIs are indeed associated with a small increased teratogenic risk, especially regarding cardiovascular anomalies. In our opinion, the current data do not support teratogenicity of SSRIs.

2.3. Miscarriage, Intrauterine Growth Restriction (IUGR), and Preterm Delivery. Most studies did not specifically focus on the impact of SSRIs on the risk of miscarriage. It was often a secondary outcome without observing a significantly increased risk. There was an increase in the miscarriage risk in two meta-analyses [64, 65]. However, in the included prospective cohort studies, crude rates were reported, and the effect of earlier gestational age at contact, which is an important factor [66], was not corrected for. In two studies that specifically focused on the risk of miscarriage, an increased risk was found with the use of antidepressants during pregnancy [67, 68], SSRIs alone, serotonin-norepinephrine reuptake inhibitors alone, and combined use of antidepressants [68]. When looking at antidepressant use by type, paroxetine alone and venlafaxine alone were associated with increased miscarriage risk. Despite an attempt to adjust for psychiatric history, the possibility of confounding by underlying psychiatric disorder could not be ruled out.

In a Finnish study, there was no increase in the rate of preterm delivery, SGA or LBW [19]. The risk of both low birth weight and preterm delivery was increased in infants who were born to mothers who had received SSRI therapy [17, 21]. Infants exposed to SSRIs had shorter gestation and lower birth weight compared to nonexposed infants [69]. The increased risk of low birth weight remained significant, even when maternal illness severity was accounted for. The adjusted OR for preterm delivery was doubled in SSRI-exposed women compared to two groups of women who had not used SSRIs during pregnancy, one with psychiatric history and another without [70]. In another study, the risk of preterm delivery was not significantly increased among SSRI users, but the risk of SGA offspring was increased among women who continued SSRI use beyond the first trimester [71]. In a study from the Quebec Pregnancy Registry, no association was found between SSRIs and the risk of SGA regardless of trimester of exposure [72]. In other studies, there was an increased risk for preterm delivery among women exposed to SSRIs in the second or third trimesters [38] or to antidepressants [73] with no increased risk for LBW or SGA. The underlying psychiatric disorder is a potential confounder in most of these studies.

In summary, associations were found in some studies between the use of SSRIs during pregnancy and risk of miscarriage, IUGR, or preterm delivery. Most of these studies are potentially confounded by the gestational age at initial contact and the underlying psychiatric disorder.

2.4. Neonatal Effects. Neonatal symptoms have been described initially following prenatal exposure to fluoxetine [74] and later on after exposure to paroxetine and other SSRIs [75–81]. Neonatal toxicity or discontinuation (withdrawal, abstinence) syndromes associated with SSRIs are characterized by irritability, abnormal crying, tremor, and poor neonatal adaptation including respiratory distress, tachypnoea, jitteriness, lethargy, poor tone or colour, and, rarely, convulsions. The neonatal effects have been described in up to 30% of neonates exposed to SSRIs late in pregnancy [82]. Most symptoms are mild and transient.

It can be concluded that SSRI use late in pregnancy, similar to many other psychotropic drugs, is associated with neonatal transient effects.

2.5. Persistent Pulmonary Hypertension of the Newborn. Some epidemiologic studies have suggested an association between maternal use of SSRIs late in pregnancy and an increased risk of persistent pulmonary hypertension of the newborn (PPHN) [38, 83, 84]. In these studies the absolute risk of PPHN was <1%. In the study which used data from the Swedish Medical Birth Register [84], the eleven infants whose mothers reported the use of SSRI in pregnancy and had PPHN survived the neonatal period. Contrary to the above, other studies, possibly underpowered, did not find such an association [26, 85]. A recent study found PPHN to be associated with mode of delivery, specifically caesarean delivery prior to the onset of labour, but not with SSRI use in the second half of pregnancy [86].

In summary, an absolute risk of <1% for PPHN in infants exposed to SSRIs cannot be excluded, although studies are not consistent.

2.6. Neurodevelopmental Effects. Most studies have focused on possible postnatal neurodevelopmental effects. Children of mothers exposed in pregnancy to fluoxetine or tricyclic antidepressants were neurodevelopmentally assessed and compared to an unexposed control group. Similar global IQ and language scores were found in the three groups [87, 88]. No significant differences in neurobehavioral scores were found between children whose mothers were taking fluoxetine during pregnancy and nonexposed children [89]. Normal development was observed in a small group of children exposed in pregnancy to citalopram and followed up to 1 year [90]. Infant developmental assessment done at 2 and 8 months of age revealed no significant differences between SSRI-exposed and unexposed infants [91]. Levels of internalizing or externalizing behaviours did not significantly differ between children prenatally exposed to SSRIs and unexposed [92, 93]. On the other hand, maternal depression and anxiety were associated with increased reports of internalizing and externalizing behaviours in their children.

Mental developmental indexes were similar in children whose mothers were diagnosed with major depressive disorder treated or untreated in pregnancy. However, children exposed to SSRIs scored lower on the psychomotor developmental indexes and the motor quality factor of the behavioural rating scale compared to unexposed children [94]. In a follow-up study using a psychomotor developmental test (Boel), abnormal test was more frequent in children prenatally exposed to antidepressants compared to unexposed [95]. In another neurobehavioral assessment study, newborns prenatally exposed to SSRIs had abnormal outcomes including increased motor activity, fewer changes in behavioural state, and abnormal sleep patterns [96].

Children's developmental milestones were assessed using a questionnaire at 6 and 19 months of age. Second or third trimester exposure to antidepressants was associated with later gross motor developmental milestones, though still within normal range, compared to unexposed children [97].

Children who had neonatal abstinence syndrome had similar mean overall developmental results compared to those who did not; however, they were more likely to have abnormal results on the social component of the Denver developmental test [98].

A recent prospective study demonstrated that SSRIs during pregnancy affect the neurobehavioral development of the human fetus [99]. Fetuses exposed to SSRIs exhibited dose-related increased motor activity and disrupted sleep. The significance of the observed changes on postnatal development is unclear.

In a recent population-based case-control study, a twofold increased risk of autism spectrum disorders was found with prenatal exposure to SSRIs [100]. Further studies are needed to verify the suggested association.

In summary, in most of the studies that focused on the possible neurodevelopmental effects of prenatal SSRI exposure, there is no conclusive evidence for an increased risk of adverse long-term effects.

2.7. Risk of Treatment Discontinuation. When evaluating the risk/benefit ratio of SSRI treatment in pregnancy, the risks associated with treatment discontinuation should also be considered. Abrupt discontinuation of psychotropic drugs in pregnancy is associated with physical and psychological adverse effects [101]. SSRI treatment discontinuation during pregnancy is associated with a higher frequency of relapse [102]. Depression is associated with an increased risk for preterm delivery [103–105]. The risk of preterm delivery increases with increasing severity of depression [106]. Treated women have lower depressive symptom scores and better functioning [105]. These risks should be a factor in the decision making in regard to treatment continuation during pregnancy.

3. Conclusion

Clinicians are faced with the difficult cost-benefit consideration of either making a recommendation to treat or not to treat maternal depression or anxiety with SSRIs in pregnancy.

In the field of teratology, decisions on new medications during pregnancy often need to be made with insufficient human pregnancy experience on their safety. In the case of SSRIs in pregnancy, despite extensive available studies on their use, quality is more important than quantity, and data are still not conclusive.

In summary, most studies on the use of SSRIs during pregnancy support that they are not major human teratogens. A small increased risk for cardiovascular anomalies, especially with paroxetine, cannot be excluded. There appears to be a small increased risk for miscarriages, which may be associated with the underlying maternal condition. Neonates of mothers treated with SSRIs should be closely followed up after delivery, as there is an increased risk of transient neonatal effects. There is no conclusive evidence for adverse long-term neurodevelopmental effects of prenatal SSRI exposure. Discontinuation of treatment may pose risks, for example, higher frequency of relapse and increased risk of preterm delivery. Hence, the general benefit of treatment seems to outweigh the potential small risk of untoward effects on the embryo, fetus, or neonate.

Disclosure

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Research Article

Ethical Issues in Pharmacologic Research in Women Undergoing Pregnancy Termination: A Systemic Review and Survey of Researchers

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Objective. To evaluate the ethics of performing research in the field of maternal-fetal medicine involving women undergoing pregnancy termination. *Methods*. We identified published pharmacological studies performed during elective pregnancy termination. In addition, a questionnaire was administered to investigate whether this research would be acceptable to professionals performing research in the field of maternal-fetal pharmacology. *Results*. The majority of participants believe that this form of research is necessary to furthering our understanding of drug use in pregnancy. Twenty studies were identified in women undergoing a pregnancy termination where exogenous drug was administered and drug measurement conducted during an abortion. The majority of studies were completed by international groups and not in North America or Western Europe. *Conclusions*. While a majority of respondents to the survey felt that, although research in women undergoing a pregnancy termination is ethically acceptable, 40% stated that it is not likely to be approved by institutional review boards of most North American medical institutions.

1. Introduction

Approximately 50% of pregnancies are unplanned [1] often making drug exposure in the first trimester unintentional. However, once a pregnant woman becomes aware of her pregnancy, a series of ethical and legal dilemmas surface. In many cases, the lack of information on safety of specific drugs in pregnancy is a problem when deciding on drug alternatives to treat or modify therapy in pregnant patients.

The information regarding teratogenicity obtained in experimental animal models is usually difficult to extrapolate to clinical decision. Most drugs that have exhibited teratogenic effects in humans have also been proven to be teratogenic in animal models [2], but not all drugs with proven teratogenicity in animal models have been found to be human teratogens [2].

Ex vivo, human placental studies have proven to be invaluable tools to answer questions regarding the trans-placental transfer of drugs [2]. However, since the *ex vivo* model uses placentas obtained at delivery, it often cannot necessarily provide useful information with regards to the first or second trimesters of pregnancy. Clinical experience is therefore critical to understand the complexity of drug behavior in pregnancy.

Because ethical challenges have made it difficult to study drug safety in pregnant women, an intriguing line of clinical research has been conducted over the last 4 decades in women undergoing pregnancy termination. This research, conducted worldwide, has focused on the study of the aborted fetus with regards to drug absorption and disposition. The objective of the present study was to systematically identify studies performed in women undergoing pregnancy termination where biological samples were obtained in order to investigate transplacental drug transfer. Subsequently, we aimed to evaluate the attitudes of scientists and physicians practicing in the field of maternal-fetal medicine with

regards to studies involving women undergoing pregnancy termination.

2. Methods

2.1. Systematic Review. Search was performed in Pubmed-Medline and M-Base for studies in women undergoing voluntary pregnancy termination who received a drug not aimed for their health. Search limits included a date span from January 1964 to 2006 and only English articles were included.

2.2. Survey. To investigate the attitudes of health professionals on ethical aspects of research in pregnant women prior, during and after abortion, we designed a questionnaire consisting of 2 hypothetical case studies. The first addressed the acceptability sampling of amniotic protein levels during an abortion, while a second case described a study of the administration of the antiretroviral drug, zidovudine, to a woman undergoing an abortion infected with HIV. The questionnaire collected data on gender and country of origin of the participants, as well as an open comments section to express personal views on the acceptability of the presented studies was offered. Participants were asked if such procedures would be acceptable in the different trimesters of pregnancy, single versus multiple dose of drug administration to the mother, and whether their institutional ethics board would approve such research protocols.

Questionnaires were distributed during two maternal-fetal pharmacology workshops, in Denver, Colo, USA, and Toronto, ON, USA. Participants included both basic and clinical scientists performing research in the area of maternal-fetal medicine and toxicology. Participation was voluntary and this study received ethical approval by The Hospital for Sick Children's research ethics board.

3. Results

3.1. Systematic Review. Twenty studies were identified, where a drug was intentionally administered to a woman undergoing an abortion. One forensic report of a woman exposed to heroin in pregnancy was also included (Table 1). Of them, 6 (28.6%) were performed in the 70's, 4 (19%) were performed in the 80's, 6 (28.6%) were performed in the 90's, and 5 (23.8%) in the 2000's. Only four (19%) studies were reported from North America, and all were reported between 1977 and 1983 whereas 17 (81%) studies were performed in other parts of the world. The studied exogenous compounds varied from ethanol and glucose to therapeutic drugs. The route of administration to the mother was mainly oral. Nine (42.9%) of the studies evaluated multiple-dose administration and 8 (38.1%) evaluated a single dose of the exogenous compound. Of the 21 studies, 5 (23.8%) included women in the first trimester, 7 (33.3%) included in the second trimester, 8 (38.1%) included women in the 1st-2nd trimesters, and only one study reported on women in the last trimester of pregnancy.

Table 1: Studies where exogenous drug was administered and sampled from women and their abortus prior to pregnancy termination.

Reference	Year	Country	Xenobiotic
[3]	2005	Hong Kong	Rosiglitazone
[4]	2002	Hong Kong	Naproxen
[5]	2002	Israel	(15S)-15 Methyl PG F2alpha
[6]	2002	Belgium ans UK and Madrid	Cefoxitin, moxalactam and ceftazidime
[7]	1999	Belgium and UK	Glucose
[8]	1999	France	Diclofenac
[9]	1998	Belgium and UK	Fentanyl
[10]	1996	Belgium and UK	Diazepam
[11]	1993	Belgium and UK	Fentanyl
[12]	1993	Germany	Thyroxine
[13]	1983	Canada	Ethanol
[14]	1980	Finland	Oxazepam
[15]	1978	Czech	Sodium salicylate
[16]	1977	USA	Cefazolin
[17]	1977	USA	Amikacin
[18]	1997	UK	Inulin
[19]	1977	USA	Tobramycin
[20]	1999	USA	Heroin
[21]	1975	Singapore	Thiamphenicol

GA: gestational age; IRB: ethics approval obtained; Consent: clearly declared consent obtained; Mat: maternal blood samples; Fetal: fetal blood samples obtained; Amniotic: amniotic/celomic samples obtained; FT: fetal tissue collected and sampled.

