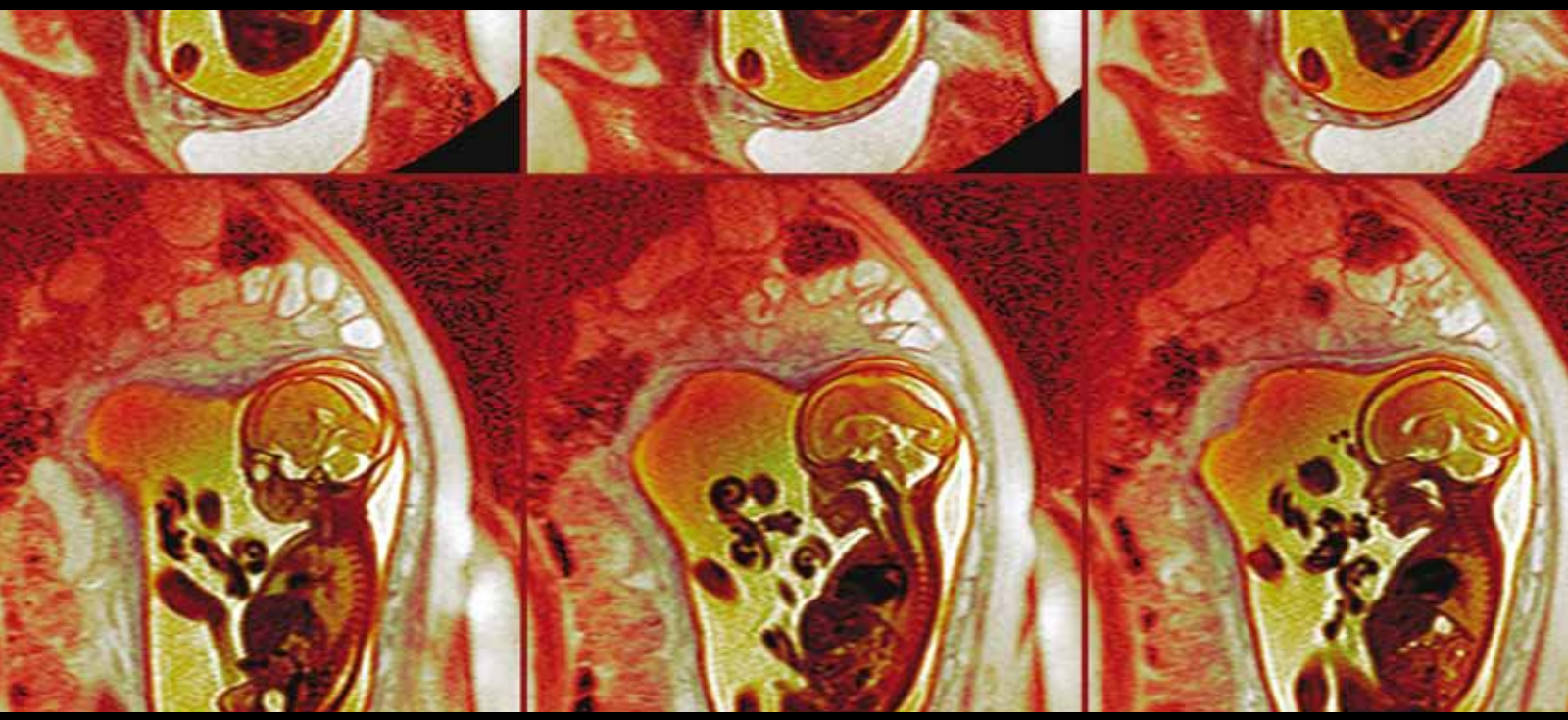
Journal of Pregnancy

Anemia and Iron Deficiency in Pregnancy

Guest Editors: Alexander Krafft, Laura Murray-Kolb, and Nils Milman



Anemia and Iron Deficiency in Pregnancy

Journal of Pregnancy

Anemia and Iron Deficiency in Pregnancy

Guest Editors: Alexander Krafft, Laura Murray-Kolb, and Nils Milman

Editorial Board

Contents

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 241869, 1 page
doi:10.1155/2012/241869

Editorial

Anemia and Iron Deficiency in Pregnancy

Alexander Krafft,[1] Laura Murray-Kolb,[2] and Nils Milman[3]

[1] *Division of Obstetrics, Department Obstetrics and Gynecology, University Hospital Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland*
[2] *Department of Nutritional Sciences, The Pennsylvania State University, 219 Chandlee Lab, University Park, PA 16802, USA*
[3] *Department of Gynecology & Obstetrics, Næstved Hospital, Ringstedgade 61, 4700 Næstved, Denmark*

Correspondence should be addressed to Alexander Krafft, alexander.krafft@usz.ch

Received 26 July 2012; Accepted 26 July 2012

Iron deficiency is still the world's most common nutritional deficiency, and generally, iron deficiency anemia is the most prevalent form of anemia. The major risk groups for iron deficiency include women of childbearing age, pregnant women, and lactating postpartum women. There exist plenty of studies attending and reconfirming this important issue. To combat this problem, different food iron fortification programmes have been implemented in some regions, iron supplementation guidelines have been elaborated in some countries, and iron therapy schemes involving both oral and intravenous administration have been proposed. But despite these efforts and the recommendations by the World Health Organization, the problem concerning iron deficiency and anemia is still unsolved in most parts of the world. Even in many industrialized countries, the topic of iron and pregnancy often stays unattended and there is a lack of consensus concerning guidelines in different countries.

Other disorders, such as hemoglobinopathies, also contribute to the high prevalence of anemia worldwide. The prevalence of anemia is influenced by a variety of deficiencies (e.g., folate, vitamin B12, vitamin A, vitamin D, and vitamin C), infectious diseases, parasitic infestations, inflammatory diseases as well as malnutrition.

As data for iron are quite profound, these are often scarce if we look on other vitamins and micronutrients, except for folic acid. As we know, periconceptional supplementation with folic acid has the potential to reduce the incidence of neural tube defects (e.g., spina bifida) dramatically. Unfortunately, folic acid prophylaxis is not commonly used for several reasons.

By this special issue, our intention was to broaden the perspective on anemia in pregnancy and propose ways to solve the problems. We have chosen three articles concerning the prevention/treatment of iron deficiency anemia in pregnancy/postpartum including papers from Australia, Nigeria, and Denmark. Another Danish study focuses on the prevention of postpartum anemia through hemostatic sealing of the placental bed at caesarean section, thereby reducing perioperative blood losses. A paper from France and Lebanon evaluates the relationship between periconceptional folate deficiency and neural tube defects. A Chinese study addresses the supposed relationship between iron deficiency and postpartum depression. Together, these papers illustrate some of the many facets of the complexity of the prevention and treatment of anemia in pregnant and postpartum women.

Alexander Krafft
Laura Murray-Kolb
Nils Milman

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 295083, 9 pages
doi:10.1155/2012/295083

Review Article

Periconceptional Folate Deficiency and Implications in Neural Tube Defects

J. Safi,[1] L. Joyeux,[2] and G. E. Chalouhi[3]

[1] *Department of Obstetrics and Gynecology, St Joseph University, Hôtel-Dieu de France, 1100 Beirut, Lebanon*
[2] *Department of Pediatric Surgery, Children's Hospital of Dijon, University Medical Center, 21000 Dijon, France*
[3] *Department of Obstetrics and Fetal Medicine, Hôpital Necker-Enfants-Malades, Paris Descartes University, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France*

Correspondence should be addressed to G. E. Chalouhi, gihad.chalouhi@gmail.com

Received 5 March 2012; Revised 3 May 2012; Accepted 4 June 2012

Academic Editor: Laura Murray-Kolb

Nutritional deficiencies are preventable etiological and epigenetic factors causing congenital abnormalities, first cause of infant mortality. Folate deficiency has a well-established teratogenic effect, leading to an increasing risk of neural tube defects. This paper highlights the most recent medical literature about folate deficiency, be it maternal or paternal. It then focuses on associated deficiencies as nutritional deficiencies are multiple and interrelated. Observational and interventional studies have all been consistent with a 50–70% protective effect of adequate women consumption of folates on neural tube defects. Since strategies to modify women's dietary habits and vitamin use have achieved little progress, scientific as well as political effort is mandatory in order to implement global preventive public health strategies aimed at improving the alimentation of women in reproductive age, especially folic acid supplementation. Even with the recent breakthrough of fetal surgery for myelomeningocele, the emphasis should still be on prevention as the best practice rather than treatment of neural tube defects.

1. Introduction

Congenital abnormalities (CAs) concern all diseases of organs or body parts developed in utero. They can be either isolated localized in one organ or multiple affecting at least two organs grouped into a syndrome, a sequence, or an association. Their prevalence is about 14% of all human fetuses considering all types of abnormalities, that is, major (3%) and minor (11%), or lethal, severe, and benign [1]. Among major CAs, congenital heart diseases account for 25%, limb defects for 20%, and nervous system abnormalities for 10% [2]. Moreover, CAs represent the first cause of infant mortalities, with an increasing proportion (more than 25%) in both developed and developing countries [1, 3]. In 2002 in the USA, CAs caused 21% of infant deaths [4, 5]. In the world, more than 10% of infant mortalities secondary to CA are caused by nervous system abnormalities [1].

Congenital abnormalities can develop at any time after the first month of pregnancy. From conception to birth, the human egg, then the embryo, and the fetus have to adapt, at a molecular and transcriptional level, to various changes in their cellular environment. At conception, this environment depends on the micronutritional status of maternal and paternal germ cells and after conception on maternal nutritional status, metabolism, and lifestyle. Maternal diet is the source of all the essential elements that will serve as basic components, transcriptional factors, growth factors, and messengers for embryological and fetal cells signaling and development.

Prevention of CAs is defined by individual and public health strategies that can reduce their prevalence. These active strategies include nutritional interventions, prevention of maternal infections and diseases, periconceptional care of sick mothers (epileptic or diabetic), control of professional and environmental exposure to teratogens, and special attention to pregnancies exposed to major health determinants such as obesity, tobacco, alcohol, and drugs [7].