Excluding the forensic case, 6 (30%) studies did not declare ethics approval from their institutions and 3 (15%) studies did not mention obtaining informed consent from the participants.

3.2. Survey. Fifty participants responded to the administered questions (26 women and 24 men). In such a protocol with 56.0% preferring to conduct the study in the first trimester, 21% in the second trimester, and 27.0% at anytime during pregnancy. In response to the scenario of exogenous drug administration, 34 (69%) respondents considered the study design as acceptable. Of them, men and women did not differ in their responses. Participants preferred to conduct the study in 1st-trimester abortions (42%), while the options of second trimester (17%) or anytime during pregnancy (31%) were less favored. With regards to dosing, 55% of participants preferred a single dose administration.

Of interest, 39.0% of participants, while considering the proposed research to be useful, believed that their institutional review boards were likely not to approve the design. Another 39.0% of participants (50.0% men and 30.0% women) considered that this type of research would be "too controversial." Finally, 20.0% of participants, all women, indicated that they would not perform this research because of fear of criticism leaving the remaining 11% of participants,

who would not perform this research because of personal reasons.

4. Discussion

In this study, we sought to investigate whether clinical trials in women undergoing pregnancy termination are ethically viable for the assessment of safety and transplacental drug transport in pregnancy. This is the first study to systematically review this topic and collect data on the attitudes of researchers regarding the ethical standards necessary to perform pharmacokinetic trials in women undergoing pregnancy termination.

The systematic review identified 20 studies of fetal drug distribution in women undergoing pregnancy termination performed since the 1970's. Studies of exogenous compounds were performed largely outside of North America between the 80's and 90's. The lack of North American abortive research may be due to dissimilar attitudes regarding abortion as compared to Europe or Asia. For example, in Sweden, legal abortion is a recurrent part of a gynecologists' work. A survey of Swedish gynecologist found that almost all believed that gynecologists should be involved in abortion care and half were opposed to the privilege of refusing to work with termination of pregnancy [22]. Alternatively, it has been suggested that the lack of North American studies in the abortus population may be due to the ethical standards in north American institutions becoming more stringent with the advent of fetal tissue research and *in utero* fetal surgery.

Of importance, 30% of those studies, despite the utmost sensitivity of the clinical situation, do not mention approval by the local ethics committee. Such approval is a legal and ethical prerequisite in all countries where these studies had been performed.

Our survey of the attitudes of North American researchers towards research in women undergoing abortion suggests that the majority of researchers in maternal-fetal medicine would respond positively to performing studies in women undergoing a pregnancy termination. Their opinions were not different from those of surveyed women [23]. According to Anderson et al., 94% of women feel that fetal tissue research was justifiable and 84% say they would allow this sort of research to be done on their own fetus [23]. In fact, this same study [23] found that, while few women felt that research on a live fetus was justifiable, significantly more women (68%) about to undergo termination of pregnancy found this idea acceptable and more than half of them would have permitted research to be carried out on their own live fetus [23]. Our present survey results are in agreement with those of Anderson et al. [23]. Both women about to undergo an abortion and our surveyed health professionals were in agreement with regards to the value of studies and information that may results from studies in the abortive population.

Overwhelmingly, the opinion of our surveyed professionals was that this type of research was useful but likely not to be approved by their respective institutions. The common fear was that such a study design would be too controversial. However, pregnancy is a dynamic state that can only be compared to itself. Without the participation of pregnant women themselves, safe and effective use of drugs during this critical period in a women's life will in no way become a reality. However, the abortive population presents itself as a relevant pharmacological comparison, to be used as an investigational population for drugs in pregnancy without the risk of any fetal adverse consequences.

The open comments section of the survey was the most informative with regards to justifications against research in women undergoing pregnancy terminations. The most pertinent reason was with regards to the quality of consent that can practically be achieved in a women undergoing pregnancy termination.

Since the Nuremberg Code, it has been widely established that ethical consent cannot be obtained from a patient who is under coercion, threat, or duress [24]. With regards to abortion, it could be argued that the consent process is in itself intrinsically coercive due to the emotional nature of the situation [25]. It has been suggested that women would be more likely to consent to participate in research as a way to alleviate their feelings of guilt surrounding the abortion [23]. Currently, in order to improve the quality of consent in the abortive population, the objective has been to achieve a practical separation of the abortion and the subsequent use of human fetal tissue [23]. The same should apply to a woman's decision to enroll in a pharmacokinetic study. In fact, Bopp Jr. observed that most women were ambivalent about abortion, with 5% changing their minds after making the abortion appointment [26].

As such, the Human Fetal Tissue Transplantation Research (HFTTR) panel recommended that a woman should not be asked for her consent to participate in a study until she has decided to obtain an abortion [8]. If such research is to happen, the women should be recruited by a recruiter not affiliated with the abortion clinic, capable of assessing the women's capacity to consent, considering her level of education, language comprehension, and cultural adaptation to an authority figure (i.e., doctor) making the request. The hope is that an independent recruiter will circumvent the risk of coercion by separating the "source" (the patient providing the samples) and the "user" (the researcher employing the samples) [27].

In addition, the consent process should be value neutral, neither approving nor disapproving of the practice of abortion. Thus, the consent process should be nondirective and noncoercive [27]. Chervenak et al. [27] have suggested that words such as "treatment" and "therapy" should not be used by the investigator to describe the intervention. Words such as "mother, father, and baby" should not be used because these suggest moral relationships. Instead, it is preferable to use words such as "pregnant woman" and "abortus." The consent form should also contain explicit details about the nature of the procedure, including the risks regarding future pregnancy and postpartum management following the study. A related recommendation, then, is that researchers should routinely test the participating woman's understanding of risk for the individual study, a practice endorsed by many and practiced by few. Autonomous decision making is a core

requirement of ethical research. Vigilance about minimizing and managing study risks is likely the best protection volunteers can have [28].

There were several limitations to this study. Firstly, there were 50 respondents recruited predominantly at 2 academic meetings in North America. This might have created a bias as those likely not to participate at meetings may have different views and may less likely approve such a protocol. Secondly, interviewing a larger, more heterogeneous study population will help to confirm or reject our findings. Finally, by design, this was not a prevalence study. Targeting enrollment in this way did not allow examination of questions related to prevalence.

5. Conclusions

We have identified published studies investigating the transplacental pharmacology in women undergoing abortion and have discussed some of their ethical implications. Progress in pregnancy drug use, design, and testing can only be made possible through the participation of pregnant women themselves. It is of interest that very few of them were conducted in North America in the last decade, while this type of research has been practiced in different parts of the world. The ability to test an abortus and fetal tissue is a relatively novel strategy, accepted by the majority of surveyed women and scientists in the field of maternal fetal pharmacology. It is our contention that the North American discomfort with the use of the abortive population, ingrained in our scientific institutions, will hinder our ability to improve drug safety and treatment in maternal-fetal pharmacology. The potential information gained from conducting such studies may be important to bridging the knowledge gap in terms of drug behavior in pregnant women and providing the necessary information to alleviate fears of prescribing drugs in pregnancy. In this way, the experience of abortus research has the potential to be transformed into a life-saving opportunity for future fetuses. Yet the extreme vulnerability and sensitivity of the woman during this time dictates that continued discussion of the risks, benefits, and quality of consent continue to take place.

Much larger debate should ensue to try to resolve these issues.

Conflict of Interests

There are no conflict of interests of any of the authors in the preparation of this paper.

Disclosure

G. Koren has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or nonexclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licenses to permit this paper (if accepted) to be published in JME and any other BMJPGL products to exploit all subsidiary rights, as set out in our license (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

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Review Article

Review of NVP and HG and Early Pharmacotherapeutic Intervention

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NVP occurs in 50–90% of pregnancies, making it a common medical condition in pregnancy. Women present differently with any combination of signs and symptoms. It is appropriate to take the pregnancy-related versus nonpregnancy-related approach when determining the cause of nausea and vomiting but other causes should be considered. The most common etiologies for NVP include the hormonal changes associated with pregnancy, the physiologic changes in the gastrointestinal tract, and a genetic predisposition. Up to 10% of women will require pharmacotherapy to treat the symptoms of NVP despite conservative measures. ACOG currently recommends that a combination of oral pyridoxine hydrochloride and doxylamine succinate be used as first-line treatment for NVP if pyridoxine monotherapy does not relieve symptoms. A review of NVP and early pharmacotherapeutic management is presented due to the fact that NVP is largely undertreated, and investigations into the safe and effective pharmacotherapies available to treat NVP are lacking.

1. Introduction

Nausea and vomiting in pregnancy (NVP) is a very common and oftentimes difficult medical condition to manage in pregnancy. The spectrum of disease ranges from a limited, mild to moderate course that resolves with conservative treatment or with the addition of an antiemetic to a severe, prolonged course requiring multiple triage visits and/or hospital admissions and pharmacotherapy. Determining the appropriate intervention while keeping fetal exposure in mind can make management of the patient challenging. Furthermore, while early recognition and treatment of symptoms is ideal, communication between the pregnant woman and her heath care provider is often lacking, allowing for progression of symptoms. A review of NVP and early pharmacotherapeutic management is needed due to the fact that NVP is largely undertreated, and there is a lack of investigation into the safe and effective pharmacotherapies available to treat NVP. This allows pregnant women to be orphaned from the benefits of existing knowledge. As a result, review of NVP is presented here, along with recommendations for early pharmacotherapeutic management.

2. Definition and Incidence

NVP occurs in 50–90% of pregnancies, with nausea and vomiting in approximately 50–55% and nausea alone in 25% [1–7]. Although NVP has been commonly referred to as "morning sickness," nausea can occur at any time of the day, last for varying periods of time, and occur with or without episodes of vomiting. The usual onset for NVP is between 4–9 weeks gestational age, with maximal symptoms at 12–15 weeks, and resolution by 20 weeks gestational age [1, 4, 8]. There are a small percentage of pregnant women (approximately 9–20%), however, who experience symptoms beyond 20 weeks gestational age and even throughout the remainder of the pregnancy [8, 9]. Although this particular group of women may indeed comprise a small percentage with prolonged symptomatology, they present a clinical dilemma with a great amount of time and effort utilized to rule out other potential causes of their nausea and

vomiting. Overall, NVP typically follows a usual course with management consisting of conservative measures to hospitalization for more acute management.

HG occurs in 0.3–3% of pregnancies and is typically defined as severe and persistent nausea and vomiting with or without retching, with a loss of 5% or more of prepregnancy body weight, electrolyte abnormalities, ketonuria, dehydration, and potential vitamin or mineral deficiencies (i.e., thiamine) [1–7]. These patients often require multiple triage visits for intravenous fluid hydration and antiemetics, with inpatient admission in the more severe cases. A prolonged hospital stay with a trial of multiple pharmacotherapies, gastrointestinal rest, and hydration can be necessary. Vitamin supplementation of intravenous fluids is typically required, with the addition of thiamine to avoid the development of Wernicke's encephalopathy [10]. The decision to admit a patient for the treatment of NVP or HG is subjective. However, any woman who is ketotic and dehydrated should be hospitalized not only for treatment but to explore any other potential causes for nausea and vomiting. HG can precipitate from NVP that has been neglected or undertreated. As a result, early recognition and inquiry regarding symptoms by the health care provider is essential.

3. Diagnosis, Differential Diagnosis, and Maternal Morbidity

Although each woman with NVP can present differently, the symptoms predominantly include any combination of the following: nausea, gagging, retching, dry heaving, vomiting, and odor and/or food aversion [11–13]. Each woman usually has a certain precipitating factor that triggers the nausea and vomiting, that is, movement-induced, heartburn, food and/or odor triggers [14]. During initial history taking, questioning on the onset, timing, severity, and aggravating and alleviating factors may point to another cause for the nausea and vomiting. This information is also helpful when formulating a treatment plan. One of the most important aspects of the history is the duration of vomiting in order to assess the potential risk for Wernicke's encephalopathy due to thiamine deficiency.

If the diagnosis of HG is made, the patient should be evaluated for urinary ketones, BUN, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), amylase, and electrolytes [15]. Thyroid stimulating hormone (TSH) and free T4 (FT4) should also be checked as human chorionic gonadotropin (hCG) cross-reacts with thyrotropin and stimulates the thyroid gland [15]. As a result, thyrotropin is typically lower in these patients. In fact, the values of TSH and FT4 in patients with HG may be similar to that seen in Graves' disease, but without the clinical symptoms and findings of Graves' disease or thyroid antibodies [16]. This form of hyperthyroidism usually resolves without treatment by 20 weeks gestational age, and management of nausea and vomiting until then is as indicated.

The vomiting observed with NVP and HG can be quantified with a scoring system, the Pregnancy-Unique Quantification of Emesis scale (PUQE) [17]. Similar to the Rhodes Scale used for the assessment for nausea and vomiting in patients receiving chemotherapy, the PUQE scoring system was designed to focus on nausea and vomiting of pregnancy [17, 18]. The 12 hour PUQE scoring system assesses the severity of NVP by focusing on the number of hours of nausea and the number of episodes of retching and vomiting, as well as an overall well-being score in the 12 hours immediately before assessment [19]. The 24 hour PUQE scoring system, validated in 2009, was subsequently developed to account for global nausea and vomiting, including the time spent sleeping and the severity of symptoms throughout the first trimester [20, 21]. The PUQE scoring system has a minimum score of 3 and maximum score of 15 with a score of <6 suggesting mild HG, 7–12 moderate, and >13 severe NVP. This scoring system has been validated and shown to correlate with clinical outcomes such as rates of hospitalization and women's subjective feelings of well-being [19]. There is also a well-being score of 0 (the worst possible) to 10 (the best possible), which is a general self-perception score of physical and psychological health and a question on the amount of sleep including naps in a 24 hour period of time [17, 19]. The PUQE scoring system is helpful not only to qualify and quantify the nausea and vomiting, but to follow the response to treatment and improvement over time.

Regardless of when the patient presents, it cannot be assumed that nausea and vomiting is due to NVP. It is more appropriate to take the pregnancy-related versus nonpregnancy-related approach when determining the etiology. More often than not, if the patient initially presents before 10 weeks, it is likely NVP. However, a thorough history and physical exam is still required to elicit any potential contributing or confounding factors at any gestational age. If the diagnosis of NVP or HG is made, but there is poor response to initial interventions, an atypical presentation, or initial presentation after 9–10 weeks, other causes must be explored [3, 4, 6, 7]. Table 1 lists other potential causes of nausea and vomiting in pregnancy. If there is fever, a source of infection should be sought or if the history suggests a CNS abnormality, check for signs of raised intracranial pressure [11]. Specific signs such as peritoneal signs, RUQ pain, or jaundice should raise the suspicion for acute abdomen, preeclampsia, and acute fatty liver of pregnancy, respectively [11]. In addition, headache with nausea and vomiting can occur with dehydration, but preeclampsia should still be ruled out, especially if there is elevated blood pressure. Although epigastric pain and hematemesis is rare, if this is observed, a Mallory Weiss tear from prolonged vomiting or gastrointestinal ulcer may be the cause. Finally, heartburn and gastric reflux occurs in a significant number of pregnant women, and appropriate recognition and treatment of this particular condition may improve symptoms quite rapidly.

Prolonged nausea and vomiting in the setting of NVP or HG can lead to maternal vitamin deficiencies. As mentioned above, Wernicke's encephalopathy is a potential serious or fatal maternal complication and is due to severe vitamin B1 (thiamine) deficiency. Approximately 47% of patients with this condition will present with a history of prolonged nausea and vomiting along with the triad of abnormal ocular

Table 1: Differential diagnosis of NVP.

Peptic ulcer	Urinary tract infection
Hepatitis	CNS abnormality
Pyelonephritis	Preeclampsia
Pancreatitis	Acute fatty liver of pregnancy
Cholecystitis	Gastroesophageal reflux disease
Appendicitis	Mallory-Weiss tear
Gastroenteritis	Hyperthyroidism
H. pylori infection	

movements, ataxia, and confusion; an additional percentage will also have diplopia [22, 23]. Symptoms can also be more variable and include memory loss, apathy, decreased level of consciousness, or blurred vision [22]. Although this condition is reversible with prompt treatment, 60% of women will have residual impairment and there is a 37% fetal loss rate [22]. Because maternal serum thiamine levels are not useful in making the diagnosis, any pregnant woman who presents with prolonged nausea and vomiting and neurologic abnormalities should be empirically treated with intravenous thiamine. Deficiencies in vitamins B6 and B12 are rare and not as potentially serious, but can cause anemia and peripheral neuropathy associated with hematemesis, malnutrition, and psychological effects [23]. Vitamin K deficiency and coagulopathy can also occur, leading to an abnormal coagulation profile and bleeding [24].

One consequence of NVP and HG that is commonly neglected, especially when the focus is on treatment, is the psychosocial impact of this disorder. NVP can adversely affect family and social life, physical and mental health, employment, and can impose an economic hardship [25, 26]. This can range from missing days of work to termination of the pregnancy due to severe symptoms. Up to 25% of pregnant women have to change their normal daily activities due to symptoms [14]. In addition, these women have lower physical and social functioning and miss more days of work [27]. Furthermore, depression and anxiety can develop, which can make management of the patient more complicated. Koken et al. investigated the association between depression and anxiety in early pregnancy, and nausea and vomiting in a cross-sectional study of 230 women using the Hospital Anxiety and Depression Scale as a measure of anxiety and depression, and the Rhode's System for nausea and vomiting [28]. A significant correlation between Rhode's score and both anxiety and depression scores was found. Gestational age showed an inverse correlation with anxiety scores. They also found an association between anxiety and depression in early pregnancy and severity of NVP. They concluded that recognizing depression in the early stages of pregnancy might be a key step in assisting the mother. As a result, health care providers should assess the severity of NVP and address the psychological situations of the patient [28]. Depression and anxiety can contribute to and confound the symptoms of NVP and render treatment more challenging.

4. Etiology and Risk Factors

A commonly accepted etiology for NVP and HG is attributed to the hormonal changes that occur during pregnancy involving hCG, estrogen, progesterone, and thyroid hormones. These hormone levels change throughout pregnancy with the most marked changes occurring during the first trimester [29, 30]. Because hCG and TSH have a similar biomolecular structure, conditions that are associated with an increase in hCG or hyperthyroidism may result in more severe NVP or HG [29, 30]. Several studies have shown a significantly higher level of serum hCG in HG patients than in controls [29]. This is further supported by the peak incidence of HG occurring when the trophoblast is most actively producing hCG. As a result, in pregnancies with increased placental mass, that is, multiple gestations and molar pregnancy, there is an increased incidence of HG [31–34]. There is also a strong association with HG and abnormal thyroid function tests (TFTs) [23]. Physiologic stimulation of the thyroid gland is common in early pregnancy due to the structural similarity between hCG and TSH, as previously stated [23]. In fact, it is recommended that TFTs be obtained with the initial workup of nausea and vomiting. Although, the TFTs may be abnormal, treatment is not typically indicated as the TFTs will normalize as the pregnancy progresses.

The physiologic changes in pregnancy notably involve the gastrointestinal (GI) tract. Not only is the GI tract anatomically affected by the enlarging uterus, but it is also affected by the hormonal influences during pregnancy. Changes within the GI tract include gastric dysrhythmia (tachygastria or bradygastria or both) or gastroparesis and abnormalities in gastric neural activity and smooth muscle function [35]. This is predominantly due to the influences of progesterone and estrogen on the GI tract. In addition, the enlarging uterus and displacement of the abdominal organs can lead to adjustment of the gastroesophageal junction and reflux or nausea and vomiting. These changes in the GI tract are more significant in women with preexisting GI disease including diabetic gastroparesis, gastroesophageal reflux disease (GERD), gastric bypass surgery, and inflammatory bowel disease, potentially resulting in more severe symptoms [35–37]. If the patient has a preexisting GI condition, the approach to management and potential pharmacotherapeutic treatment of NVP or HG must be tailored to the particular condition.

Helicobacter pylori (H. Pylori) is a gram-negative flagellated spiral bacterium found in the stomach. It has long been established that prolonged infection with this organism causes chronic gastritis, duodenal and gastric ulceration, and gastric cancer. It is commonly treated with triple therapy consisting of two antibiotics and a proton pump inhibitor or H2 blocker [38]. More recently, H. pylori infection has been associated with more severe HG and NVP, with some studies showing a higher incidence of infection with H. pylori in women with HG than in normal pregnant controls [23]. In a systematic review and meta-analyses of case-control studies

by Sandven et al. examining the association between H. pylori infection and HG, 25 case-control studies were identified [39]. They found that exposure to H. pylori is associated with an increased risk of HG. Another study by Guven et al. investigated the relationship between H. pylori infection and HG in early pregnancy through serologic and stool antigen tests in a prospective cross-sectional study on 40 women with HG and 40 controls at 7–12 weeks of pregnancy [40]. They found that the rate of serology-specific H. pylori IgG positivity was 80% in subjects with HG and 35% in controls—a significant difference. There was also a significant difference in the rate of H. pylori stool antigen test positivity, with a rate of 87.5% in subjects with HG and 62.5% in controls. They concluded that both serologic and stool antigen testing were good screening methods to identify those subjects in early pregnancy with H. pylori infection and HG [40]. If a patient presents with excessive symptoms of nausea and vomiting that persist beyond the second trimester, greater or longer than expected symptoms of nausea and vomiting and/or weight loss, testing for the presence of H. pylori may be indicated [38].

Much attention has been given to the role that genetics plays in the development and severity of NVP and HG. Not only are NVP and HG likely heritable diseases, but the severity of the disease appears to be associated with a genetic predisposition [41]. It appears that women are at the greatest risk if their mother or sister had NVP or HG, or if the patient herself had severe disease in a previous pregnancy [4, 33]. In a study by Fejzo et al. 2008, the prevalence of severe NVP and HG among relatives of affected individuals was explored [42]. 1224 self-reported cases of HG along with their family histories were used for the purpose of the study. Each subject completed an online survey administered by the Hyperemesis Education and Research Foundation between 2003 and 2006. Approximately 28% of cases reported that their mother had severe NVP or HG while pregnant with them and of the 721 sisters with pregnancy history, 137 (19%) had HG. In severe cases requiring total parenteral nutrition (TPN) or nasogastric tube (NGT) feeds, the proportion of affected sisters was 25% [42]. With these results, strong preliminary evidence for a genetic component to extreme NVP or HG was established.

Several risk factors have been associated with NVP and HG, with the most recognized being multiple gestation, molar pregnancy, positive family history. It also appears that NVP and HG are more common in young, nulliparous, obese women. In those who have NVP later in pregnancy (after 20 weeks), the women are older, have higher parity and BMI, and are more likely to develop gestational diabetes [43]. Factors that worsen NVP include stress, lack of sleep, chronic H. pylori infection, peptic or duodenal ulcers, migraines [25, 44]. Prenatal vitamins are often cited by women as initiating exacerbating symptoms of NVP and HG [45]. A study by Louik et al. in 2006 investigated the potential risk factors for NVP occurrence, time of onset, and duration of disease [46]. They found that the overall risk of NVP was 67%, with the risk, timing of onset, and duration of NVP nearly identical for mothers of both normal and malformed infants. They also found that younger women, multiparas, and multiple gestations had increased risk for NVP. They did not find an association between NVP and increased prepregnancy weight, black race, or low education, or sex of the infant. Finally, a longer duration of NVP increased with increasing prepregnancy weight, and late-onset NVP subjects were more likely to be less educated and have lower incomes [46].

Table 2: Early pharmacotherapies for NVP/HG.

First-line therapy:
Pyridoxine hydrochloride monotherapy 10–25 mg po tid-qid
-or-Pyridoxine hydrochloride 10–25 mg po tid or qid *plus* Doxylamine succinate 25 mg 1/2 tablet po tid-qid
-or-Diclectin (pyridoxine hydrochloride 10 mg *plus* doxylamine succinate 10 mg) 4 tablets qd given 1 qam, 1 at lunch, and 2 qhs with a maximum of 8–12 tablets qd if increased BMI
Breakthrough therapy:
Dimenhydrinate 50–100 mg po/iv q 4–6 hours
Promethazine 12.5–25 mg po/iv/pr q 4–6 hours
Metoclopramide 5–10 mg po/iv tid
Ondansetron 4–8 mg iv/po tid

5. Early Pharmacotherapeutic Intervention

It is estimated that up to 10% of women will require pharmacotherapy to treat the symptoms of nausea and vomiting despite changes in lifestyle and nutrition [15, 47]. The American College of Obstetricians and Gynecologists (ACOG) currently recommends that a combination of oral pyridoxine hydrochloride (vitamin B6) and doxylamine succinate be used as first-line treatment for NVP if pyridoxine monotherapy does not relieve symptoms (Table 2) [4]. Pyridoxine is a water soluble vitamin that is involved in the metabolism of amino acids, lipids, and carbohydrates [48]. Doxylamine is a histamine-1 (H1) receptor antagonist marketed in the USA as Unisom Night Time Sleep Aid (25 mg) that is typically given with pyridoxine. Doxylamine directly inhibits the action of histamine at the H1-receptor, acts indirectly at the vestibular system, and exhibits some inhibition of muscarinic receptors to decrease stimulation of the vomiting center [49, 50]. Although these medications are available individually over-the-counter in the United States (USA), in Canada the combination is available as Diclectin (Duchesnay, Inc., Lava QC, Canada), a sustained-release formulation of 10 mg of pyridoxine and 10 mg doxylamine [50]. It is currently recommended that 4 tablets of Diclectin be given a day. This dosage can be adjusted for severity of symptoms and/or maternal BMI. If the patient has a higher BMI, she may take up to 8–12 tablets a day without increasing maternal adverse effects, fetal risk, degree of tiredness, and birth defects [51]. These higher doses appear to be more efficacious. As symptoms improve and then resolve, patients should be tapered off Diclectin to avoid recurrence of symptoms [13].

The combination of pyridoxine and doxylamine has the most data on safety and efficacy, including data in the first trimester [4, 7, 52, 53]. It was originally available in both the USA and Canada as Bendectin, a delayed-release combination of doxylamine and pyridoxine. Bendectin had a similar formulation to Diclectin in that they contained the same active ingredients, but Diclectin utilizes modern manufacturing technology for a delayed-release tablet [54]. Bendectin was removed from the US market in 1983 due to allegations of teratogenicity, including fetal heart and limb reduction defects [1, 13, 55]. This left no available FDA-approved medication for the treatment of NVP in the USA Since its removal from the US market, the incidence of hospitalization for HG has increased 2-3-fold while the incidence remains unchanged in areas where Diclectin is now available, that is, namely Canada and Europe, and the rate of birth defects in the USA has not changed since its withdrawal [1, 4, 56, 57]. Despite the controversy and the fact that it is no longer available, Bendectin is still the most studied drug in pregnancy and no evidence shows a relationship between Bendectin use in the first trimester and congenital anomalies [58]. In Canada, Diclectin has been associated with a decreased incidence of hospitalization for NVP in observational studies [57, 59]. Furthermore, the combination of over-the-counter oral vitamin B6 and Unisom in the USA has been studied in over 6000 patients and controls with no evidence of teratogenicity, and in randomized trials it has been associated with a 70% reduction in nausea and vomiting [4, 60]. Many case-control and cohort studies, including over 170000 exposures, have demonstrated the safety of doxylamine and pyridoxine [48].