One of the major breakthroughs in CA prevention has been the evidence that periconceptional folate supplementation can reduce the risk of neural tube defects (NTDs) [8–11] and other congenital abnormalities like cardiovascular malformations (CVMs), cleft lip and palate [12], urogenital

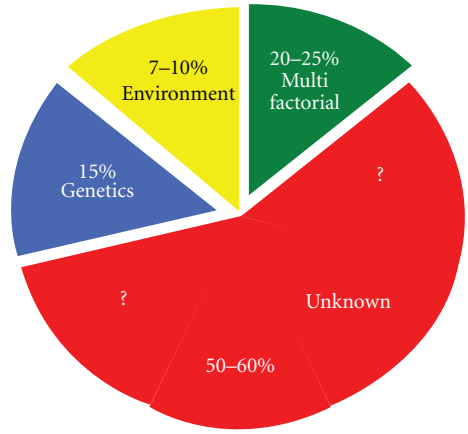


Figure 1: Causes of human congenital abnormalities (adapted from [6]).

abnormalities, and limb reductions [13]. It is essential to point out here that NTDs preventable through folate supplementation are isolated NTDs, and exclude other associated NTDs—grouped in syndrome, sequence, or association of CAs—which do not fall within the scope of this paper.

2. Nutritional Deficiencies and Teratogenicity

Congenital heart and central nervous system abnormalities encompass approximately 50% (resp., 40 and 10%) of the worldwide infantile deaths attributable to congenital abnormalities [14, 15]. Major congenital anomalies are also a source of high morbidity, distress, and severe physical, psychological, and social handicaps [14].

Teratology, the science of the precise etiologies of CA, defines these causes as unknown in 50–60% of cases. The other etiologies are epigenetic and multifactorial in 20–25% of cases, chromosomic or genetic with a single gene mutation in almost 15% of cases, and epigenetic, acquired, and monofactorial under the influence of environmental factors (such as maternal sickness, infections, medications, ionizing radiations, and alcohol) in about 10% of cases [15] (Figure 1).

Clinical studies [3] have revealed that a specific teratogen can induce various malformations, or none, depending on the timing of exposure of the developing embryo. Thereby, each organ or system displays a critical, yet brief, window, considered as a phase of susceptibility to environmental teratogens. It is commonly known that the earlier the exposure, the more severe the abnormalities, which can even lead to death of the embryo during the first month postconceptionally. Most deleterious teratogens produce nonspecific congenital abnormalities such as general dysmorphic features, intrauterine demise, or intrauterine growth restriction, as well as specific CA, which can characterize a particular agent. Nevertheless, a specific CA can result from various environmental agents. For example, spina bifida occurrence is increased with three principal maternal risk factors and still exhibits the same clinical aspect: maternal valproic acid intake, insulin-dependent diabetes, and folate deficiency.

Improved comprehension of etiopathogenesis has led to the emerging evidence that equilibrating and optimizing maternal dietary intake can reduce the incidence of CA. Influence of nutrition on fetal development has been repeatedly proven, at the molecular as well as the clinical level. Very recently, pilot data from a randomized double blind controlled trial showed that periconceptional maternal micronutrient supplementation affected fetal genome methylation patterns in DNA samples drawn from cord blood [16]. Any nutritional imbalance can alter genotype expression and induce abnormal phenotype. This is the fundamental epigenetic gene/nutrients link.

3. Characteristics of Folate Deficiency

Folate, or vitamin B9, is most abundantly found in dark green leafy vegetables, but also in orange juice, legumes (e.g., black beans and kidney beans), nuts, asparagus, and strawberries. With the exception of liver, meat is not a good source of folate [17]. Folic acid is the synthetic form of folate and is usually more bioavailable than natural food folate. Due to its lower bioavailability from natural foods, many countries have adopted mandatory folic acid food fortification programs.

Folates are essential for the synthesis of thymidylate and purines, precursors required for *de novo* DNA synthesis and hence, cell division [22]. This feature is of particular importance in a rapidly dividing and developing embryo. Folate coenzymes are also implicated in amino acid metabolism (homocystein) and methylation. In order to be stored intracellularly, folate ought to be metabolized into tetrahydrofolate (THF) by methionine synthase, a B12-dependent enzyme. In humans, the association of CA and folate deficiency began to be acknowledged in the 1950s, when Methotrexate was widely used for abortions. Moreover, Methotrexate and Aminopterin, both folic acid antagonists, were being used for the treatment of psoriasis and certain cancers in pregnant women, which resulted in CA, thus

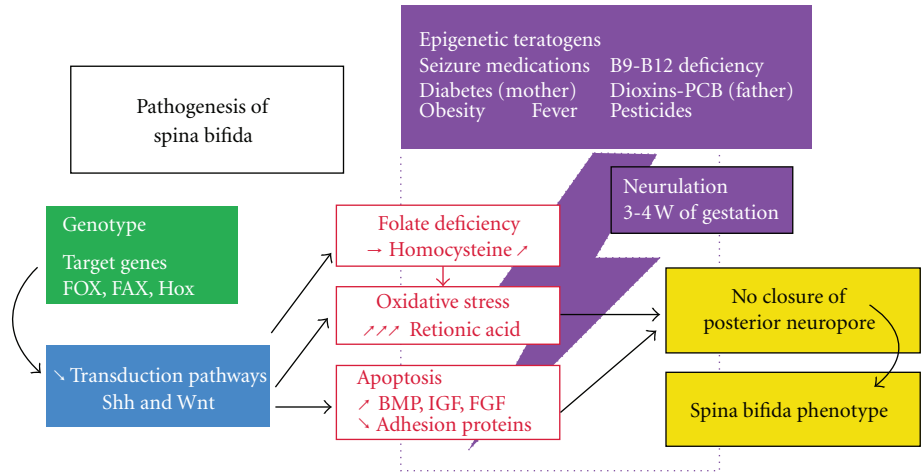


Figure 2: Combined etiopathogenesis of spina bifida (Shh: sonic hedgehog, Wnt: Wnt ligand in Wnt/β catenin signaling pathway, BMP: bone morphogenic protein, IGF: insulin-like growth hormone, and W: weeks) [18].

Table 1: Proven and suspected risk factors for spina bifida (NP = not proven).

Risk factors: proven and certain	Relative risk
History of NTD-affected pregnancy	30
Valproic acid and carbamazepine	10–20
Pregestational maternal diabetes	2–10
Inappropriate/deficient folic acid supplementation	2–8
Paternal exposure to dioxins in Agent Orange [19]	2
Risk factors: suspected	**Relative risk**
Maternal vitamin B12 status	3
Maternal diarrhea	3-4
Maternal obesity	1.5–3.5
Maternal hyperthermia	2
Nonproven (NP) risk factors, with epidemiological associations	**Relative risk**
Gestational diabetes	NP
Pesticides	NP
Herbicides	NP
Fumonisins	NP
Water chlorination	NP
Heavy metals: lead	NP
Organic solvents	NP
Plastic byproducts (vinyl chloride, PVC)	NP
Toxic waste sights	NP
Electromagnetic field	NP
Retinoic acid (vitamin A) excess [20, 21]	NP

starting to reveal an association. Additional research into neural tube defects and their etiologies was further facilitated by the advances in genetics and nonmendelian complex diseases, paving the way for the study of metabolism and transport of folate-homocysteine as potential risk factors for spina bifida. Since then, folic acid supplementation has remained one of the few interventions, if not the only, that can prevent major CA in the human fetus.

3.1. Maternal Folate Deficiency. During pregnancy, folate requirements increase to accommodate embryonic and fetal development and maternal tissue growth. While folate is actively transported to the fetus as demonstrated by higher cord blood folate concentrations relative to maternal blood [23], maternal serum and RBC concentrations of folate decline for several reasons [24–29]: increased demand, dilution secondary to increased intravascular volume, increased folate catabolism and clearance, decreased absorption, and inadequate intake [24, 27]. Folate deficiency is known to lead to maternal megaloblastic anemia, which may be fatal if left untreated [30].

3.1.1. Prevention of NTDs. Addressing folate deficiency as it relates to NTDs occurrence or recurrence has been the subject of considerable study. The evidence in public health that daily folic acid supplementation (alone or in combination with other vitamins and minerals) has a significant protective effect in preventing NTDs, that is, anencephaly and spina bifida as well as cardiovascular malformations is now overwhelming [31]. There is also a significant reduction in risk of recurrence, while prevention of other birth defects (cleft palate cleft lip) and or miscarriages was not proven to be statistically significant. The controversy about the potential role played by folic acid supplementation in the rising colon cancer rates should no longer be defended, as the majority of the evidence available is reassuring [30].

The current identified maternal risk factors for NTDs include four established factors: personal or familial past history of NTD (relative risk RR of 30), maternal diabetes (RR, 2–10), certain antiseizure medications (carbamazepine and valproic acid, with RR of 10 to 20), and maternal folate deficiency (RR, 2–8) [32] (Table 1 and Figure 2). Maternal factors such as obesity, hyperthermia, race, ethnicity, smoking, alcohol abuse, malabsorption, intestinal disease, and

liver or renal failure, can also contribute to genesis of NTDs either directly or indirectly by folate deficiency [30, 33]. Low folate intake, in addition to inadequate absorption of food folate and further loss through cooking practices, leaves the majority of women of reproductive age deficient in folates. As closure of the developing neural tube occurs by the 28th postconceptional day, that is, the 42nd gestational day, before the majority of women are aware of their pregnancy, this precludes the efficacy of folic acid given after the diagnosis of pregnancy.

Based on current evidence, it is recommended that all women of childbearing age receive 0.4 mg (400 μg) of folic acid daily periconceptionally (1 month before and 2 months after). Women at high risk for NTDs, that is, women with previous NTD-affected pregnancy, obesity (BMI > 30), diabetes, and epilepsy, should receive 4 to 5 mg of folic acid daily preconceptionally, starting at least one month before conception and continuing throughout the first trimester of pregnancy [30]. The recommended dose of 4 mg/d was chosen for a Medical Research Council trial that resulted in a 72% reduction in NTD recurrence [17, 34]. The adequate blood folate concentration and minimum supplemental dose shown to be effective for the prevention of NTDs are not precisely known. The only Randomized Controlled Trial (RCT) showing reduction in *occurrence* of NTDs used an 800 μg/d dose, whereas other intervention trials studying occurrence or case control studies of *recurrence* used a 400 μg/d dose. All of the studies demonstrated significant reduction of NTDs [9, 11, 35]. However, the NTD risk reduction with higher blood folate concentrations is well documented, as is the enhancement of folate status with the combined consumption of folic acid supplements or fortified foods and a healthy diet containing natural folate [36–38].

Proper evidence on folate dose remains limited. For instance, the precise red blood cell folate concentration of 906 nmol/L was demonstrated to be related to a lowest risk of NTDs in the offspring. This concentration was not reached within four weeks of the currently recommended supplementation, according to Daly et al. [37]. However, Brämswig et al. were able to reach that same target level within four weeks of supplementation with a daily intake of 800 μg/d folic acid. These results suggest the need for the reevaluation of the current dosage recommendation of folic acid supplementation with respect to NTD prevention [39].

3.1.2. Prevention of Cardiovascular Malformations (CVMs). Although the preventive efficacy of NTDs by folic acid-containing multivitamins (MV) or folic acid alone has been well established and demonstrated to be better than any other CA prevention, the available data also supports the essential role of folic acid for normal fetal cardiac development during early embryogenesis. The combination of the results of two Hungarian intervention trials [40, 41] (OR with 95% CI: 0.57, 0.39–0.85) showed a 43% risk reduction of cardiovascular malformations after MV supplementation.

Two more recent population-based observational studies demonstrated a significant reduction in the rates of CVM with folic acid intake [42, 43]. Furthermore, a significant reduction in the birth prevalence of severe CVMs was reported in Quebec, Canada, after folic acid fortification of grain products [44]. Another Canadian study, a systematic review and meta-analysis by Goh et al., concluded that maternal consumption of MV was associated with decreased risk for several congenital anomalies (OR 0.78, 95% CI 0.67–0.92 in case control studies and OR 0.61, 95% CI 0.40–0.92 in cohort and randomized controlled studies for cardiovascular defects) [45].

In conclusion, the available evidence concerning CVMs shows that any public health action of CA prevention with periconceptional MV or folic acid supplementation should necessarily take into consideration CVMs, with regard not only to demonstrated efficacy but also to the more elevated prevalence of CVM as compared to NTD or other defects, and thus to the superior absolute number of preventable cases of CVM per 100,000 births. This should be particularly true in countries with a low NTD prevalence, and a low NTD: CVM ratio, such as the USA.

3.2. Paternal Folate Deficiency. Teratogenicity may exist at the conceptional level as well at the preconceptional level, thus affecting both maternal and paternal gametes. A recent proven example, although it has not been fully elucidated, is the effect of paternal exposure to dioxins. A statistically significant causal link has been demonstrated between dioxin exposure and spermatozoid folate deficiency leading to spina bifida [19, 46, 47].

The chemical name for dioxin is *2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD)*. The media term "dioxins" is often used for a family of structurally and chemically related products. Dioxins are mainly unwanted byproducts of a wide range of industrial processes. In terms of dioxin release into the environment, uncontrolled waste incinerators (solid waste and hospital waste) are often the worst culprits, due to incomplete burning. Although formation is local, environmental distribution is global. Dioxins accumulate throughout the food chain, with increasing concentrations. The highest levels of these compounds are found in some soils, sediments, and food, especially dairy products, meat, fish, and poultry. Once the human body has absorbed dioxins, they persist for a long time because of their chemical stability and their ability to accumulate in fat tissue.

After preconceptional exposure to dioxins, the risk of mutations in spermatozoids is significantly increased, leading to an increased risk of spina bifida [19, 46, 47] through mechanisms involving folate deficiency [48]. In animal models, the teratogenic and mutagenic effect of Dioxin has been extensively proven, while light had just started to be shed on the mechanism by which human paternal Dioxin exposure can lead to congenital abnormalities. The causative and statistically significant association between the Dioxin containing Agent Orange, which was used in the Vietnam War, and spina bifida, is irrefutable [19, 46, 47]. Precise biological mechanisms of exposure to Dioxin are epigenetic, based on activation of the AhR/ARNT (aryl hydrocarbon receptor/aryl hydrocarbon receptor nuclear translocator)

complex of spermatogenesis, leading to folate deficiency as the cause of NTD phenotype [48, 49]. This complex is widely distributed, but is particularly abundant in the human testicle, which renders it one of the most sensitive organs to Dioxins. This explains its direct interference with human spermatogenesis and male fertility [50]. Halwachs et al. have recently demonstrated that dioxins deregulate the AhR signaling pathway [48]. This effect is mediated by a downregulation of Rfc 1 (reduced folate carrier 1) gene expression and reduced carrier protein levels. This downregulation by TCDD was shown to be time- and dose-dependent in rat livers and resulted in functional folate deficiency in male and female cells and tissues, including germ cells [48].

In summary, dioxins are diffusely distributed in the environment and tend to accumulate along the food chain. Chronic consumption of contaminated food can lead to deregulation of genetic mechanisms implicated in folate homeostasis. Consequently, widespread folate deficiency in men and women, generally due to inadequate consumption of alimentary folates, can be increased. The final consequences are NTDs in fetuses born to mothers, but also fathers, deficient in intracellular folate concentration in germ cells. Paternal folate deficiency could be one of the factors explaining the incomplete success of recommended folate supplementation to prevent NTDs.

3.3. Associated Deficiencies

3.3.1. Vitamin B12. Vitamin B12 (cobalamin) is a pivotal cofactor for key enzyme reactions including the generation of methionine and tetrahydrofolate. This vitamin is found almost exclusively in foods of animal origin (meats, dairy products). Although inadequate vitamin B12 status is thought to be limited to the aging population, it has been found with a relatively high prevalence in women of reproductive age with restricted consumption of animal-based food, an increasingly popular dietary trend [17], and in pregnant women who are more likely to be deficient than nonpregnant women [51].

Vitamin B12 deficiency may impair folate metabolism through impairment of methionine synthase enzyme. It has been associated with NTDs in a number of studies. Ray and Blom identified 17 NTD case-control studies related to B12 status, with an overall reported trend towards lower mean B12 concentration in mothers with NTD-affected pregnancies [52]. The two largest positive studies conducted after the introduction of folate fortification in the United States and Canada [53, 54] showed that the risk of NTDs was inversely proportional to the measured serum concentrations of vitamin B12 (holotranscobalamin). Furthermore, in Ireland, risk of NTDs was strongly positively correlated to low B12 status in a population not exposed to folic acid fortification or supplements [55, 56]. Kirke et al. uncovered a fivefold increase in NTD risk for women in the lower quartile of associated folate and B12 deficiencies, compared to half this rate for only folate deficiency, thus demonstrating the synergistic actions of both vitamins. More recently, Zhang et al. [57] and Molloy et al. [56] reported higher NTD risk in mothers within the lowest quartile for B12 concentrations, with an approximate three-fold increase. Both Kirke and Zhang demonstrated that B12 and folate were two independent risk factors. In 2009, the National Institutes of Health validated the results of Molloy et al., and concluded that improving B12 status in women of childbearing age would prevent NTDs. The recommended daily Vitamin B12 allowance for pregnant women is 2.6 μg/day [17, 58].

Caregivers should be aware that high levels of folic acid intake (tolerable upper intake level from fortified foods or supplements is 1000 μg/d for adults), can mask vitamin B12 deficiency, resulting in permanent nerve damage, especially in elderly individuals [30].

3.3.2. Other Deficiencies. As previously mentioned, the etiology of CA is multifactorial, and most factors are still unknown. Toxic chemicals are detected everywhere, in the dietary products of the general population [59], in the inhaled air [60], and even in neonates' cord blood [61]. According to a WHO report in 2010 [62], the top three most common groups of etiologies for CA in developed countries are epigenetic: maternal diseases (diabetes and hyperthermia), pathologic maternal deficiencies (folate and iodine deficiency), and exposure to teratogens (medications, drugs including tobacco and alcohol, environmental chemicals like pesticides, and ionizing radiations).

The unfolding of new associations between malnutrition and diseases has made it clear that women in their reproductive years have multiple complex nutritional deficiencies; this might also be true for the general population. Recent studies showed that prenatal multimicronutrient supplementation was associated with a significantly reduced risk of low birth weight when compared with iron-folic acid supplementation [63, 64]. Moreover, Chen et al. proved that periconceptional multivitamin supplementation containing folic acid—two months before conception and until completion of the second month—containing folic acid can prevent the occurrence of NTDs [65]. These maternal and paternal nutritional deficiencies are probably multicausal. They can be due to digestive malabsorption, but also to excessive cooking of fresh food that destroys most of the vitamins, and to widespread consumption of industrial food products. Future policies should be directed towards improving food quality.

4. Prenatal Management of NTDs

4.1. Prevention: Current Strategies and Their Benefits. Epidemiological studies, both observational and interventional, have all been consistent with a 50 to 70% protective effect of adequate consumption of folates on NTDs [66]. Since strategies to modify women's dietary habits and vitamin use have achieved little progress [67] and since about half of all the pregnancies are unplanned, maternal supplementation alone cannot be an effective approach. Only maintenance of optimal nutritional status throughout the reproductive years will help ensure normal fetal development [17].

Table 2: MOM study results, January 2011 [68].

Results (%)	Prenatal surgery	Postnatal surgery	*P* value
At 12 months			
Shunt placement	40	82	<0.001
Hindbrain herniation	64	96	<0.001
At 30 months			
Psychomotor development (Bayley index mean)	64	58,3	0.03
Motor function & independent walking on examination	42	21	0.01

Starting in North America, fortification of food with folic acid has made folic acid accessible to all men and women of childbearing age without necessitating behavioral change and has proven to be both efficient and more homogeneous [33]. An additional rationale for fortification is that, in contrast with food folate, bioavailability of folic acid from fortified food is 85% (it is a 100% from vitamin supplement) [30]. In 1992, the US Public Health Service (USPHS) recommended that all women in their reproductive years consume 400 μg of folic acid daily for prevention of NTDs. By 1998, and following Food and Drug Administration (FDA) regulations, all standardized enriched cereal grain products sold in the United States included 140 μg folic acid/100 g. Folic acid was also added to breakfast cereals, corn grits, infant formulas, medical foods, and foods for special dietary use. In 2009, the US Preventive Services Task Force published updated grade A recommendations reinforcing these guidelines [69]. By 2007, over 50 countries had implemented their own folic acid flour fortification programs, including Canada, Costa Rica, Chile, Australia, New Zealand, South Africa, and some Middle Eastern countries [70]. In the USA, the National Birth Defects Prevention Network reported a 36% decrease in the prevalence of NTDs, from 10.8 per 10,000 population during 1995-1996 to 6.9 at the end of 2006 [71]. In Europe, EUROCAT registries reported a 10% decrease, from 10.5 per 10,000 in 2004 to 9.4 in 2008 [72]. A greater decline in NTDs was predicted [73], raising the question of what additional measures should be undertaken. According to the CDC 2010 report, disparities still exist among diverse ethnicities, as well as on a global worldwide basis. As current fortification programs only prevent about 9% of total annual cases of NTDs, an international public health solution is to expand the number of countries with mandatory fortification programs that have the potential to safely diminish the fraction of folic acid-preventable NTDs [74].