Despite the fact that allegations of teratogenicity have been unsubstantiated, no randomized controlled trial on the effectiveness of Diclectin for the treatment of NVP had been done in order to support its reintroduction back into the US market until recently. In 2010, Koren et al. took this first step by evaluating the effectiveness of Diclectin as compared with placebo for NVP in a randomized, double-blind, multicenter placebo-controlled trial [54]. Women received Diclectin ($n = 133$) or placebo ($n = 128$) for 14 days, with symptoms of NVP evaluated using the 2-part PUQE score (clinical and quality of life). The subjects were instructed to take two tablets of Diclectin at bedtime on Day 1. If symptoms persisted into the afternoon of Day 2, the subject was instructed to take two tablets at bedtime on Day 2 followed by an additional tablet in the morning of Day 3. If assessment of the subject on Day 4 warranted an additional tablet to control evening symptoms, a fourth tablet was added in the mid-afternoon. The minimum dosage was 2 tablets at bedtime and the maximum was 4 tablets a day. Results showed that women receiving Diclectin had a significant greater improvement in symptoms when compared to placebo when considering the PUQE score and assessment of quality of life from day 1 to 15, as well as in day-to-day improvement in symptoms and well-being. In addition, approximately 48.9% of women opted to continue compassionate use of Diclectin in comparison to 32.8% of placebos, and women receiving placebo were 50% more likely to report use of alternative therapies to relieve symptoms when compared to the Diclectin group [54]. Finally, Diclectin was not associated with an increased risk of any adverse effects when compared to placebo. They concluded that Diclectin delayed-release formulation was both effective and well tolerated in the treatment of NVP.

After initiating treatment of NVP with a combination of doxylamine and pyridoxine, breakthrough nausea and vomiting can be treated with the addition of a different antihistamine or a dopamine antagonist. Dimenhydrinate is an H1-receptor antagonist that is widely used for the treatment of NVP. In addition, it is often useful to initiate treatment with an H2-receptor antagonist as their safety and efficacy are evident when using these agents for treating the reflux and heartburn symptoms associated with NVP [61]. Cimetidine, ranitidine, or famotidine are H2-receptor blockers that can be used especially if the patient has a history GERD, gastroduodenal ulcers, or other GI disease. Another second-line choice of therapy for NVP and HG in addition to dimenhydrinate is promethazine. Promethazine belongs to a class of dopamine (D2) receptor antagonists called phenothiazines that exhibit antiemetic properties by inhibiting gastric motility through the D2 receptors located in the GI tract and by inhibiting the chemoreceptor trigger zone [23, 49, 50]. Numerous human and animal studies, including those in the first trimester, show a lack of association between the use of promethazine during pregnancy and an increased risk for malformations [50]. Metoclopramide is another dopamine receptor antagonist that works as both an antiemetic and prokinetic by decreasing gastrointestinal emptying time and acting on the central chemoreceptor trigger zone [15, 23, 50]. Metoclopramide is particularly useful in patients where gastric dysrhythmia and gastric stasis are factor, that is, diabetic patients [13]. Both promethazine and metoclopramide can be added in the presence or absence of dehydration when antihistamines fail to treat the nausea and vomiting. Although data is limited, no animal or human studies have shown an increased risk for birth defects in animals and humans with these dopamine receptor antagonists. Matok et al. investigated the safety of metoclopramide during the first trimester in a retrospective cohort study of 3458 infants exposed to metoclopramide [62]. They found that exposure to metoclopramide in the first trimester was not associated with a significantly increased risk of adverse outcomes, including major congenital malformations, low birth weight, preterm delivery, and perinatal death.

Serotonin 5-hydroxytryptamine3-receptor (5-HT3) antagonists have been primarily used for the treatment of chemotherapy-induced nausea and vomiting. However, the use of ondansetron for NVP and HG is widely accepted. Although ACOG Guidelines recommend the use of serotonin 5-HT3 antagonists as a third-line pharmacotherapeutic intervention for NVP and HG, ondansetron is commonly used earlier in treatment due to less sedating effects when compared to promethazine [4]. Ondansetron works both centrally and peripherally at the 5-HT3 receptors located in the small bowel, vagus nerve, and at the chemoreceptor trigger zone, resulting in decreased stimulation of the medullary vomiting center [49]. Despite a lack of evidence on its use in pregnancy, data to date have been favorable. There

has been no evidence of teratogenicity in animal studies even at doses significantly higher than that used in humans or in case reports of use in the first trimester [63–65]. In a prospective comparative observational study involving 169 infants exposed to ondansetron in the first trimester, 3.6% had major malformations, which was not significantly different from the rates in 2 control groups [65].

6. Conclusion

Although NVP and HG are two of the most common medical conditions of pregnancy, management can be very challenging for the clinician. Not only is appropriate diagnosis essential in order to initiate treatment, but timing of diagnosis is just as crucial to avoid delay in management. There are multiple pharmacotherapies available today, and each treatment regimen should be tapered to the particular patient. Due to the favorable effectiveness and safety profiles of the over-the-counter combination of pyridoxine and doxylamine in the USA and Diclectin in Canada, initiation with these medications early on is reasonable and recommended.

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Review Article

The Problem of Confounding in Studies of the Effect of Maternal Drug Use on Pregnancy Outcome

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In most epidemilogical studies, the problem of confounding adds to the uncertainty in conclusions drawn. This is also true for studies on the effect of maternal drug use on birth defect risks. This paper describes various types of such confounders and discusses methods to identify and adjust for them. Such confounders can be found in maternal characteristics like age, parity, smoking, use of alcohol, and body mass index, subfertility, and previous pregnancies including previous birth of a malformed child, socioeconomy, race/ethnicity, or country of birth. Confounding by concomitant maternal drug use may occur. A geographical or seasonal confounding can exist. In rare instances, infant sex and multiple birth can appear as confounders. The most difficult problem to solve is often confounding by indication. The problem of confounding is less important for congenital malformations than for many other pregnancy outcomes.

1. Introduction

The golden standard in medical clinical science is the randomized double-blind study. There are, however, many situations when this method is not applicable for ethical reasons. One such situation refers to use of drugs during pregnancy and pregnancy outcome. It would be unethical to randomize sick or healthy pregnant women or women who plan pregnancy to the use of a specific drug or a placebo. Conclusions therefore have to be based on nonrandomized epidemiological studies when exposure (use of drugs) occurs spontaneously. Notably when moderate effects occur, such studies are open to criticism for many reasons, for example, bias in exposure or outcome data and difficulty in the control of confounding.

If one is studying the relationship between maternal use of a specific drug (e.g., an antidepressant) and the presence of, for instance, congenital malformations in the offspring an observed relationship may not be due to effects of the drug. If a factor directly affects both exposure and outcome, a confounding will exist and adjustment for it is needed. This situation is schematically shown in Figure 1(a) and can be exemplified with maternal age as a confounder in the analysis of maternal smoking and the risk for Down syndrome. In a crude analysis, maternal smoking seems to decrease the risk for Down syndrome with an odds ratio (OR) of 0.77. If, however, one adjusts for the fact that pregnant women smoke less with increasing age at delivery and that the risk for Down syndrome increases with woman's age, the OR changes to 0.94 and is far from being statistically significant. The opposite effect is obtained if the exposure is a drug, the use of which increases with maternal age, and Down syndrome is the outcome. This will result in an increased crude OR. If adjustment is made for maternal age, the effect may disappear. These two examples also show that confounding can result in a too low risk estimate or a too high estimate, depending on whether the effects of the confounder are in the opposite or the same direction on exposure and outcome.

Various methods have been used in studies on the effect of maternal drug use on pregnancy outcome. These were discussed by the author in an earlier article [1]. Many different pregnancy outcomes can be studied, for example, miscarriage, congenital malformations, preterm birth, low birth weight, intrauterine growth retardation, neonatal morbidity, and long-term morbidity including effects on neuropsychiatric development and risk of cancer. The problem of confounding will be relevant for all outcomes.

2. Material and Methods

Most data discussed in the paper are based on published material. Some new data are obtained by analyses of Swedish Health Registers and notably of the Swedish Medical Birth Register. Such analyses were made with Mantel-Haenszel methodology with adjustment for relevant covariables. Details of this register are available in [2].

3. Results and Discussion

3.1. Methods for the Control of Confounding. Different methods exist for the control of confounders. This can be done by matching. If the study is a case-control study, controls to cases are then selected with, for instance, the same maternal age and other characteristics one wants to adjust for. If it is a cohort study, the unexposed subjects are selected with the same characteristics as the exposed subjects. Either matching is made by selection of pairs or triplets (or more) of case and control(s) with similar characteristics, or a group of controls is chosen with a composition similar to the whole group of cases ("frequency matching").

More common, notably when large data sets are analyzed, is to adjust for the confounder(s) in the statistical analysis. The most common way to do this is by using a logistic regression model. This is a regression method to predict outcome (e.g., rate of congenital malformations) as influenced by one or more confounding factors. In the standard analysis, such predictions are based on linear regressions which may be inadequate, but it is obviously possible to replace them with other mathematical functions which more adequately describe the relationship between a certain variable and the outcome. (The basic formula for a logistic regression is: $\ln(p/(1-p)) = \alpha + \beta_1 * X_1 + \beta_2 * X_2 + \cdots + \beta_n * X_n$, where $\ln(p/(1-p))$ is the logarithm for the odds of the occurrence of the outcome, α is a constant, and the various β are regression coefficients for X, where, for instance, β_1 and X_1 represent the exposure under study and β_2 to β_n and X_2 to X_n the various studied confounders. The regression coefficients can be transformed to odds ratios.) When the relationship is U-formed, a linear regression may not reveal the relationship properly but the fitted straight line may be nearly horizontal, indicating no relationship. There are many advantages with this method, for instance, that quantitative data do not have to be grouped and that estimates can be made by interpolations when control data are missing. It should be remembered that the effect of each one of the studied variables represents the effect after adjustment for the other included factors. If, for instance, maternal age and parity are both added in the formula, the odds ratio for maternal age will represent the effect of age adjusted for parity and *vice versa*.

Another method, especially useful when analyses are based on very large materials, is the Mantel-Haenszel technique. In this technique, cases and controls are compared within a number of strata, defined by chosen confounders, for example, maternal age group, parity group, and smoking group. Within each stratum, the occurrence of exposure among cases is compared with the occurrence of exposures among controls and a summary chi-square is calculated (based on one degree of freedom) which gives the average association between exposure and outcome after adjustment for the confounders. When this method is applied to materials of limited size, controls may be missing in some strata which are then rejected, reducing the power of the study. When large control materials are present (like in register studies) this risk is small.

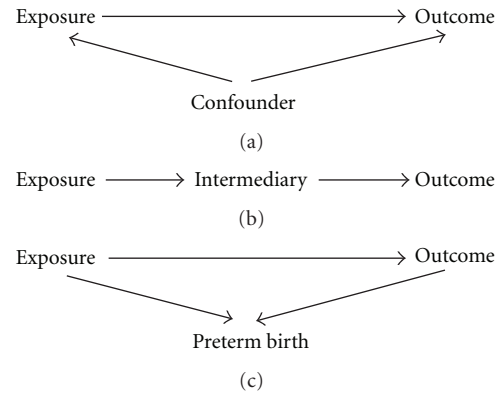

Figure 1: Diagrams showing relationships between exposure, outcome, and a third factor.

The methods can of course also be used to characterize the importance of the selected putative confounders for exposure and for outcome separately and in the final analysis only true confounders (affecting both exposure and outcome) can be included.

In most instances, the two methods give rather similar results.

Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for instance, presence or absence of a malformation. When outcome can show a number of quantitative effects (e.g., IQ) a multiple regression model will be used instead. The adequacy of the statistical model is equally important in both methods.

The decision on the inclusion of confounders in the final analysis can be made in different ways. It is obvious that factors which in the analysis are identified as confounders (i.e., affect both exposure and outcome) should be included. Sometimes other factors, known from previous studies or the literature as confounders, are included. It is rather common that one includes also factors which only affect exposure or outcome but not both. Such factors are thus not confounders and should not be included but if they are, it does not matter much.

3.2. Confounding and Stratification: The Example of Infant Sex. Confounding should be kept apart from the possibility that the effect of the exposure differs, for instance, in male and female fetuses, that infant sex modifies the effect of exposure. If this is the case, the odds ratio obtained with or without sex adjustment will be somewhere between that for male and that for female infants. This can be seen from a study of meclozine and subluxation of the hip. The odds ratio for this condition after maternal use of meclozine in male

infants is 1.16 (95% CI 0.92–1.45) and in the female infant 0.83 (95% CI 0.70–0.99). These two estimates differ: $z = 2.27$, $P = 0.03$. This means that the drug (or the condition which is the indication for drug use) reduces the risk for hip subluxation in girls but not (or at least less) in boys. There exist arguments that this condition has different etiology in the two sexes. This procedure is an example of stratification in the analysis in order to see if an effect differs in subgroups of the material, in this case between boys and girls. When one makes such subgroup analyses it is important to remember that the chances for random "significances" increases with the number of subgroups studied and if differences are found one must verify that they are not due to chance (which thus seems not to be the case in example above). One way to explore such a possibility is to add, in a logistic regression analysis, an interaction term between exposure and infant sex to see if the latter factor modifies the effect of the exposure. If this interaction term is statistically significant, it means that both sex and exposure affect the outcome risk and that the effect of exposure differs according to infant sex.

An extreme situation is when outcome like hypospadias is only present in one sex. Intuitively, one would then compare exposures between infants with hypospadias and male infants without hypospadias. If exposure is independent of infant sex (which is true for most drugs), the result of only comparing with male control infants is to reduce the material which is used for estimating the background exposure rate and therefore slightly widen the confidence interval.