However, while the abundant literature depicts mandatory fortification programs as massive public health success stories [75], one study found that neither periconceptional supplementation nor dietary folic acid intake reduced the risk of NTDs, including spina bifida [76]. Moreover, another confirmed the protective effect of dietary folic acid alone, regardless of supplementation status, which did not appear to offer further benefit in reducing the risk of spina-bifida-affected pregnancies, even among women with very low dietary folic acid consumption [77]. It is worth mentioning here that these were case-control studies that relied on self-reported maternal questionnaires, which raises the question of reporting accuracy, in the era of global awareness of the protective effect of folic acid. Furthermore, despite folic acid fortification and maternal supplementation, the incidence of NTDs has stabilized in the United States [33] and many other countries [78].

All this knowledge highlights the need for paired management strategy: prevention by folic acid and vitamin B12 maternal and paternal supplementations associated with a decreased exposure to the multiple risk factors and treatment such as fetal surgery.

4.2. Fetal Surgery. The first prenatal myelomeningocele (MMC) repair was performed in 1994 by Bruner and Tulipan endoscopically on 4 cases. Due to premature labor and birth, this technique was considered dangerous and unsatisfactory and was abandoned [79]. In 1997, the first cases of open MMC repair by hysterotomy were realized [80, 81].

Very recently, Adzick et al. proved, in the Management of Myelomeningocele Study (MOMS), the efficacy of fetal MMC surgery as compared to standard postnatal repair [68]. Prenatal surgery resulted in significant reduction of hindbrain herniation (Chiari II malformation), a reduction in need for shunting to relieve hydrocephalus, as well as improvements in motor function and mental development at 30 months (Table 2) [68, 82]. However, preterm delivery and obstetrical complications were increased.

5. Conclusion

The etiologies of congenital abnormalities lie in epigenetics in the vast majority of cases. They are multifactorial, maternal as well as paternal, but universally associated with environmental teratogens. Future research and multicentric, large-scale trials should be directed to epigenetic profiling of congenital diseases, including neural tube defects.

Nutritional deficiencies are multiple, interrelated, and concern both men and women. Scientific as well as political effort is mandatory in order to implement global preventive public health strategies using fortification and supplementation.

References

[1] A. Rosano, L. D. Botto, B. Botting, and P. Mastroiacovo, "Infant mortality and congenital anomalies from 1950 to 1994: an international perspective," *Journal of Epidemiology and Community Health*, vol. 54, no. 9, pp. 660–666, 2000.

[2] EUROCAT, "Surveillance of Congenital Anomalies in Europe, 1980–1999," E.S.o.C.A. EUROCAT, European surveillance of congenital anomalies: University of Ulster, Newtownabbey, Northern Ireland, 2002.

[3] A. Correa-Villaseñor, J. Cragan, J. Kucik, L. O'Leary, C. Siffel, and L. Williams, "The metropolitan atlanta congenital defects program: 35 years of birth defects surveillance at the centers

for disease control and prevention," *Birth Defects Research Part A*, vol. 67, no. 9, pp. 617–624, 2003.

[4] J. Petrini, K. Damus, R. Russell, K. Poschman, M. J. Davidoff, and D. Mattison, "Contribution of birth defects to infant mortality in the United States," *Teratology*, vol. 66, no. 1, supplement, pp. S3–S6, 2002.

[5] CDC, "Periconceptional use of multivitamins and the occurrence of anencephaly and spina bifida," *Morbidity and Mortality Weekly Report*, vol. 37, no. 47, pp. 727–730, 1988.

[6] K. L. Moore and T. V. N. Persaud, *The Developing Human: Clinically Oriented Embryology*, Saunders, Philadelphia, Pa, USA, 2003.

[7] H. Dolk, "What is the "primary" prevention of congenital anomalies?" *The Lancet*, vol. 374, no. 9687, p. 378, 2009.

[8] K. M. Laurence, N. James, M. Miller, and H. Campbell, "Increased risk of recurrence of pregnancies complicated by fetal neural tube defects in mothers receiving poor diets, and possible benefit of dietary counselling," *British Medical Journal*, vol. 281, no. 6255, pp. 1592–1594, 1980.

[9] R. W. Smithells, S. Sheppard, and C. J. Schorah, "Possible prevention of neural-tube defects by periconceptional vitamin supplementation," *Lancet*, vol. 1, no. 8164, pp. 339–340, 1980.

[10] N. Wald, J. Sneddon, J. Densem, C. Frost, and R. Stone, "Prevention of neural tube defects: results of the medical research council vitamin study," *Lancet*, vol. 338, no. 8760, pp. 131–137, 1991.

[11] A. E. Czeizel and I. Dudas, "Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation," *New England Journal of Medicine*, vol. 327, no. 26, pp. 1832–1835, 1992.

[12] M. Tolarova, "Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip," *Lancet*, vol. 2, no. 8291, p. 217, 1982.

[13] A. E. Czeizel, "Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation," *American Journal of Medical Genetics*, vol. 62, no. 2, pp. 179–183, 1996.

[14] EUROCAT, "Surveillance of Congenital Anomalies in Europe, 1980–1999," E.S.o.C.A. EUROCAT, European surveillance of congenital anomalies, University of Ulster, Newtownabbey, Northern Ireland, 2002.

[15] EUROCAT, "A Review of Environmental Risk Factors for Congenital Anomalies," E.S.o.C.A. EUROCAT, EUROCAT, European surveillance of congenital anomalies, University of Ulster, Newtownabbey, Northern Ireland, 2004.

[16] B. Khulan, W. N. Cooper, B. M. Skinner et al., "Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: a study of a unique resource in the Gambia," *Human Molecular Genetics*, vol. 21, no. 9, pp. 2086–2101, 2012.

[17] J. L. Simpson, L. B. Bailey, K. Pietrzik, B. Shane, and W. Holzgreve, "Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part i Folate, Vitamin B12, Vitamin B6," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 23, no. 12, pp. 1323–1343, 2010.

[18] L. Joyeux, *Etiopathogenesis and treatment of for congenital malformations curable in utero [medical thesis]*, p. 196, June 2011.

[19] A. D. Ngo, R. Taylor, and C. L. Roberts, "Paternal exposure to Agent Orange and spina bifida: a meta-analysis," *European Journal of Epidemiology*, vol. 25, no. 1, pp. 37–44, 2010.

[20] E. Danzer, U. Schwarz, S. Wehrli, A. Radu, N. S. Adzick, and A. W. Flake, "Retinoic acid induced myelomeningocele in fetal rats: characterization by histopathological analysis and magnetic resonance imaging," *Experimental Neurology*, vol. 194, no. 2, pp. 467–475, 2005.

[21] E. Danzer, A. Radu, L. E. Robinson, M. V. Volpe, N. S. Adzick, and A. W. Flake, "Morphologic analysis of the neuromuscular development of the anorectal unit in fetal rats with retinoic acid induced myelomeningocele," *Neuroscience Letters*, vol. 430, no. 2, pp. 157–162, 2008.

[22] L. B. Bailey, "Folic acid," in *Handbook of Vitamins*, J. Zempleni, D. B. McCormick, and J. W. Suttie, Eds., p. 387, CRC Press, Taylor & Francis Group, Boca Raton, Fla, USA, 2007.

[23] J. Ek, "Plasma and red cell folate values in newborn infants and their mothers in relation to gestational age," *Journal of Pediatrics*, vol. 97, no. 2, pp. 288–292, 1980.

[24] I. Chanarin, *The Megaloblastic Anaemias*, Blackwell, London, UK, 1969.

[25] H. W. Bruinse, V. H. D. Berg, and A. A. Haspels, "Maternal serum folacin levels during and after normal pregnancy," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 20, no. 3, pp. 153–158, 1985.

[26] I. Qvist, M. Abdulla, M. Jagerstad, and S. Svensson, "Iron, zinc and folate status during pregnancy and two months after delivery," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 65, no. 1, pp. 15–22, 1986.

[27] T. Tamura and M. F. Picciano, "Folate and human reproduction," *American Journal of Clinical Nutrition*, vol. 83, no. 5, pp. 993–1016, 2006.

[28] H. Takimoto, N. Mito, K. Umegaki et al., "Relationship between dietary folate intakes, maternal plasma total homocysteine and B-vitamins during pregnancy and fetal growth in Japan," *European Journal of Nutrition*, vol. 46, no. 5, pp. 300–306, 2007.

[29] J. M. W. Wallace, M. P. Bonham, J. J. Strain et al., "Homocysteine concentration, related B vitamins, and betaine in pregnant women recruited to the Seychelles Child Development Study," *American Journal of Clinical Nutrition*, vol. 87, no. 2, pp. 391–397, 2008.

[30] V. S. Talaulikar and S. Arulkumaran, "Folic acid in obstetric practice: a review," *Obstetrical and Gynecological Survey*, vol. 66, no. 4, pp. 240–247, 2011.

[31] L. M. De Regil, A. C. Fernández-Gaxiola, T. Dowswell, and J. P. Peña-Rosas, "Effects and safety of periconceptional folate supplementation for preventing birth defects," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD007950, 2009.

[32] L. E. Mitchell, N. Scott Adzick, J. Melchionne, P. S. Pasquariello, L. N. Sutton, and A. S. Whitehead, "Spina bifida," *Lancet*, vol. 364, no. 9448, pp. 1885–1895, 2004.

[33] CDC, "CDC grand rounds: additional opportunities to prevent neural tube defects with folic acid fortification," *Morbidity and Mortality Weekly Report*, vol. 59, no. 31, pp. 980–984, 2010.

[34] N. Wald, J. Sneddon, J. Densem, C. Frost, and R. Stone, "Prevention of neural tube defects: results of the medical research council vitamin study," *Lancet*, vol. 338, no. 8760, pp. 131–137, 1991.

[35] R. J. Berry, Z. Li, J. D. Erickson et al., "Prevention of neural-tube defects with folic acid in China," *New England Journal of Medicine*, vol. 341, no. 20, pp. 1485–1490, 1999.

[36] G. P. A. Kauwell, Q. Yang, and L. B Bailey, "Folate: recommended intakes, consumption, and status," in *Folate in Health*

and Disease, L. B Bailey, Ed., pp. 467–490, CRC Press, Taylor and Francis Group, Boca Raton, Fla, USA, 2009.

[37] L. E. Daly, P. N. Kirke, A. Molloy, D. G. Weir, and J. M. Scott, "Folate levels and neural tube defects: implications for prevention," *Journal of the American Medical Association*, vol. 274, no. 21, pp. 1698–1702, 1995.

[38] G. J. Cuskelly, H. McNulty, and J. M. Scott, "Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects," *Lancet*, vol. 347, no. 9002, pp. 657–659, 1996.

[39] S. Brämswig, R. Prinz-Langenohl, Y. Lamers et al., "Supplementation with a multivitamin containing 800 μg of folic acid shortens the time to reach the preventive red blood cell folate concentration in healthy women," *International Journal for Vitamin and Nutrition Research*, vol. 79, no. 2, pp. 61–70, 2009.

[40] A. E. Czeizel, "Periconceptional folic acid containing multivitamin supplementation," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 78, no. 2, pp. 151–161, 1998.

[41] A. E. Czeizel, M. Dobó, and P. Vargha, "Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities," *Birth Defects Research Part A*, vol. 70, no. 11, pp. 853–861, 2004.

[42] L. D. Botto, J. Mulinare, and J. D. Erickson, "Occurrence of congenital heart defects in relation to maternal multivitamin use," *American Journal of Epidemiology*, vol. 151, no. 9, pp. 878–884, 2000.

[43] I. M. Van Beynum, L. Kapusta, M. K. Bakker, M. Den Heijer, H. J. Blom, and H. E. K. De Walle, "Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands," *European Heart Journal*, vol. 31, no. 4, pp. 464–471, 2010.

[44] R. Ionescu-Ittu, A. J. Marelli, A. S. Mackie, and L. Pilote, "Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada," *British Medical Journal*, vol. 338, p. b1673, 2009.

[45] Y. I. Goh, E. Bollano, T. R. Einarson, and G. Koren, "Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis," *Journal of Obstetrics and Gynaecology Canada*, vol. 28, no. 8, pp. 680–689, 2006.

[46] M. C. Hatch and Z. A. Stein, "Agent Orange and risks to reproduction: the limits of epidemiology," *Teratogenesis Carcinogenesis and Mutagenesis*, vol. 7, no. 4, pp. 423–424, 1987.

[47] A. K. Giri, "Mutagenic and genotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. A review," *Mutation Research*, vol. 168, no. 3, pp. 241–248, 1986.

[48] S. Halwachs, C. Lakoma, R. Gebhardt, I. Schäfer, P. Seibel, and W. Honscha, "Dioxin mediates downregulation of the reduced folate carrier transport activity via the arylhydrocarbon receptor signalling pathway," *Toxicology and Applied Pharmacology*, vol. 246, no. 1-2, pp. 100–106, 2010.

[49] D. A. Hansen, "Paternal environmental exposures and gene expression during spermatogenesis: research review to research framework," *Birth Defects Research Part C*, vol. 84, no. 2, pp. 155–163, 2008.

[50] R. Schultz, J. Suominen, T. Värre et al., "Expression of aryl hydrocarbon receptor and aryl hydrocarbon receptor nuclear translocator messenger ribonucleic acids and proteins in rat and human testis," *Endocrinology*, vol. 144, no. 3, pp. 767–776, 2003.

[51] J. G. Ray, J. Goodman, P. R. A. O'Mahoney, M. M. Mamdani, and D. Jiang, "High rate of maternal vitamin B12 deficiency nearly a decade after Canadian folic acid flour fortification," *QJM*, vol. 101, no. 6, pp. 475–477, 2008.

[52] J. G. Ray and H. J. Blom, "Vitamin B12 insufficiency and the risk of fetal neural tube defects," *QJM*, vol. 96, no. 4, pp. 289–295, 2003.

[53] L. Suarez, K. Hendricks, M. Felkner, and E. Gunter, "Maternal serum B12 levels and risk for neural tube defects in a Texas-Mexico border population," *Annals of Epidemiology*, vol. 13, no. 2, pp. 81–88, 2003.

[54] J. G. Ray, P. R. Wyatt, M. D. Thompson et al., "Vitamin B12 and the risk of neural tube defects in a folic-acid-fortified population," *Epidemiology*, vol. 18, no. 3, pp. 362–366, 2007.

[55] P. N. Kirke, A. M. Molloy, L. E. Daly, H. Burke, D. G. Weir, and J. M. Scott, "Maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects," *Quarterly Journal of Medicine*, vol. 86, no. 11, pp. 703–708, 1993.

[56] A. M. Molloy, P. N. Kirke, J. F. Troendle et al., "Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic acid fortification," *Pediatrics*, vol. 123, no. 3, pp. 917–923, 2009.

[57] T. Zhang, R. Xin, X. Gu et al., "Maternal serum vitamin B12, folate and homocysteine and the risk of neural tube defects in the offspring in a high-risk area of China," *Public Health Nutrition*, vol. 12, no. 5, pp. 680–686, 2009.

[58] (IOM), I.o.M.a.C., *Dietary Reference Intake: Folate, Other B Vitamins and Choline*, National Academy Press, Washington, DC, USA, 1998.

[59] Association générations futures A, r.e.A.e.s.H., WWF-France, Menus toxiques-Enquete sur les substances chimiques presentes dans notre alimentation: campagne "Environnement cancer", 2010.

[60] Narbonne, *Sang pour sang toxique*, 2010.

[61] Environmental Working Group, "The Pollution in Newborns: A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood," edited by B. Burden, 2005.

[62] WHO, "Malformations congénitales," in *Soixante-Troiseeéme Assemblée Mondiale de la Santé*, World Health Organization, Geneva, Switzerland, 2010.

[63] P. S. Shah and A. Ohlsson, "Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis," *Canadian Medical Association Journal*, vol. 180, no. 12, pp. E99–E108, 2009.

[64] L. Zeng, Y. Cheng, S. Dang et al., "Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial," *British Medical Journal*, vol. 337, article a2001, 2008.

[65] G. Chen, X. Song, Y. Ji et al., "Prevention of NTDs with periconceptional multivitamin supplementation containing folic acid in China," *Birth Defects Research Part A*, vol. 82, no. 8, pp. 592–596, 2008.

[66] H. Blencowe, S. Cousens, B. Modell, and J. Lawn, "Folic acid to reduce neonatal mortality from neural tube disorders," *International Journal of Epidemiology*, vol. 39, pp. i110–121, 2010.

[67] R. J. Berry, L. Bailey, J. Mulinare, and C. Bower, "Fortification of flour with folic acid," *Food and Nutrition Bulletin*, vol. 31, no. 1, pp. S22–S35, 2010.

[68] N. S. Adzick, E. A. Thom, C. Y. Spong et al., "A randomized trial of prenatal versus postnatal repair of myelomeningocele," *New England Journal of Medicine*, vol. 364, no. 11, pp. 993–1004, 2011.

[69] Force, U.S.P.S.T., "Folic acid for the prevention of neural tube defects: U.S. Preventive services task force recommendation statement," *Annals of Internal Medicine*, vol. 150, no. 9, pp. 626–631, 2009.

[70] G. Maberly, L. Grummer-Strawn, M. E. Jefferds et al., "Trends in wheat-flour fortification with folic acid and iron—worldwide, 2004 and 2007," *Morbidity and Mortality Weekly Report*, vol. 57, no. 1, pp. 8–10, 2008.

[71] National Birth Defects Prevention Network, "Neural tube defect ascertainment project 2010," 2010.

[72] B. Khoshnood, R. Greenlees, M. Loane, and H. Dolk, "Paper 2: EUROCAT public health indicators for congenital anomalies in Europe," *Birth Defects Research Part A*, vol. 91, no. 1, pp. S16–S22, 2011.

[73] Prevention, C.f.D.C.a., "Effectiveness in disease and injury prevention use of folic acid for prevention of spina bifida and other neural tube defects—1983–1991," *Morbidity and Mortality Weekly Report*, vol. 41, pp. 513–516, 1992.

[74] K. N. Bell and G. P. Oakley Jr., "Update on prevention of folic acid-preventable spina bifida and anencephaly," *Birth Defects Research Part A*, vol. 85, no. 1, pp. 102–107, 2009.

[75] S. G. Običan, R. H. Finnell, J. L. Mills, G. M. Shaw, and A. R. Scialli, "Folic acid in early pregnancy: a public health success story," *FASEB Journal*, vol. 24, no. 11, pp. 4167–4174, 2010.

[76] B. S. Mosley, M. A. Cleves, A. M. Siega-Riz et al., "Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States," *American Journal of Epidemiology*, vol. 169, no. 1, pp. 9–17, 2009.

[77] K. Ahrens, M. M. Yazdy, A. A. Mitchell, and M. M. Werler, "Folic acid intake and spina bifida in the era of dietary folic acid fortification," *Epidemiology*, vol. 22, no. 5, pp. 731–737, 2011.

[78] Y. Yi, M. Lindemann, A. Colligs, and C. Snowball, "Economic burden of neural tube defects and impact of prevention with folic acid: a literature review," *European Journal of Pediatrics*, vol. 170, no. 11, pp. 1391–1400, 2011.

[79] J. P. Bruner, W. O. Richards, N. B. Tulipan, and T. L. Arney, "Endoscopic coverage of fetal myelomeningocele in utero," *American Journal of Obstetrics and Gynecology*, vol. 180, no. 1 I, pp. 153–158, 1999.

[80] N. Tulipan and J. P. Bruner, "Myelomeningocele repair in utero: a report of three cases," *Pediatric Neurosurgery*, vol. 28, no. 4, pp. 177–180, 1998.

[81] N. S. Adzick, L. N. Sutton, T. M. Crombleholme, and A. W. Flake, "Successful fetal surgery for spina bifida," *Lancet*, vol. 352, no. 9141, pp. 1675–1676, 1998.

[82] N. S. Adzick, "Fetal myelomeningocele: natural history, pathophysiology, and in-utero intervention," *Seminars in Fetal and Neonatal Medicine*, vol. 15, no. 1, pp. 9–14, 2010.