3.3. Adjusting for Intermediary Factors in the Pathway of the Effect of the Exposure on the Outcome. To adjust for a nonconfounder usually does not change the effect of the exposure—sometimes confounders are simply defined as factors which change the risk estimate with, for instance, 10% or more. There is another common situation, where adjustment may give results which can easily be misunderstood. If the exposure acts via an intermediary phenomenon which affects outcome, adjustment for the phenomenon may remove the effect more or less completely (Figure 1(b)).

We can exemplify this phenomenon from studies of neonatal conditions where the effect is more easily seen than in studies of birth defects. If maternal use of a drug increases the risk for preterm birth, any neonatal condition which occurs at an increased rate among preterm newborns will probably be increased after the exposure. If this is the only way in which the drug affects the neonatal condition, the effect will disappear after adjustment for gestational duration or a paradoxical effect can even be obtained. A classical example is that maternal smoking increases perinatal mortality but after adjustment for gestational duration or birth weight, the increased risk changes to a seemingly protective effect [3]. One will then compare infants born of smoking women (which are born preterm or with low birth weight because of the smoking but may be otherwise healthy) with infants born of nonsmoking women. Some of the latter infants are born preterm or with low birth weight because of fetal pathology and are therefore at an increased risk for perinatal death.

In such situations, the proper way of analysis is to look at the effect of exposure without considering the intermediary factor. If one wants to see, if the effect of the exposure is solely or partly due to an intermediary factor, the effect will disappear if adjustment is made for it. This may be of interest, for instance, if one wants to find out if an effect of a specific drug occurs by a direct pharmacological action on the infant or if it an effect of an intermediary, for example, an increased risk for preterm birth.

We can exemplify this with the effect of late pregnancy use of certain CNS active drugs on neonatal morbidity (Table 1). Such neonatal morbidity is markedly more frequent in preterm than in term infants and also occurs more often in infants born by mothers using CNS-active drugs during late pregnancy than in other infants. If this had merely been an effect of preterm birth, a risk among term birth should not be seen but it is actually slightly higher than for all births.

In studies of birth defects, which originate early in the pregnancy, such intermediary effects are more difficult to detect. In this situation, another relationship may appear. Infants with some congenital malformations are born preterm more often than expected and use of a drug may increase the risk for preterm birth. Figure 1(c) illustrates this situation. As a rule, preterm birth cannot cause the malformation, so gestational duration is no intermediary and no confounder and generally no adjustment should be made for gestational duration. The drug could, however, affect for instance the placenta, which could both increase the risk for preterm birth and for the occurrence of a congenital malformation. That such a mechanism can exist may be suggested by the observation that malformed fetuses already in mid-gestation may have an increased risk of being small for date, leading to misdating from 2nd trimester sonography [4]. The placenta effect would then be an intermediary in both causative pathways and the situation is the same as in the situation of an intermediary as discussed in the former paragraph.

3.4. Confounding by Maternal Characteristics

3.4.1. Maternal Age. This is a classical confounder in many studies of teratogenic effects of drugs. The effect of maternal age (5-year classes) on the risk for any relatively severe congenital malformation is seen in Table 2. Note that each studied variable in this Table is adjusted for all other variables in the table in order to identify specific effects of each variable. There is a not very strong J-shaped relationship between maternal age and the risk for any relatively severe malformation. Malformations vary with respect to maternal age dependency, however. In a few, a strong increase in infants born of young women is seen. The most well-known example is gastroschisis, for which the odds ratio at age <20 in the present material is 4.51 (95% CI 2.63–7.71) and at age 20–24 it is 2.41 (95% CI 1.67–3.48), using age 25–29 as a reference. For many other malformations, the risk increases with maternal age, and for some, like trisomies, the risk increases sharply at high age. For Down syndrome,

Table 1: Risk of neonatal morbidity [a] according to preterm birth and maternal use of CNS-active drugs [b] after the first trimester (both 2nd and 3rd trimester). Among all infants, 6.0% were born preterm, and among infants of women using CNS-active drugs, 8.2% were born preterm.

Infant group	With neonatal pathology	Total number	%	OR	95% CI
All infants	22015	315975	7.0	1.00	Reference
Preterm births	7465	18836	39.6	12.3	12.0–12.7
CNS-active drugs, all infants	541	4425	12.2	1.83	1.67–2.00
CNS-active drugs, term infants	380	4009	9.5	2.05	1.84–2.28

[a]Infant morbidity consists of one or more of the following conditions: respiratory disorders (ICD-10 codes P22–P28), hypoglycaemia (P70.4–P70.9), neonatal convulsions (P90), other disturbances of cerebral status (P91), low Apgar score (Apgar 5 minutes <7).
[b]The drugs studies include opioids, anticonvulsants, antipsychotics, sedative/hypnotics, and antidepressants.

Table 2: Impact of various maternal variables on the risk for any relatively severe congenital malformation in the infants and on the use of antidepressant drugs.

	Relatively severe malformation [a]		Maternal use of antidepressants	
Variable	OR	95% CI	OR	95% CI
Maternal age				
<20	1.07	0.99–1.15	0.69	0.60–0.79
20–24	1.04	1.00–1.07	0.91	0.86–0.97
25–29	1.00	Reference	1.00	Reference
30–34	1.00	0.97–1.02	1.19	1.14–1.24
35–39	1.02	0.99–1.06	1.52	1.99–1.60
40–44	1.15	1.08–1.23	1.78	1.62–1.96
≥45	1.02	0.74–1.41	2.36	1.60–3.49
Parity				
1	1.00	Reference	1.00	Reference
2	0.89	0.87–0.91	0.67	0.64–0.70
3	0.90	0.87–0.93	0.85	0.80–0.89
≥4	0.89	0.85–0.93	0.84	0.78–0.90
Smoking				
None	1.00	Reference	1.00	Reference
<10 cigs/day	1.06	1.03–1.11	2.39	2.27–2.51
≥10 cigs/day	1.09	1.03–1.15	3.84	3.63–4.07
Body mass index				
<19.8	1.00	0.96–1.04	1.03	0.96–1.20
19.8–25.9	1.00	Reference	1.00	Reference
26–29.9	1.09	1.06–1.11	1.22	1.17–1.27
30–39.9	1.15	1.11–1.20	1.49	1.41–1.57
≥40	1.39	1.23–1.56	2.19	1.92–2.50
Number of years of unwanted childlessness				
0	1.00	Reference	1.00	Reference
1	1.02	0.95–1.09	0.89	0.88–0.99
2	1.08	1.01–1.15	0.90	0.81–1.01
3	1.12	1.02–1.29	0.66	0.56–0.78
4	1.30	1.17–1.45	0.80	0.65–0.98
≥5	1.30	1.25–1.41	0.82	0.71–0.95
Number of previous miscarriages				
0	1.00	Reference	1.00	Reference
1	1.05	1.02–1.05	0.99	0.95–1.04
2	1.05	0.98–1.11	1.08	0.99–1.17
≥3	1.12	1.02–1.32	1.15	1.01–1.30

[a]Any congenital malformation with the exception of the following conditions which are common and variably registered: preauricular tag, patent ductus at preterm birth, undescended testicle, hip (sub)luxation, tongue tie, single umbilical artery, nevus.

for instance, the risk increases at 30–34 years to 1.76 (95% CI 1.52–2.03) and at 40–44 years age to 6.66 (95% CI 1.94–24.4). The effect of maternal age will therefore depend on the specific malformation under study.

Often the maternal age effect on the use of drugs is strong. In Table 2, data for the use of antidepressant drugs in early pregnancy is shown as an example. The maternal age effect on drug use varies markedly with the drug type [2]. Use of antiasthmatic drugs is, for example, more prevalent among women delivering at a young age (<25 years) than among older women while antihypertensives show the opposite distribution.

If adequate adjustment for maternal age is not made, the estimated risk after maternal use of a drug may be falsely exaggerated or underestimated according to the directions of the age effect on malformation risk and on the use of the drug. For the outcome of any congenital malformation the effect is usually weak but for specific malformations it can be of greater importance.

3.4.2. Maternal Parity. The definition of the parity concept differs. In this text, parity 1 means that the woman had her first child and, for instance, parity 3 that she had two previous children (which could have been twins). Sometimes parity 0 or nulliparity is used for women at their first delivery.

The risk for any relatively severe congenital malformation (Table 2) is slightly higher at parity 1 than at higher parities but there is no change of risk between parities 2 and higher parities. For most specific malformations, the parity effect is small. For esophageal and anal atresia, an increased risk at parity 1 is seen [5] but for cleft lip/palate, an increased risk at high parity seems to exist [6].

3.4.3. Maternal Smoking and Use of Alcohol or Illegal Drugs in Early Pregnancy. The effect of maternal smoking on the risk for infant malformation has been much discussed. According to Table 2, there is a weak effect on any relatively severe congenital malformation with an odds ratio of less than 1.1. The effect of smoking varies according to malformation type studied [7] but is much stronger for intrauterine growth and birth weight [8]. For cleft lip/palate the increased risk after maternal smoking is rather well established while data for many other conditions are scarce. As seen in Table 2, smoking is much more prevalent among women who use antidepressants and the same is true for the use of many other CNS active drugs. The specific relationship with different drug groups can be found in [2]. One interesting such relation is with antihistamines where smoking is less prevalent than expected, notably for antihistamines used for nausea and vomiting in pregnancy (NVP). There are arguments suggesting that the relation is not explained by the fact that women with NVP stop smoking but that NVP is less prevalent among smoking women who get pregnant [9].

Adjustment for maternal smoking is thus at least sometimes needed. Such adjustment can be made using a yes/no question but a quantitative estimate is often preferable, notably when the smoking effect is strong. How detailed such a quantification should be made depends on the available possibilities. Often a division into smoking <10 cigarettes per day and 10 or more cigarettes per day is made as in Table 2. There is no convincing difference between the groups in the column for relatively severe malformations but definitely one in the column for antidepressant use.

Also the use of other nicotine preparations may occur, for example, snuffing and nicotine applications for treatment of smoking addiction. Some evidence has been presented for a teratogenic effect also at these administrations but no firm conclusions can yet be drawn and more data are needed. Hypoxia or carbon monoxide and not nicotine may cause the teratogenic action of maternal smoking [10].

In a few instances, maternal smoking appears to have a "protective" effect with a lower malformation risk among infants of smokers than of nonsmokers, for example, neural tube defects and hypospadias [7]. The mechanism behind this is unclear.

Complex addiction is common, and there is a strong association between smoking and alcohol use. The effect of the use of large amounts of alcohol on the embryo is well known and can result in a recognizable "fetal alcohol syndrome" [11] in which presence of a cardiac defect is one component. A teratogenic effect of moderate amounts of alcohol is more dubious [12]. Associations between alcohol use and some specific malformations like omphalocele and gastroschisis have been based on retrospective studies with a risk for recall bias [13]. Information on alcohol use in large numbers of individuals is difficult to get from routine questionnaires or interviews, and efforts to adjust for confounding from alcohol use are therefore often ineffective. The importance of alcohol as a confounder obviously depends on the prevalence of alcohol use and abuse among pregnant women which probably varies much between different populations. Because of a strong association between smoking and alcohol use, adjustment for smoking (which is usually easier to get reliable data on) may take care of at least part of the confounding obtained by alcohol use.

It is also difficult to get information on the use of illegal drugs, notably in populations where such use is regarded as unacceptable social behaviour. Use of many of these drugs can have important effects on pregnancy and infant morbidity but usually they are not very important confounders in studies of congenital malformations. It is true that some of these drugs have been associated with specific teratogenic effects but these studies have been based on retrospective exposure data collection with a risk for recall bias [14].

3.4.4. Body Mass Index. Increasing interest is being paid to the possible impact of the ongoing obesity epidemic in many parts of the world. Many ill effects of prepregnancy obesity on pregnancy outcome has been found, including an increased risk for many (but not all) congenital malformations [15]. As is seen in Table 2, there is a clear-cut increased risk in the risk for any relatively severe malformation and obesity is also associated with a strongly increased use of antidepressant drugs. Leanness, on the other hand, in general seems not to affect malformation risk.

The mechanism behind the effect of obesity on malformation risk is unclear. A possible explanation is that obesity

is associated with an increased risk for diabetes type 2 which often goes unnoticed and undiagnosed for a long time and which seems to have a teratogenic action similar to but weaker than that of diabetes type 1 [16].

Information on the two variables which define body mass index, weight and height, should refer to the time just before pregnancy or possibly to early pregnancy while weight at delivery is affected by weight changes during pregnancy which are of little interest for teratogenesis. The information can be based on anamnestic information given by the pregnant woman (with some uncertainty) or actual measurements at the first antenatal visit if this occurs early in pregnancy. As long as the information is collected before the outcome of pregnancy is known, it will be unbiased.

3.4.5. Subfertility. The usual measure of subfertility is how many years the couple has tried to get a pregnancy before they succeeded. Clinically, a waiting time of less than one year is not regarded as indicating subfertility and the concept of subfertility should not be mixed with the concept "time to pregnancy," which usually indicates the number of menstrual cycles which has passed before conception. It is known that a period of unwanted childlessness increases the risk for adverse pregnancy outcomes [17] including a moderately increased risk for infant congenital malformations (Table 2). This factor is of course especially important in studies of drugs or other treatment for infertility, including in vitro fertilization [18], but also the use of other drugs may be affected by subfertility. In Table 2 it is seen that antidepressant use is reduced at long-standing subfertility (3 years or more), a situation where various treatments including in vitro fertilization may be considered. The same phenomenon is seen for sedatives and hypnotics [2]. Under these circumstances, the women may actively try to increase the chance for conception and a healthy pregnancy by avoiding use of these drug. Use of, for instance, antihypertensives or antiasthmatics, on the other hand, is associated with an increased occurrence of subfertility [2]. This may be due to a direct effect of the underlying disease or the drug on the possibility to conceive.