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 521431, 7 pages
doi:10.1155/2012/521431

Clinical Study

No Relationship between Maternal Iron Status and Postpartum Depression in Two Samples in China

Rinat Armony-Sivan,[1,2] Jie Shao,[3] Ming Li,[4] Gengli Zhao,[5] Zhengyan Zhao,[3] Guobing Xu,[6] Min Zhou,[5] Jianying Zhan,[3] Yang Bian,[4] Chai Ji,[3] Xing Li,[4] Yaping Jiang,[6] Zhixiang Zhang,[4] Blair J. Richards,[1] Twila Tardif,[1,7] and Betsy Lozoff[1,8]

[1] *Center for Human Growth and Development, University of Michigan, Ann Arbor, MI 48109, USA*
[2] *Department of Psychology, Ashkelon Academic College, 78109 Ashkelon, Israel*
[3] *Department of Child Health Care, Children's Hospital Zhejiang University School of Medicine, Hangzhou 310003, China*
[4] *Department of Pediatrics, Peking University First Hospital, Beijing 100034, China*
[5] *Women's and Children's Health Center, Peking University, Beijing 100034, China*
[6] *Department of Clinical Laboratory, Peking University First Hospital, Beijing 100034, China*
[7] *Department of Psychology, University of Michigan, Ann Arbor, MI 48109, USA*
[8] *Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI 48109, USA*

Correspondence should be addressed to Betsy Lozoff, blozoff@umich.edu

Received 2 February 2012; Revised 27 April 2012; Accepted 30 April 2012

Academic Editor: Laura Murray-Kolb

Maternal iron status is thought to be related to postpartum depressive symptoms. The purpose of the present study was to evaluate the relationship between pre- and postnatal maternal iron status and depressive symptoms in pilot ($n = 137$) and confirmatory ($n = 567$) samples of Chinese women. Iron status was evaluated at mid- and late pregnancy and 3 days postpartum. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess maternal postpartum depression 24–48 hours after delivery and 6 weeks later. In the pilot sample, correlations between early- and late-pregnancy maternal Hb and EPDS scores at 6 weeks were $r = 0.07$ and -0.01, respectively (nonsignificant). In the confirmatory sample, the correlations between maternal iron measures (Hb, MCV, ZPP, ferritin, sTfR, and sTfR Index) in mid- or late pregnancy or 3 days postpartum and EPDS scores shortly after delivery or at 6 weeks were also low (r values < 0.10). EPDS scores in anemic and nonanemic mothers did not differ, regardless of sample or timing of maternal iron status assessment. In addition, women with or without possible PPD were similar in iron status in both samples. Thus, there was no relationship between maternal iron status and postpartum depression in these samples.

1. Introduction

Iron deficiency anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. Although direct estimates of the worldwide prevalence of iron deficiency are problematic [1], anemia—a late manifestation of iron deficiency—affects an estimated 30% of nonpregnant women of reproductive age and 42% of pregnant women [2].

Iron deficiency in women has been related to fatigue and poorer general health [3–5] and emotional and cognitive function [6–11]. However, the relationship between postpartum depression (PPD) and maternal iron status remains unclear. One of the earliest studies reported that low Hb was associated with such postnatal symptoms as low energy, faintness/dizziness, painful perineal sutures, and tingling of fingers and toes but not with PPD [12]. In contrast, several subsequent studies found that anemia and/or iron deficiency were associated with increased symptoms of postpartum blues and depression [8, 13–15]. Although postpartum depression was assessed in most of these studies by the Edinburgh Postnatal Depression Scale (EPDS) [16], differences in iron measures make direct comparisons difficult. Some

studies focused on anemia [12–14], while others considered iron deficiency anemia (low Hb and at least two other iron deficiency parameters) [8] or iron deficiency based on low ferritin concentration [15]. Furthermore, relations between iron status and postpartum depression were analyzed in disparate ways. Some studies compared depressive symptoms in women with low versus high iron status [8, 14] others compared iron status in women with and without PPD symptoms [15]. Studies also differed in when maternal iron status was assessed, for example, during pregnancy, at delivery, or postpartum (see Table 1).

The purpose of this study was to assess the relationship between prenatal and postnatal maternal iron status and depressed mood. We hypothesized that lower maternal iron status would be associated with more maternal postpartum symptoms of depression.

2. Materials and Methods

This observational study was conducted in two phases: pilot and confirmatory. Both phases used data from ongoing longitudinal studies in China of developmental effects of iron deficiency in early life (supported by US NIH P01 HD39386 and R01 HD52069, B. Lozoff, Principal Investigator), one of which is conducted in conjunction with a study of iron supplementation in pregnancy (supported by a grant from Vifor Pharma, G. Zhao, Principal Investigator). The pilot sample consisted of 137 mothers from a rural area in Zhejiang province, in southeastern China. Because this sample was relatively small and Hb was the only measure of maternal iron status, we added a confirmatory sample with large n and a full panel of measures of maternal iron status. The confirmatory sample consisted of 567 mothers from a rural area in Hebei province in northern China. The studies were approved by the appropriate ethics committees of the University of Michigan and Children's Hospital Zhejiang University School of Medicine or Peking University First Hospital. Signed informed consent was obtained at enrollment.

2.1. Participants and Data Collected. Recruitment in both pilot and confirmatory studies was based on convenience samples. The participants were healthy pregnant women, 18 years or older, with a singleton pregnancy and no major complications. Women in the pilot sample were recruited during a routine prenatal visit at about 36 weeks of gestation at Fuyang Women and Children's Hospital, from May 2008 to January 2011. Hb concentrations in early and late pregnancy were obtained by chart review. To have conditions similar to the pilot sample, the confirmatory sample was drawn from the no-iron supplementation arm of an ongoing randomized clinical trial of supplementing women with folic acid with or without iron during pregnancy. Women were recruited at the initial prenatal visit between 13 and 20 weeks of gestation at Sanhe City Maternity and Child Health Institute, from November 2009 to November 2011. A complete blood count, ZPP (zinc protoporphyrin), serum ferritin, and sTfR (soluble transferrin receptor) were assessed. sTfR Index was calculated by dividing sTfR values (nmol/L) by the $\log_{10}$ of the ferritin concentration (ng/mL) [17, 18]. Maternal iron status was evaluated again in late pregnancy at about 36 weeks of gestation. For a subset of the confirmatory sample, Hb and MCV concentrations at 3 days postpartum were available from chart review. Anemia was defined as Hb < 110 g/L [2, 19], and high values of sTfR Index were considered indicative of iron deficiency. A sTfR Index cutoff point of 14 was used as recommended by the manufacture for clinical populations (>80% sensitivity and specificity; Beckman Coulter) [18]. In both studies, health providers used routine clinical practices for treating anemia in pregnancy, such as recommending increased dietary iron intake and iron supplements. In keeping with common practice in China [20–22], over 60% of births in both samples were by elective Caesarian section.

In both samples, depressive symptoms were assessed at 6 weeks postpartum using a Chinese version of the Edinburgh Postnatal Depression Scale (EPDS) [23]. The EPDS is a 10-item self-report scale widely used to screen for PPD [16]. The tester gave the instructions to the mother and made sure the mother understand them before filling out the form. If the mother requested, the tester read the questions and/or explained them to her. Similar to previous studies, a total score of 10 or higher was considered as probable PPD [15, 23, 24]. In the confirmatory sample, the EPDS was also administered 24–48 hours postpartum. Reliability analysis of the EPDS (internal consistency) yielded Cronbach's α of 0.71 in the pilot study and 0.79 shortly after delivery and 0.78 at 6 weeks in the confirmatory study.

2.2. Statistical Analysis. Background characteristics, Hb concentrations, and EPDS scores were compared in the pilot and confirmatory samples using t-tests for continuous variables and Fisher's exact analyses for categorical variables. Repeated measures analyses of variance were used to compare iron status in early/mid- and late-pregnancy and 3 days postpartum in each sample and EPDS score at 24–48 hours and 6 weeks after delivery in the confirmatory sample.

Correlations between iron measures and EPDS scores were performed for each sample. Given that EPDS and several iron measures were not normally distributed, nonparametric correlations were used (Spearman's rho). EPDS total scores were compared in anemic and nonanemic women.

To evaluate the possibility that maternal depression contributed to iron deficiency, we compared iron measures in PPD (EPDS score $\geq$ 10) and non-PPD women (EPDS score < 10). We repeated the analysis of an EPDS total score of 12 or higher since cutoffs of 10 or 12 have been reported in previous studies [24]. General linear model (GLM) analyses were used to assess the effects controlling for covariates. To evaluate potential covariates, the relations between each background characteristic and iron status and EPDS scores were evaluated using correlations for continuous variables and Chi-square analyses for categorical variables. In the pilot sample, potentially confounding variables were considered in the initial models if they were

Table 1: Summary of studies on maternal iron status and postpartum depression.

Country, year	Study design	Iron status measures and timing	Postpartum depression measures and timing	Findings
UK, 1994 [12]	Observational	pre- and postnatal Hb ($n = 1010$)	EPDS: 10 d, 4 wk, 6 wk	No relationship
Germany, 1995 [13]	Intervational	Postnatal: anemic treated by placebo ($n = 36$) versus anemic treated by rhEPO[a] ($n = 35$) versus nonanemic ($n = 274$)	blues questionnaire and SCL-90-R: 5 d	Depressive symptoms: anemic > nonanemic anemic: placebo = rhEPO
US, 2003 [14]	Observational	Postnatal Hb: anemic ($n = 8$) versus nonanemic ($n = 29$)	CES-D: 28 d	depressive symptoms: anemic > nonanemic
S. Africa, 2005 [8]	Intervational	Postnatal: Hb, MCV, ferritin, sTfR IDA treated by placebo ($n = 21$) versus IDA treated by iron ($n = 30$) versus nonanemic ($n = 30$)	EPDS: 10 wk, 9 mo	depressive symptoms: IDA + iron: 10 w > 9 mo IDA + placebo: 10 wk = 9 mo
Spain, 2011 [15]	Observational	Postnatal: ferritin, transferrin, iron, sTfR	EPDS: 2 d, 8 wk, 32 wk Women with PPD at 32 wk ($n = 65$) versus non-PPD ($n = 664$)	Ferritin concentration: PPD < non-PPD

[a] rhEPO : recombinanthumanerythropoietin.

Table 2: Background characteristics of the two samples in China[a].

	Sample		
	Pilot ($n = 137$)	Confirmatory ($n = 567$)	P[b]
Mother and family			
Mother age, years	27.0 ± 2.9	24.6 ± 3.7	<0.001
Mother high school graduate % (n)	66.2 (90/136)	31.5 (174/552)	<0.001
Annual household income % (n)			<0.001
<5000, ¥[c]	46.5 (59/127)	87.1 (481/552)	
>5000, ¥	53.5 (68/127)	12.9 (71/552)	
Infant			
Gender, %male (n)	53.3 (73/137)	54.5 (305/560)	0.44
Gestational age, weeks	39.6 ± 0.9	39.7 ± 1.2	0.36
Birth weight, g	3420.1 ± 452.8	3375.6 ± 426.4	0.28

[a]n varies slightly due to occasional missing data for some measures. Values are expressed as means ± SD or % (n) for categorical variables.
[b]P values are based on t-tests for continuous variables and Fisher's exact analyses for categorical variables.
[c]Yuan Renminbi, sign ¥, is the official currency of China. Approximate exchange rate 1\$ = 6.31¥.

Table 3: Maternal iron status in the confirmatory sample (mid- and late pregnancy, 3 days postpartum).

Iron measure	Mid pregnancy ($n = 567$)[a]	Late pregnancy ($n = 557$)[b]	3 days postpartum ($n = 265$)
Hemoglobin, g/L	121.5 ± 9.8	114.7 ± 9.9	104.2 ± 11.2[c]
MCV, fl	85.1 ± 4.8	84.8 ± 4.7	78.9 ± 8.3[d]
ZPP, μmol/mol	54.9 ± 31.6	88.4 ± 44.2[e]	—
Ferritin, ng/mL	41.9 ± 35.3	14.1 ± 13.8[e]	—
sTfR, nmol/L	15.6 ± 5.3	30.6 ± 10.7[e]	—
sTfR Index	11.6 ± 7.4	31.9 ± 17.0[e]	

[a]ZPP values were available for 330 subjects.
[b]ZPP values were available for 452 subjects, ferritin and sTfR for 543 subjects.
[c]Significant differences were found between the 3 measures, $P < 0.001$.
[d]Significant differences were found between the 3 measures: mid pregnancy compared to late pregnancy, $P < 0.05$; mid pregnancy and late pregnancy compared to postpartum, $P < 0.001$.
[e]Significant differences were found between the 2 measures, $P < 0.001$.

Table 4: EPDS total scores in anemic and nonanemic mothers[a].

	Pilot sample			Confirmatory sample		
	Anemic	Non-anemic	P	Anemic	Non-anemic	P[b]
Early/mid pregnancy						
EPDS scale, 24–48 h				($n = 72$)	($n = 483$)	
				6.4 ± 4.1	6.6 ± 4.3	0.43[c]
EPDS scale, 6 wk	($n = 12$)	($n = 125$)		($n = 71$)	($n = 417$)	
	7.9 ± 6.1	7.4 ± 3.4	0.69	5.7 ± 4.4	6.4 ± 4.1	0.16
Late pregnancy						
EPDS scale, 24–48 h				($n = 181$)	($n = 366$)	
				7.0 ± 4.1	6.3 ± 4.3	0.10
EPDS scale, 6 wk	($n = 54$)	($n = 81$)		($n = 165$)	($n = 315$)	
	7.7 ± 4.1	7.2 ± 3.4	0.51	6.6 ± 4.3	6.1 ± 4.0	0.26
3 days postpartum						
EPDS scale, 24–48 h				($n = 140$)	($n = 124$)	
				7.2 ± 3.9	7.2 ± 4.1	0.48
EPDS scale, 6 wk				($n = 130$)	($n = 118$)	
				5.9 ± 4.0	6.4 ± 4.0	0.40

[a]Values are unadjusted means ± SD.
[b]P values are based on GLM analyses with covariate control as indicated.
[c]Maternal education was a significant covariate.

Table 5: Iron status in mothers with possible PPD and non-PPD in the confirmatory sample[a].

EPDS	24–48 hours			6 weeks		
	Possible PPD	Non-PPD	P[b]	Possible PPD	Non-PPD	P[b]
Mid pregnancy	(n = 136)	(n = 418)		(n = 99)	(n = 389)	
Hemoglobin g/L	121.2 ± 9.5	121.5 ± 9.9	0.76	120.5 ± 9.6	121.3 ± 10.3	0.49
MCV, fl	85.2 ± 3.6	85.1 ± 5.1	0.77	85.6 ± 3.5	85.1 ± 5.2	0.41
ZPP, μmol mol[c]	58.5 ± 39.9	54.2 ± 29.2	0.41[d]	61.0 ± 42.7	56.5 ± 29.8	0.32
Ferritin, ng/mL	41.4 ± 32.5	41.5 ± 35.8	0.84[e]	43.7 ± 30.9	42.9 ± 36.9	0.83[e]
sTfR, nmol/L	15.4 ± 4.6	15.7 ± 5.5	0.52[d–g]	14.3 ± 3.8	15.9 ± 5.7	0.02[e–g,i]
sTfR Index	11.8 ± 8.2	11.8 ± 7.7	0.82[f,g]	10.5 ± 6.5	11.9 ± 7.8	0.12[g]
Late pregnancy	(n = 134)	(n = 413)		(n = 96)	(n = 384)	
Hemoglobin g/L	113.9 ± 9.7	115.0 ± 10.0	0.27[e]	114.0 ± 9.2	114.4 ± 10.0	0.73
MCV, fl	84.6 ± 3.9	84.9 ± 4.9	0.56	85.4 ± 3.8	84.7 ± 4.8	0.15
ZPP, μmol mol[c]	88.4 ± 41.1	88.5 ± 45.4	0.98	91.1 ± 47.8	91.9 ± 44.9	0.89
Ferritin, ng/mL	14.8 ± 16.5	13.7 ± 12.8	0.61	14.3 ± 11.3	14.0 ± 14.6	0.87
sTfR, nmol/L	29.4 ± 9.7	31.0 ± 10.9	0.11	30.0 ± 10.2	30.9 ± 10.8	0.50
sTfR Index	30.2 ± 14.4	32.5 ± 17.9	0.20	31.6 ± 16.9	32.3 ± 17.5	0.72
3-days postpartum	(n = 69)	(n = 195)		(n = 44)	(n = 204)	
Hemoglobin g/L	103.3 ± 12.2	104.6 ± 10.8	0.62[e]	103.5 ± 11.2	104.5 ± 11.4	0.51[e]
MCV, fl	77.6 ± 11.7	79.3 ± 6.7	0.07[h]	77.2 ± 12.0	79.4 ± 6.6	0.09[h]

[a]n varies slightly due to occasional missing data for some measures. Values are unadjusted means ± SD.
[b]P values are based on GLM analyses controlling for significant covariates as indicated by d–h.
[c]At 24–48 hours, ZPP values in mid pregnancy are available for 330 subjects, 70 possible PPD and 250 non-PPD, and for late pregnancy are available for 442 subjects, 101 possible PPD and 341 non-PPD. At 6 weeks, ZPP values in mid pregnancy are available for 268 subjects, 60 possible PPD and 208 non-PPD, and for late pregnancy are available for 378 subjects, 78 possible PPD, and 300 non-PPD.
[d]Maternal education, [e]birth weight, [f]maternal age, [g]gestational age, and [h]annual income were significant covariates.
[i]Note that the direction of effect is higher sTfR (worse iron status) in the non-PPD group.

even weakly related to either maternal iron status or EPDS score ($P < 0.10$). Due to the large sample size in the confirmatory sample, background variables were considered as potential covariates if $r \geq 0.10$ and $P < 0.05$. Analyses within a sample were conducted in SPSS 19.0 (SPSS, Chicago, IL, USA); comparisons between samples used GraphPad QuickCalc software (GraphPad, La Jolla, CA, USA).

3. Results and Discussion

In the pilot sample, 137 participants had Hb from chart review and EPDS at 6 weeks postpartum. One woman who was severely anemic at both assessments (Hb < 70 g/L) was not included. In the confirmatory sample, 567 women had a complete assessment of iron status at mid pregnancy. Almost all (98%, 557/567) also had a second iron status assessment at late pregnancy. One woman with Hb concentrations >250 g/L was not included. ZPP concentrations were available for 330 women at mid pregnancy and 452 at late pregnancy. For 265 women, Hb and MCV concentrations at 3 days postpartum were available by chart review.

Background characteristics of the pilot and confirmatory samples are presented in Table 2. Infant characteristics were similar in the two samples. Women in the pilot sample were older (2.4 years), more educated (34.7% more high school graduated), and had higher annual income (40.6% more with income >5000¥) compared to the confirmatory sample. Hb concentrations in late pregnancy were similar in the pilot and confirmatory samples ($t_{(691)} = 1.5$, $P = 0.13$). As expected, a reduction in iron status was observed during pregnancy. In both samples, Hb concentrations decreased and percentage of anemia increased in late pregnancy. In the pilot sample, Hb concentrations were significantly higher (paired $t_{(134)} = 8.6$, $P < 0.001$) at early pregnancy (124.8 ± 10.9 g/L) compared to late pregnancy (113.2 ± 12.2 g/L). The percentage of anemic mothers in late pregnancy (54/135; 40%) was more than 4 times higher than in early pregnancy (12/137; 9%). We considered it highly likely that most anemia in late pregnancy in the pilot sample was due to iron deficiency, because a prior study of over 3500 pregnant women in the same rural area in China found that 87% of those with Hb < 110 g/L had ferritin < 20 ng/mL [25]. In the confirmatory sample, iron status measures at the first assessment correlated with those in late pregnancy and 3 days postpartum (rs ranging from 0.26 to 0.55, P values < 0.001). The proportion of women with anemia increased from 13% at the first assessment (74/567) to 33% in late pregnancy (186/557) and 53% after delivery (141/265). As indicated by sTfR Index >14, 30% of the anemic women were iron deficient in mid pregnancy whereas 93% were iron deficient in late pregnancy. Other iron measures in the confirmatory sample also indicated poorer iron status in late pregnancy and after delivery (Table 3). The prevalence of anemia among pregnant women in our study is similar to previous reports among pregnant women in China [2, 19].