3.4.6. Previous Miscarriages. A previous miscarriage may increase the risk for a congenital malformation in a newborn, and this risk may increase slightly if more than two previous miscarriages have occurred (Table 2). For some conditions, the relationship can be stronger than that. This can—like threatened abortion during an ongoing pregnancy—act as an important confounder in analyses of drugs which are used to treat these conditions. Some confounding effect can also be obtained for other drugs. In Table 2, for instance, it can be seen that repeated previous miscarriages (3 or more) are associated with an increased use of antidepressants and a similar relation exists for sedatives and hypnotics [2].

3.4.7. Previous Birth of a Malformed Infant. For many malformations, a genetic component is important, for example, orofacial clefts, neural tube defects, and cardiac defects. The presence of an older sibling or other close relative with such a malformation will therefore affect the risk for a malformation in a new pregnancy. This phenomenon will be a confounder in analyses of drug effects only if the birth of an infant with a malformation will affect the use of drugs in the following pregnancy. There is little information on this available. An ongoing study using the Medical Birth Register in Sweden indicates the complexity of this issue. The odds ratio for using (and reporting) a drug in early pregnancy is actually higher in women who had a malformed infant in a previous pregnancy compared to other women after adjustment for year of birth, maternal age, parity, smoking in early pregnancy, and BMI. The OR is only 1.14 (95% CI 1.08–1.21), and its size depends on the type of malformation that occurred: it is increased for neural tube defects and for cardiovascular defects but not for orofacial clefts, alimentary tract atresia, severe kidney malformations, hypospadias, or chromosome anomalies. The increased OR for neural tube defects is nearly exclusively explained by the use of folic acid. For cardiac defects, the main contribution is not only from insulin but also from psychopharmaca.

For any relatively severe malformation, the OR varies with the drug category (Table 3). The highest OR has folic acid, insulin, psychopharmaca, thyroid drugs, and NSAID (nonsteroid anti-inflammatory drugs). Also for anticonvulsants and antihypertensives ORs are high although not statistically significant.

That folic acid is used more often in the pregnancy following a birth of a malformed infant (notably neural tube defect) is reasonably the result of a therapeutic tradition, notably the recommendation of high doses of folic acid after a pregnancy complicated with a neural tube defect. A protective effect of folic acid for cardiovascular defects has also been suggested even though evidence is less clear in that case. In the (rather few) instances when folic acid use is due to a previous malformation with a significant recurrence risk, a confounding will exist.

For some other drugs the explanation of an increased OR may be the following. If the woman has a chronic disease like diabetes type 1 which has a marked teratogenic effect, the presence of such a defect (e.g., a cardiovascular defect) in a previous pregnancy can be due to the disease. As this is a chronic condition, any following pregnancy in such women will be characterized by maternal diabetes type 1 and use of insulin. Possibly a similar relationship is seen for hypothyreosis, epilepsy, and chronic hypertonia; all these diseases and drugs used for treating them are associated with a moderately increased risk for infant cardiovascular defects. A previous child with a malformation caused by the disease will then not act as a confounder.

A third possible explanation is especially applicable to psychoactive drugs. If the burden of a handicapped or sick child increases the use of this type of drugs, women with a previous birth of a malformed infant will be more likely to use such drugs, and in this situation, the presence of a previous child with a malformation will represent a true confounder.

There is little evidence that the birth of a previous malformed child will reduce drug use in a following pregnancy. In none of the analyses performed, an OR significantly under 1.0 was found.

Table 3: Use of drugs in early pregnancy among women with a previous relatively severely malformed infant compared with women who had no known previous such malformed infant. Odds ratio (OR) with 95% confidence interval (95% CI) adjusted for year of delivery, maternal age, parity, smoking in early pregnancy, and BMI.

Drug group	Among women with previous malformed infant	Among all women	OR	95% CI
Any drug	2078	290480	1.14	1.08–1.21
Drugs for stomach ulcer and reflux	53	6062	1.17	0.89–1.55
Insulin	43	2614	2.46	2.81–3.32
Multivitamins	218	56200	0.99	0.86–1.15
Folic acid	276	43780	1.26	1.12–1.43
Antihypertensives	35	3147	1.39	0.99–1.94
Thyroid drugs	104	10728	1.31	1.07–1.59
Antibiotics	186	19036	1.04	0.89–1.20
NSAID	127	13047	1.27	1.06–1.52
Opioids	38	3974	1.18	0.85–1.63
Minor analgesics	449	51043	0.96	0.87–1.06
Anticonvulsants	20	2037	1.44	0.92–2.26
Antipsychotics	26	1992	1.53	1.03–2.39
Sedatives/hypnotics	32	3301	1.21	0.91–1.83
Antidepressants	95	11714	1.26	1.02–1.55
Any psychopharmacon	137	15558	1.29	1.08–1.53
Drugs for rhinitis	67	9944	0.86	0.68–1.10
Antiasthmatic drugs	180	22702	1.07	0.92–1.25
Antihistamines	300	38689	0.98	0.87–1.10

A different question is if a drug effect differs between cases with and without a known genetic risk for a malformation. By identifying women who already had a pregnancy with the same malformation as in the current pregnancy product, a crude division can be made between genetic high-risk and low-risk fetuses. To explore the impact of genetics on the drug effect a stratification of the material can be made into women with and without previous pregnancies with the malformation in question [19]. Unfortunately, numbers are usually so low in the former group that the study does not become informative. One could believe that by excluding infants with a genetic load from the study, the sensitivity for the drug teratogeneic effect should increase. On the other hand, the drug may act only on a genetic background by increasing the penetrance of the genes which contribute to the origin of the malformation.

Similarly, studies have been made where cases were divided into presence or absence of specific genes, associated with the origin of a certain malformation—again numbers have usually been so low that no firm information was obtained [20].

3.4.8. Prenatal Diagnosis and Induced Abortion. Some congenital malformations can be identified by various methods applied during pregnancy, and if the malformation is regarded as serious this may result in an interruption of the pregnancy. This is a problem in data collection but could also lead to confounding. Use of a drug—or more likely the underlying disease—may affect the probability that a prenatal fetal investigation is carried out or could affect its degree of detail. This has, for instance, been suggested to occur in depressed women. This problem is most important in populations where all pregnant women do not routinely get a sonographic examination which, for instance, is the case in the Scandinavian countries.

3.4.9. Socioeconomy. The importance of parental socioeconomy varies according to the pregnancy outcome investigated and the population studied. To a large extent, socioeconomic effects can be explained by lifestyle factors, for example, smoking and obesity, the effects of which can be directly controlled when such data are available. For some outcomes, some effects of socioeconomy will remain but it is doubtful to what extent this is true for birth defects. One possible pathway would be via nutrition and food quality. Such effects are probably much stronger in societies with large socioeconomic differences than in wellfare societies. This may be an explanation that socioeconomy appears to be related to neural tube defects in some countries like Great Britain [21] and USA and is hardly discernible in North European countries like Sweden.

Also the impact of socioeconomy on drug usage depends on the wellfare situation in the society. When medical care is free or associated with low costs, the impact will probably be less than in societies where the patients to a large extent have to pay for medical care and drugs. Obviously, there are also socioeconomic differences in disease rates which affect drug use. Table 4 shows the different effects of maternal education level for some drug groups. Even though many show statistically significant deviations, the ORs are only

Table 4: Importance of maternal education level in Sweden for the use and/or reporting of various categories of drugs in early pregnancy [2]. Nine years of education is compulsory. Most women have 12 years of education which is used as the reference group. Adjusted for year of delivery, maternal age, parity, smoking, and BMI.

	Low education, <12 years of education		High education, ≥14 years of education	
Drug group	OR	95% CI	OR	95% CI
Drugs for ulcer and gastrointestinal reflux	1.20	1.08–1.53	0.81	0.75–0.88
Multivitamins and minerals	0.92	0.66–1.29	1.11	0.89–1.38
Anticoagulants	1.04	0.81–1.33	0.96	0.81–1.14
Haemostatics	1.42	1.01–2.00	1.08	0.85–1.38
Antihypertensives	0.85	0.71–1.00	0.82	0.73–0.92
Oral contraceptives in early pregnancy	0.88	0.87–1.02	0.72	0.62–0.83
Systemic corticosteroids	0.86	0.72–1.01	1.03	0.92–1.15
Thyroxine substitution	0.91	0.82–1.01	0.91	0.84–0.97
Antibiotics	0.90	0.85–0.95	1.07	1.03–1.11
Antivirus drugs	0.84	0.85–1.37	1.35	1.08–1.69
Vaccines	0.92	0.62–1.35	1.53	1.26–1.86
NSAID	0.90	0.83–0.97	0.87	0.82–0.92
Analgesics	1.04	1.01–1.08	0.93	0.91–0.96
Drugs for migraine	0.92	0.76–1.11	0.85	0.75–0.97
Anticonvulsants	1.49	1.26–1.76	0.71	0.61–0.82
Antipsychotics	1.52	1.17–1.99	0.97	0.93–1.28
Sedatives/hypnotics	1.75	1.56–1.96	0.86	0.76–0.98
Antidepressants	1.48	1.35–1.61	0.78	0.72–0.85
Drugs used for malaria prophylaxis	0.87	0.55–1.37	2.08	1.08–2.57
Antiasthmatics	0.96	0.91–1.02	0.90	0.97–0.99
Antihistamines used for allergy	0.77	0.70–0.82	1.11	1.05–1.17
Ophthalmics	0.63	0.47–0.86	1.35	1.17–1.56

Table 5: Importance of maternal education or non-cohabitation for occurrence and diagnosis of congenital malformations in Sweden. Odds ratios (ORs) with 95% confidence intervals (95% CI) for various malformation groups at different maternal education levels. For educational level, the reference is 12 years of education, for non-cohabitation, the reference is cohabitation. Adjustment for year of birth, maternal age, parity, smoking, and BMI.

	<12 years of education		≥14 years of education		Non-cohabiting in early pregnancy	
Malformation group	OR	95% CI	OR	95% CI	OR	95% CI
Relatively severe malformations	1.05	1.00–1.10	0.97	0.93–1.00	0.99	0.95–1.06
Chromosome anomalies	1.04	0.86–1.26	0.96	0.84–1.10	0.99	0.75–1.29
Neural tube defects	0.75	0.40–1.16	0.97	0.73–1.30	1.49	0.89–2.48
Orofacial clefts	0.99	0.81–1.21	0.89	0.77–1.03	0.95	0.71–1.26
Cardiovascular defects	1.02	0.94–1.61	0.97	0.87–1.08	1.08	0.97–1.22
Severe kidney malformation	1.07	0.78–1.46	0.98	0.86–1.13	0.99	0.62–1.57
Hypospadias	1.24	1.06–1.45	0.78	0.62–0.98	0.85	0.66–1.10
Pes equinovarus	0.86	0.69–1.07	0.94	0.69–1.26	1.00	0.75–1.33
(Sub)luxation of hip	0.90	0.80–1.01	0.98	0.64–1.49	0.76	0.63–0.91
Craniostenosis	0.75	0.53–1.07	1.01	0.68–1.51	0.94	0.58–1.54

slightly increased or decreased, but for some drug groups and notably for CNS active drugs, more marked differences are seen. To what extent these differences are due to different prevalence of underlying disease or to different drug use at similar underlying disease patterns is difficult to disentangle.

The significance of socioeconomic factors as confounders varies between populations, mainly according to the impact on malformation risk. Table 5 indicates that, in Sweden, maternal education as a proxy for socioeconomic level has little impact on malformation rate if adjustment is made for age, parity, smoking, and BMI. For specific malformations and notably for hypospadias, an association seems to exist with a moderately increased risk at short education and a possibly lower risk at high education. This could confound

an analysis, for instance, of the possible effect of hormonal treatment on hypospadias risk. For severe kidney malformations, a reduced risk is seen for infants of women with a high education. It can be noted that no effect of socioeconomic level is seen on the risk for an infant with a chromosome anomaly which indicates no difference in prenatal detection rate according to maternal education, and there is no effect on (sub)luxation of the hip, a condition sensitive to variable diagnostic and reporting completeness. The classical effect of socioeconomy on neural tube defect risk is not seen in this material.

Maternal education is one way to evaluate socioeconomic conditions. In some societies, the man's education plays a more important role than the female's for the socioeconomy of the family. Formal social group classifications exist in some countries. Family income may be a useful variable when known, but in many wellfare societies with extensive social security systems and usually also high tax rates, this measure may be less sensitive.

A further variable which can be used is if the woman is cohabiting or not with the man at the beginning of pregnancy. In Sweden only 3.3% of the women who give birth are not cohabiting in early pregnancy—this may be the result of the abortion law which permits abortions without any restrictions before week 12. Table 5 demonstrates the weak effect of this variable on malformation risk—a "protective" effect is seen on (sub)luxation of hip which may be a result of multiple testing.

When other outcomes than congenital malformations are studied, like preterm birth and intrauterine growth retardation, socioeconomic level can have a stronger effect.

3.4.10. Race/Ethnicity and Country of Birth. In many populations, race or ethnicity is an important confounder in reproduction epidemiology. Other populations are rather homogeneous from a racial point of view. In some societies information on race is not politically possible to record (e.g., in Sweden). In such areas, sometimes country of birth can give an idea of these factors but noticed effects can also be related to the status of being an immigrant. Analyses of the effect of maternal country of birth on pregnancy outcome in Sweden indicated that only few groups may deviate from Swedish-born women, among them women from Sub-Saharan Africa [22]. They will make up a rather small proportion of the studied population.

Table 6 shows that the country of birth of the woman sometimes slightly affects the risk for an infant with a relatively severe malformation. Due to the large numbers involved, some odds ratios reach statistical significance even though the magnitude of the deviation is small. Both women born in the other Nordic countries and women born in non-Nordic countries have a slightly decreased risk for a malformation in the infant. These women have moved to Sweden for various reasons. One group (often from Asia) were adopted as children and have lived most of their life in the Swedish society and have Swedish as their native language but carry the genetic load of their country of origin. Some women were born by Swedish parents who at that time were living abroad. Other women have immigrated as refugees from catastrophe or war areas; some have immigrated for purpose of searching work (often highly educated) or because they had a relationship with a Swedish man.

The weak tendency to a malformation risk slightly below that for Swedish-born women could perhaps be explained by a "healthy immigrant" effect, that at least some of the reasons listed above will favour women without chronic diseases.

The genetic composition will vary between geographical areas why specific conditions may be present for specific malformations. As an example different rates of neural tube defects in USA are seen when white, black, and Hispanic populations are compared [23].

The pattern of drug use during pregnancy often differs according to country of birth [2]. As a confounder, country of birth will be rather weak but when in doubt it may be wise to repeat an analysis based only on nonimmigrant women.

3.4.11. Confounding by Concomitant Use of Other Drugs. Women often use combinations of drugs, and in studies of one specific drug, other drugs may act as confounders, if they are used more often together with than without the drug under study and if they in themselves increase the risk for instance of a birth defect. In Table 7 some examples are given based on maternal use of antidepressants [24]. Many drug groups are used in excess by these women. The strongest relationship is seen with oral contraceptives and psychoactive drugs: opioids, antipsychotics, and sedatives/hypnotics. Weaker but statistically significant relationships are seen with drugs for stomach ulcer and reflux, systemic corticosteroids, thyroid drugs, NSAIDs, antiasthmatic drugs, and antihistamines. Much of these associations can be explained by known comorbidity. On the other hand no associations is seen with some drug groups, and some are used less often by women taking antidepressants than by other women: multivitamins, folic acid, and minor analgesics. It can be debated if this mirror an actually lower use or is an effect of the fact that women may concentrate on reporting the use of potentially harmful drugs and neglect common and apparently harmless drugs.

Coexposure for different drug categories can have different results. In order to act as confounders, the codrug must in itself affect outcome. This may be true for some of the drugs listed but probably not for other, for example, drugs for stomach ulcer or reflux and antihistamines. The use of a nonteratogenic drug will not appear as a confounder in studies of birth defects: even if it is associated with the exposure under study as it does not associate with the outcome under study. The number of women who have been exposed to a putative teratogenic drug by coexposure is usually low, and the exclusion of such cases in the analysis may be the easiest way to deal with the problem.

There is another complication which can occur due to exposure for two drug categories. Neither of the two drug groups may have a noticeable teratogenic activity but when used together they may—they would act synergistically. This, for instance, was suggested in a study [25] indicating that neither SSRI drugs nor benzodiazepines had an observable

Table 6: Importance of the mother's country of birth on the occurrence of relatively severe malformations in the infant. Odds ratios adjusted for year of birth, maternal age, parity, smoking, and BMI. Reference is infants born by mothers born in Sweden. Data for years 2000–2008.

Geographic area	Number of infants	% of all infants	% malformed infants	OR	95% CI
Sweden	727166	81.9	2.7	1.00	Reference
Other Nordic countries	16612	1.9	2.5	0.87	0.79–0.96
Western Europe, Northern America, Australia, New Zealand	10504	1.2	2.6	0.96	0.85–1.08
Eastern Europe and former Soviet Union	25855	2.9	2.5	0.89	0.83–0.97
Sub-Saharan Africa	15488	1.7	2.7	0.97	0.88–1.08
North Africa and Middle East	54186	6.1	2.9	1.04	0.98–1.09
Asia	27405	3.1	2.2	0.82	0.75–0.89
South and Middle America	10373	1.2	2.4	0.84	0.74–0.96
All non-Nordic countries	143811	16.2	2.6	0.94	0.91–0.98

Table 7: Concomitant drug use in early pregnancy among 11,181 women who used antidepressants [2]. Odds ratios (ORs) with 95% confidence intervals (95% CI) for use of specific group categories in women using antidepressants compared with women who did not. Adjustment for year of birth, maternal age, parity, smoking in early pregnancy, and BMI.

Drug group	Number of users	OR	95% CI
Drugs for stomach ulcer and reflux	316	2.92	2.61–3.26
Drugs for inflammatory bowel disease	41	1.27	0.93–1.73
Insulin	49	1.13	0.85–1.50
Multivitamins	559	0.78	0.72–0.85
Folic acid	519	0.82	0.75–0.90
Oral contraceptives during pregnancy	160	3.52	3.02–4.11
Gonadotropins	22	0.85	0.56–1.28
Systemic corticosteroids	65	1.55	1.21–1.98
Thyroid drugs	317	1.89	1.69–2.11
Antibiotics	321	0.92	0.82–1.03
NSAIDs	300	1.21	1.08–1.36
Opioids	261	3.48	3.09–3.93
Minor analgesics	835	0.83	0.77–0.89
Anticonvulsants	110	3.17	2.63–3.82
Antipsychotics	283	7.13	6.39–7.97
Sedatives, hypnotics	1202	25.9	24.6–27.3
Drugs for rhinitis	146	0.92	0.78–1.09
Antiasthmatics	533	1.40	1.28–1.53
Antihistamines	1097	1.79	1.68–1.90

teratogenic effect, but the combination of the two drugs had. This observation, based on rather few cases, has not yet been confirmed in an independent material.

3.5. Confounding by Infant Characteristics

3.5.1. Infant Sex. Some malformations show a deviating sex ratio, sometimes extreme (like hypospadias which in practice only exists in males). Is there then a reason to adjust for infant sex in the analysis of drug effects?

If the use of a drug is affected by infant sex, this would lead to confounding and adjustment for sex should be made. Thus, for instance, subluxation of the hip is more common in girls than in boys (sex ratio 0.37 instead of 1.06 among all neonates) and women who carry a girl fetus are slightly more likely to experience nausea and vomiting in pregnancy (NVP) and therefore also to use drugs for that condition (for instance, antihistamines with an antiemetic effect). In a study of the use of meclozine, the infant sex ratio was 0.92 instead of 1.06 [26]. If one wants to study the possible relationship between the use of meclozine (or NVP) and occurrence of subluxation of the hip in the newborn, an adjustment for infant sex is therefore called for. Actually, this changes the odds ratio very little: from 0.95 (95% CI 0.82–1.08) to 0.91 (95% CI 0.71–1.05).

In most situations, infant sex is unrelated to drug exposure and is therefore not confounder, even if the sex distribution among the outcome is skewed. No adjustment for infant sex is then called for. As pointed out above, infant sex may modify the effect of the drug which can be analyzed by subgroup analysis according to sex.

3.5.2. Multiple Birth. The occurrence of multiple birth may be affected by drug treatments even though this situation is rare. One such example is ovulation stimulation with, for instance, clomiphene, leading to an increased rate of twin pregnancies. In most instances, drug treatment in early pregnancy does not affect the rate of multiple births. An example of a possible effect is exposure to SSRI (but not tricyclic antidepressants) when the twinning rate is significantly low [2] Some evidence exists that use of folic acid may increase the twinning rate. Most of the changes in twinning rate refer to dizygotic twins.

The malformation rate in twin infants differs only little from that in singletons and an increased risk is mainly seen in monozygotic twins. Among dizygotic twins, some conditions associated with prematurity and perhaps with intrauterine crowding may be increased.

In a situation when adjustment for twinning is needed, it should be remembered that the effect of drug use on twinning rate concerns dizygotic twins, and if adjustment is made for any twinning, one will underestimate the risk for malformation after the exposure because in the reference population the percentage of monozygotic pairs will be higher than in the exposed population. This was clear in studies of twins born after in vitro fertilization (IVF)—when IVF twins were compared with spontaneously conceived twins, the former appeared to show less neonatal pathology than the latter, but when comparisons were made between unlike sexed (dizygotic) pairs the IVF twins had a worse outcome than the non-IVF twins [27].

3.5.3. Gestational Duration, Birth Weight, and Intrauterine Growth. Infants with birth defects are sometimes born preterm with low birth weight and signs of intrauterine growth restriction. These expressions are the result of the malformations or have a common cause with the malformations, for example, placental insufficiency. They are thus neither intermediaries, nor confounders, and there is generally no reason to adjust for them. Only when a birth defect is studied which is the result of preterm birth, gestational duration can appear as an intermediary. This could, for instance, be the case with undescended testicle and persistent ductus arteriosus, both strongly associated with preterm birth and hardly true malformations.

Birth weight strongly depends on gestational duration. If the use of a drug increases the risk of short gestational duration, it will usually also affect birth weight as an intermediary between exposure and outcome and gestational duration should not be adjusted for when one is interested in the effect on birth weight. If one makes such adjustments, a remaining effect on birth weight will indicate that the weight of the infant at each gestational week deviates from the expected weight, which is reasonably an effect of a disturbed intrauterine growth, resulting in small-for-gestational age (SGA) or large-for-gestational age (LGA) infants. These are often interesting outcomes but they can be studied more directly.

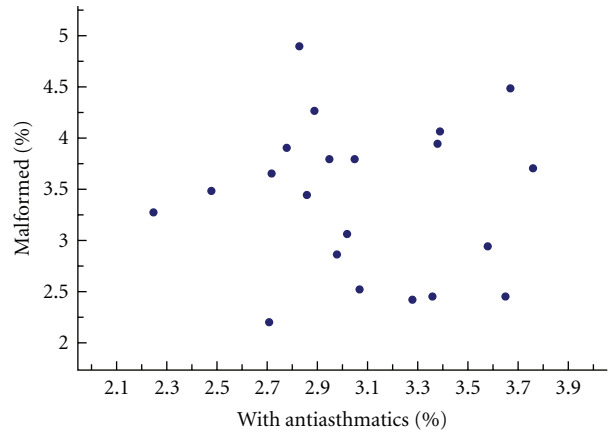

Figure 2: Percentage of infants with relatively severe malformations and percentage of women who used antiasthmatics in early pregnancy in 21 counties in Sweden (2000–2008).

3.6. Geographical and Seasonal Confounding. A confounding situation can occur due to an uneven distribution of both drug use and the occurrence or completeness of registration of birth defects. Geographical confounding will be most pronounced when the studied population is distributed over a large area where variations in disease rates and/or in therapeutic traditions may occur and where also occurrence or registration of birth defects may vary. These two sources of variation are usually independent, but if they covary, a confounding can arise. Such an analysis is shown in Figure 2 which compares rates of infants with relatively severe malformations (varying between 2.25 and 3.76%) and rates of women who reported the use of antiasthmatic drugs in early pregnancy (varying between 2.20 and 4.89%) in 21 Swedish counties. A correlation analysis gives $r = 0.13$, $P = 0.57$, which suggests that the two variables do not covary significantly.

Sometimes there is a clear seasonality in drug use. A typical example is drugs for allergy which at least in Northern Europe shows a peak of use during spring. A similar peak is also seen in the use of antidepressants (Figure 3). If also the malformation studied shows a seasonality, a confounding may arise if the effect of such drugs is studied. Obviously, it is not the seasonality at birth which is of interest but the seasonality at the formation of the malformation. An example is a possible association between use of SSRI and hypospadias [24] which could tentatively be due to the fact that use of antidepressants in early pregnancy may coincide with a peak of hypospadias in infants conceived during spring. The seasonality of hypospadias is rather weak but there is a peak among infants conceived during April and May which corresponds to the peak in antidepressant use (Figure 3). The correlation between the monthly rate of antidepressant use

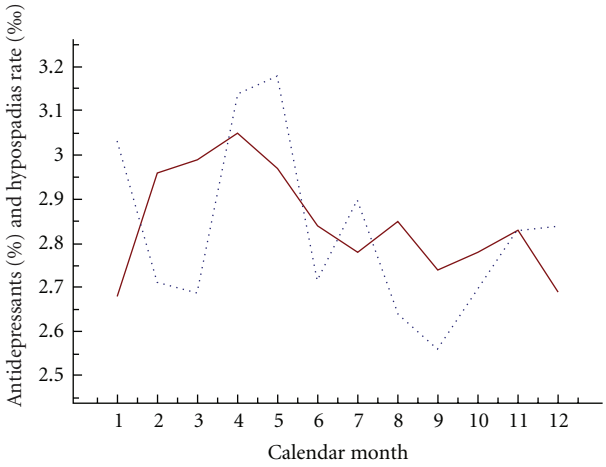

Figure 3: Rates of antidepressant use (percentage, unbroken line) and of hypospadias (per thousand, broken line) for the different calendar months.

and the monthly rate of conceptions leading to hypospadias is, however, rather weak and not statistically significant ($r = 0.26$, $P = 0.20$), and this correlation is still weaker if the formative period of hypospadias (8 weeks or more after LMP) is considered instead.

3.7. Confounding by Indication. The strongest and most difficult to control confounding is confounding by indication: that the disease or complaint which is the reason for drug use in itself affects pregnancy outcome.

The use of insulin during early pregnancy is associated with an increased risk for many types of congenital malformations. As insulin is practically only used at diabetes and a pregnant woman with diabetes type 1 always gets insulin, it is theoretically impossible to separate the effect of disease and treatment. As clinical experience indicates that strict blood suger control in pregnant diabetic women is important for the success of the pregnancy and also probably reduces the birth defect risk, it is generally accepted that the increased malformation risk is due to diabetes and not to insulin even if it can be debated if strict scientific evidence for this exists.

In most instances, the degree of overlap between disease and drug use is not so strong but to disentangle the contribution of the drug and the underlying condition is often difficult. We will take a number of examples to illustrate the dilemma.

3.7.1. Epilepsy and Anticonvulsants. The first study that linked epilepsy with an increased risk for a birth defect concerned orofacial clefts [28] and could not distinguish between disease and treatment. Numerous studies have verified that the relationship between epilepsy and birth defects includes many different malformations, for example, spina bifida, cardiovascular defects, orofacial clefts, hypospadias, that the effects of different anticonvulsants vary, and that untreated epilepsy seems not to be associated with an increased birth defect risk.

Anticonvulsants are also used for other medical conditions than epilepsy, for example, as mode stabilizers at bipolar disease and sometimes for neuropathic pain (e.g., gabapentin). No large enough studies have been published to evaluate if such use carries a similar risk as when the drugs are used at epilepsy.

The general opinion is that anticonvulsant drugs *per se* represent a teratogenic risk, and notably for valproic acid this risk can be large why such use should be avoided during pregnancy.

3.7.2. Depression and Antidepressants. Antidepressants have in general a low teratogenic potential but some data indicate that tricyclic antidepressants (TCAs) carry a higher birth defect risk than selective serotonin reuptake inhibitors (SSRIs) do, while data for serotonin/noradrenalin inhibitors (SNRIs) are still incomplete. The teratogenicity of TCA is notably evident for cardiovascular defects—a similar effect is indicated in some studies for paroxetine but may be absent for other SSRIs [29] while other studies have found also an effect of fluoxetine [30].

More common effects are seen after antidepressant use in late pregnancy, resulting in preterm birth and increased risks for various forms of neonatal morbidity. In this situation, the importance of the effect of the underlying disease, usually depression, has been much discussed. Some studies describe such effects associated with maternal depression but it is not always clear if consideration has been taken to drug treatments.

3.7.3. NVP and Antihistamines. A classical example of confounding by indication is the use of certain antihistamines for the treatment of nausea and vomiting in pregnancy (NVP). Studies of such antihistamines have shown a lower than expected rate of birth defects in the offspring and also other signs of a better than expected pregnancy outcome [26]. It does not seem likely that the drugs actually prevent the occurrence of birth defects, and there is some evidence that the strength of NVP is a factor which positively correlates with pregnancy outcome. The probable mechanism is that among the factors causing NVP are hormones produced from the placenta, so a strong NVP (perhaps needing drug therapy) may indicate a well functioning placenta and thereby a decreased risk for a congenital malformation or other pregnancy complications.

3.7.4. Hypertension and Antihypertensives. Some studies have associated the use of antihypertensive drugs in early pregnancy with an increased risk of birth defects and notably cardiovascular defects. The first major study found such a link for ACE-inhibiting drugs [31] but a later study [32] found no difference between such drugs and other antihypertensives in the risk for birth defects. Little is known about the effect of untreated essential hypertonia on birth defect risk but the possibility that the drug effect is due to confounding by indication has been raised.

3.7.5. Infections and Antibiotics. Most antibiotics have no apparent teratogenic effects in man but in a few such associations have been suggested, either from epidemiological studies (e.g., erythromycin [33]) or from pharmacological considerations (e.g., trimethoprim which has a folic-acid antagonistic effect [34]). Among infections, most interest has been shown in viral infections because of the well-known teratogenic effect of rubella and some other viral infections. Viral infections are no reason for antibiotic use but undoubtedly such treatment is often given anyway. It is also possible that adequate antibiotic treatment is given for a secondary infection following a virus infection which could have increased the birth defect risk. Secondary effects of the infection can also be considered, for example, the possible harmful effects of high fever [35].

3.7.6. How to Deal with the Problem of Confounding by Indication? One straight forward way is to compare women treated with drugs with women not treated with drugs but with the same disease. A classical example is anticonvulsants and epilepsy where untreated epilepsy repeatedly has been shown to have no detrimental effect on the embryo [36]. Epilepsy is a heterogeneous disease with very variable severity and it is therefore likely that the disease panorama is different among untreated and treated women. Certain other diseases are so severe that treatment is always needed, for example, diabetes type 1, and untreated patients are nearly impossible to find.

A second possibility exists when various drugs can be used at the same underlying disease. An example is the use of SSRI drugs at maternal depression. Among the four main SSRI drugs used in Sweden, a significant difference was seen between the effect of paroxetine and the other SSRI drugs on cardiovascular defects (Table 8) [24]. This approach, however, is complicated by the fact that SSRI drugs are used at many different conditions other than depression. One such indication is anxiety and panic disorders where a special drug, for example, paroxetine, may be favoured. So there may still remain a confounding by indication. Detailed information on the indication for use may be difficult to get in a study large enough for the detection of teratogenic effects on specific malformations. Also given the same underlying disease, differences in severity could be related to drug selection. This, for instance, could explain the difference in teratogenic effects of tricyclic antidepressants and SSRI drugs [24].

Another example of the use of two alternative drugs for similar (although not quite identical) reasons is erythromycin and phenoxymethyl penicillin. The former drug but not the latter was associated with an increased risk for a cardiovascular defect [33].

In order to characterize disease status and severity, various clinical measurements can be used. In small studies this can be based on questionnaire or interview information aimed at such a characterization, ideally performed prospectively before the outcome of the pregnancy is known. Examples are studies based on information from teratology information services where, at the contact with the woman who seeks advice, specific questions on the reason for the drug use can be made and also some standardized quantification of disease severity. Unfortunately such projects usually result in rather small numbers of exposed infants, and for studies of birth defect risks, they would most likely be strongly underpowered. The same is true for specific research projects based on data from one or a few clinics dealing with a specific group of diseases, for example, centres for the treatment of epilepsy. In retrospective case-control studies, a memory bias can be obtained not only on drug use, but also on disease characterization.

Table 8: Association between maternal use of SSRI drug in early pregnancy and occurrence of cardiovascular defects in the infant [21]. Odds ratio (OR) with 95% confidence intervals (95% CI) adjusted for year of birth, maternal age, parity, smoking, and BMI. The cardiovascular defect rates in the four SSRI groups differ significantly: $\chi^2_{(3\ d.f)} = 12.5$, $P < 0.01$.

SSI drug	Number of cardiovascular defects	OR	95% CI
Fluoxetine	21	1.31	0.85–1.02
Citalopram	37	0.86	0.62–1.20
Paroxetine	24	1.66	1.09–2.53
Sertraline	26	0.74	0.50–1.09

Most studies on birth defect risks which are powered to detect moderate risk increases must utilize register information where a recording of detailed disease histories is difficult. One way to solve the problem is to use a case-control design and base disease evaluations on medical records, prepared before the pregnancy outcome was known, if such records can be retrieved and are reasonably well standardized.

Another possibility which has been used for instance in studies by SSRI drugs [37] is to characterize disease and disease severity by available health data, for example, number of visits to doctors for specific reasons. Based on such information a propensity score can be built for each patient which makes it possible to match or adjust for disease severity. The efficiency of this method depends on the selection of variables used for the propensity scoring. Often information from the time before the pregnancy is used which may not be a valid scoring for the patient in the beginning of the pregnancy when birth defects are formed.

3.8. How Effective Is an Adjustment for Confounding? Whatever the technique of identification and adjustment for confounding which has been used, the question of its effectiveness remains. The situation is rather simple if an observed effect disappears when a true confounder has been taken into consideration, like in the examples of smoking or drug use and the birth of an infant with Down syndrome (see the previous). It is then reasonable to conclude that no direct effect of the exposure has been demonstrated. If a residual effect of the exposure remains, however, this can be due to incomplete identification or adjustment for the confounder(s). Some examples will be discussed.

In most instances, the confounding effect of maternal age is moderate and adjustments based on 5-year maternal

Table 9: The effect of adjustment for some maternal characteristics on the effect of tricyclic antidepressants (TCAs) on the occurrence of infant cardiac defect and on the effect of antidepressants on preterm birth.

	Cardiac defects after TCA		<37 weeks after antidepressants	
Variables adjusted for	OR	95% CI	OR	95% CI
None (=crude)	1.64	1.14–2.36	1.60	1.50–1.72
Year of delivery	1.75	1.22–2.52	1.60	1.44–1.77
Year of delivery and maternal age	1.74	1.21–2.50	1.58	1.40–1.79
Year of delivery and maternal age and parity	1.74	1.21–2.50	1.54	1.37–1.77
Year of delivery and maternal age and smoking	1.72	1.19–2.49	1.44	1.23–1.69
Year of delivery and maternal age and smoking and BMI	1.68	1.15–2.45	1.42	1.32–1.52

Table 10: Effect of stepwise adjustment for maternal characteristics in the analysis of the risk for drug-treated ADHD in infants conceived by IVF [34].

Variables adjusted for	OR	95% CI
None (=crude)	0.71	0.62–0.81
Year of delivery	0.77	0.68–0.87
Year of delivery, maternal age, parity, smoking and country of birth	0.91	0.81–1.05
Year of delivery, maternal age, parity, smoking, country of birth, and BMI	0.95	0.83–1.08
Year of delivery, maternal age, parity, smoking, country of birth, and education	1.14	0.99–1.31
Year of delivery, maternal age, parity, smoking, country of birth, and education, with exclusion of non-cohabiting women	1.18	1.05–1.36

intervals will be adequate. When very strong effects are seen of maternal age, notably in the lower or upper end of the age range, more exact maternal age adjustments, for example, based on one-year intervals, may be needed. Examples are the steeply increasing risk for a Down infant birth with high maternal age and a steeply increasing risk for an infant with gastroschisis with low maternal age. In both these examples, the regression between age and outcome is nonlinear, that is why a linear regression analysis may underestimate maternal age as a risk factor.

If maternal smoking appears as a risk factor, adjustment for any smoking may be insufficient and so may a crude division into <10 and ≥10 cigarettes per day. In the latter group will be included both women who smoke 10 cigarettes per day and women who smoke 20 or more cigarettes per day, and the proportion of these groups may well vary between women who have used for instance psychoactive drugs and women who have not used such drugs. If the adjustment for smoking results in a reduction of the risk estimate, one should consider the possibility that the remaining estimate may be too high due to crude information on smoking. A similar effect can occur at adjustment for BMI, if only crude groups are used.

An adjustment for the use of any other drug than the drug under study may in a similar way be insufficient if the patterns of drug use differ. A substantial percentage of women using antidepressants also use sedatives while adjustment for any other drug use will ineffectively adjust for the possible effect of the sedatives.

3.9. The Effect of Adjusting for Confounding on Risk Estimates. The effects of confounders on outcome vary according to the nature of exposure and outcome. The most important effects should be expected in analyses of drugs which are used at different rates in different groups of women, for instance, different age groups. The confounding variables must, however, also affect outcome in order to be relevant. Most variables studied in Table 2 had only moderate effect on the risk for any relatively severe malformation, that is why the effect of the clear differences in the use of antidepressants in early pregnancy will be weak. In Table 9 it is also seen that the stepwise adjustment for some of these variables does not markedly change the risk estimate for a cardiac malformation after maternal use of a tricyclic antidepressant in early pregnancy: the estimates vary around 1.6 and 1.7, and the crude estimate is close to the estimate after adjustment for year of delivery, maternal age, parity, smoking in early pregnancy, and prepregnancy BMI.

The table also shows similar stepwise adjustments for risk estimates of preterm birth after maternal use of antidepressants, and here the adjustment reduces the excess risk with nearly one-third, from 60% increased risk to 42% increased risk, and the strongest effects are seen from maternal smoking and obesity.

In special circumtances, the significance of confounding becomes very important. One example is a recent study on the risk for infants conceived after IVF to develop drug-treated ADHD [38]. A summary is given in Table 10. The crude OR indicates a statistically significant protective effect, that IVF children have a lower risk for this condition than other children. As in all studies of long-term effect, year of delivery can be an important confounder if exposure rate (in this case use of IVF) increases during the observation period while the follow-up time of the children decreases. Adjustment for year of delivery increases the OR but it is still significantly below 1.0. Adjustment for some maternal

characteristics including age, parity, smoking, country of birth, and (in the next step) BMI removes the apparent protective effect and leaves an OR close to 1.0. As low maternal education is associated with an increased risk for infant ADHD, and high education with a decreased risk, adjustment for maternal education increases the risk estimates but it does not quite reach statistical significance (lower CI is 0.99). Also non-cohabitation in early pregnancy is associated with an increased risk for ADHD and when these (relatively few) women are removed from the analysis, the OR increases further and becomes statistically significant. What we see here is the opposite effects of some variables on exposure (IVF) and outcome (drug-treated ADHD) which initially results in an apparent protective effect which gradually disappears when such factors are added in the analysis and finally results in an apparent over-risk. It should be stressed that some of these factors (e.g., low maternal education and not cohabiting) reasonably have no direct effects but may be proxies for two things: socioeconomic level and possibly parental signs of ADHD with a genetic background. So, for instance, some studies indicate that the increased risk for ADHD if the mother smoked is due to the fact that women with genes for ADHD and perhaps have signs of ADHD smoke more than other women [39, 40]. The basic question if infants conceived by IVF do have an increased risk for ADHD is not definitely solved. This may be a good example of how complex and difficult to handle confounding can be under certain circumstances.

4. Concluding Remarks

The problem with confounding is not solved by uncritically adding a number of variables to a logistic regression model. Variables used for adjustment should be carefully selected according to their properties to affect both exposure rate and outcome rate. It should be realized that efforts to adjust for them may be ineffective because the available information on the confounders may be too crude or the statistical models used may be inadequate. It should be realized that the major problems in epidemiological studies of the effects of maternal drug use on birth defects are to be found in biased data and low statistical power, not so much in confounding. For studies of other pregnancy outcomes like preterm birth, low birth weight, neonatal and long-term morbidity, confounding plays a more important role. The most difficult confounding refers to confounding by indication, often stated as important but usually without any offer of a good solution for its elimination.

Conflicts of Interests

The author declares no conflicts of interest.

Ethical Considerations

The analyses were performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was needed.

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