In the pilot sample, the mean total EPDS score at 6 weeks was 7.4 ± 3.7, and the proportion of women with

a total score ≥10, suggesting PPD, was 23.4% (32/137). In the confirmatory sample, EPDS data were available for 555 women at 24–28 hours after delivery; 488 had EPDS data at 6 weeks postpartum. The mean EPDS scores were similar at 24–48 hours and 6 weeks (6.7 ± 4.3 and 6.4 ± 4.1, respectively, paired $t_{(474)} = 1.5$, $P = 0.13$). The proportion of women with possible PPD was also similar (24.5% (136/555) at 24–48 hours and 20.3% (99/488) at 6 weeks (Fisher's exact test $P = 0.06$). Although the mean EPDS score in both samples was well below the cutoff for possible PPD, scores were somewhat higher in the pilot sample compared to the confirmatory sample (7.4 ± 3.7 and 6.3 ± 4.1, respectively, $t_{(623)} = 2.9$, $P < 0.01$). The proportion of women with possible PPD was similar in both samples (Fisher's exact test $P = 0.48$). The prevalence of PPD in Chinese women has ranged from 5.5% to 25.0% in previous studies, with the exception of higher prevalence among women exposed to domestic violence [23, 26–30]. The wide range appears related to background and methodological characteristics, such as socioeconomic status and education, social support, the questionnaire and timeframe used to measure postpartum depression, and severity of depression [24]. Using EPDS with a cutoff score of 10, the percentage of PPD in our study (20–23%) is within the range in other studies with Chinese women.

EPDS scores in anemic and nonanemic women did not differ in either sample (Table 4). Furthermore, maternal iron status showed no correlation with EPDS score in either the pilot or confirmatory sample. In the pilot sample, the r values between maternal Hb and EPDS at 6 weeks were $r = 0.07$ and $r = -0.01$ for early and late pregnancy Hb, respectively. In the confirmatory sample, the correlations between iron measures (Hb, MCV, ZPP, ferritin, sTfR, and sTfR Index) in mid- or late pregnancy or 3 days postpartum and EPDS scores shortly after delivery or at 6 weeks were also low (r values < 0.10). Even in this large sample, no correlation reached statistical significance with the exception of sTfR at mid and late pregnancy and EPDS at 6 weeks ($rs = -0.11$, $P = 0.02$). The direction of the effect, that is, higher sTfR (worse iron status) related to lower depressive symptoms, was opposite from what would be expected.

These negative findings regarding prenatal and postpartum maternal iron status and PPD do not support a previous study linking PPD and postpartum maternal iron status as a risk factor for maternal functioning during the postpartum period [8]. The small sample size in that study might limit reproducibility of results. However, its strong treatment design provides compelling evidence of an effect of iron therapy on maternal functioning. The observational nature of our study might explain in part the differing findings.

Women with or without possible PPD were similar in iron status in both Chinese samples. In the pilot sample, Hb concentrations in PPD (EPDS > 10) and non-PPD (EPDS ≤ 10) women averaged 124.6 ± 8.9 g/L versus 125.4 ± 11.8 g/L in early pregnancy ($F_{(1,137)} = 0.03$, $P = 0.85$; infant gender was a significant covariate) and 110.2 ± 9.5 g/L and 114.0 ± 12.8 g/L in late pregnancy ($F_{(1,132)} = 2.02$, $P = 0.16$; maternal education was a significant covariate). Iron status measures in possible PPD and non-PPD women in the confirmatory sample are compared in Table 5. The findings were the same with an EPDS cutoff of 12 (data not shown). Our findings do not support previous findings of lower ferritin concentrations in women with PPD compared to controls [15]. The higher prevalence of depression in our samples compared to the previous study (>20% versus 10%) might contribute to the different results.

4. Conclusions

There were no relations between maternal iron status and maternal symptoms of postpartum depression in two independent samples from different regions of China. These negative findings are similar to results in one other large observational study [12] but differ from several studies that found an association [8, 13–15]. There are no obvious or consistent differences between our study and, previous ones in study design, timing, and measures of iron status or PPD. Moreover, the severity of anemia and the prevalence of PPD in our study are generally comparable to others. Thus, we could not identify likely reasons for the negative findings in our study, in contrast to positive findings in others. Turning to studies of iron status and depressive symptoms in women of reproductive age more broadly, methodological differences limit direct comparisons with our study. Prior studies are heterogeneous in design. About half were observational and half were interventional. Some focused on pregnant women and others on nonpregnant women. The majority of the studies were conducted in developing countries, and a variety of iron measures were used. Although several studies reported an association between iron status and depressive symptoms, some did not (see Table 1 and a review [31]). Our large study in China adds to the group of studies finding no relationship between women's iron status and depressive symptoms. Further research is needed to determine why iron status relates to depressive symptoms in some contexts but not others.

Abbreviations

Hb: Hemoglobin
MCV: Mean corpuscular volume
ZPP: Zinc protoporphyrin
PPD: Postpartum depression
EPDS: Edinburgh Postnatal Depression Scale
sTfR: Soluble transferrin receptor
sTfR Index: soluble transferrin receptor/log ferritin index.

Acknowledgments

This paper is supported by grants from the US National Institutes of Health (Eunice Kennedy Shriver National Institute of Child Health and Human Development (P01 HD39386 and R01 HD52069, B. Lozoff, Principal Investigator) and the Office of Dietary Supplements (R01 HD52069)), and Vifor Pharma, Switzerland (G. Zhao, Principal Investigator). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National

Institutes of Health. The authors are grateful to the mothers who participated in the study and Liqin Chen for assessment of ferritin concentrations in the pilot sample.

References

[1] R. J. Stoltzfus, "Defining iron-deficiency anemia in public health terms: a time for reflection," *Journal of Nutrition*, vol. 131, no. 2, pp. 565S–567S, 2001.

[2] World Health Organization, *Worldwide Prevalence of Anaemia 1993–2005: WHO Global Database on Anaemia*, WHO, Geneva, Switzerland, 2008.

[3] A. J. Patterson, W. J. Brown, J. R. Powers, and D. C. K. Roberts, "Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health," *Quality of Life Research*, vol. 9, no. 5, pp. 491–497, 2000.

[4] A. J. Patterson, W. J. Brown, and D. C. K. Roberts, "Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Australian women of childbearing age," *Journal of the American College of Nutrition*, vol. 20, no. 4, pp. 337–342, 2001.

[5] M. A. Grondin, M. Ruivard, A. Perrève et al., "Prevalence of iron deficiency and health-related quality of life among female students," *Journal of the American College of Nutrition*, vol. 27, no. 2, pp. 337–341, 2008.

[6] J. A. Groner, N. A. Holtzman, E. Charney, and E. D. Mellits, "A randomized trial of oral iron on tests of short-term memory and attention span in young pregnant women," *Journal of Adolescent Health Care*, vol. 7, no. 1, pp. 44–48, 1986.

[7] A. B. Bruner, A. Joffe, A. K. Duggan, J. F. Casella, and J. Brandt, "Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls," *The Lancet*, vol. 348, no. 9033, pp. 992–996, 1996.

[8] J. L. Beard, M. K. Hendricks, E. M. Perez et al., "Maternal iron deficiency anemia affects postpartum emotions and cognition," *Journal of Nutrition*, vol. 135, no. 2, pp. 267–272, 2005.

[9] L. E. Murray-Kolb and J. L. Beard, "Iron treatment normalizes cognitive functioning in young women," *American Journal of Clinical Nutrition*, vol. 85, no. 3, pp. 778–787, 2007.

[10] M. V. Shariatpanaahi, Z. V. Shariatpanaahi, M. Moshtaaghi, S. H. Shahbaazi, and A. Abadi, "The relationship between depression and serum ferritin level," *European Journal of Clinical Nutrition*, vol. 61, no. 4, pp. 532–535, 2007.

[11] L. E. Murray-Kolb and J. L. Beard, "Iron deficiency and child and maternal health," *American Journal of Clinical Nutrition*, vol. 89, no. 3, pp. 946S–950S, 2009.

[12] J. A. Paterson, J. Davis, M. Gregory et al., "A study on the effects of low haemoglobin on postnatal women," *Midwifery*, vol. 10, no. 2, pp. 77–86, 1994.

[13] J. W. Meyer, K. H. Eichorn, K. Vetter et al., "Does recombinant human erythropoietin not only treat anemia but reduce postpartum (emotional) distress as well?" *Journal of Perinatal Medicine*, vol. 23, no. 1-2, pp. 99–109, 1995.

[14] E. J. Corwin, L. E. Murray-Kolb, and J. L. Beard, "Low hemoglobin level is a risk factor for postpartum depression," *Journal of Nutrition*, vol. 133, no. 12, pp. 4139–4142, 2003.

[15] G. Albacar, T. Sans, R. Martín-Santos et al., "An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression," *Journal of Affective Disorders*, vol. 131, no. 1–3, pp. 136–142, 2011.

[16] J. L. Cox, J. M. Holden, and R. Sagovsky, "Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale," *British Journal of Psychiatry*, vol. 150, pp. 782–786, 1987.

[17] T. Walsh, S. D. O'Broin, S. Cooley et al., "Laboratory assessment of iron status in pregnancy," *Clinical Chemistry and Laboratory Medicine*, vol. 49, no. 7, pp. 1225–1230, 2011.

[18] B. S. Skikne, K. Punnonen, P. H. Caldron et al., "Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index," *American Journal of Hematology*, vol. 86, pp. 923–927, 2011.

[19] L. Jin, L. F. Yeung, M. E. Cogswell et al., "Prevalence of anaemia among pregnant women in south-east China, 1993–2005," *Public Health Nutrition*, vol. 13, no. 10, pp. 1511–1518, 2010.

[20] J. Zhang, Y. Liu, S. Meikle, J. Zheng, W. Sun, and Z. Li, "Cesarean delivery on maternal request in southeast China," *Obstetrics and Gynecology*, vol. 111, no. 5, pp. 1077–1082, 2008.

[21] P. Lumbiganon, M. Laopaiboon, A. M. Gülmezoglu et al., "Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08," *The Lancet*, vol. 375, no. 9713, pp. 490–499, 2010.

[22] C. Qin, M. Zhou, W. M. Callaghan et al., "Clinical indications and determinants of the rise of Cesarean section in three hospitals in rural China," *Maternal and Child Health Journal*, in press.

[23] D. T. S. Lee, S. K. Yip, H. F. K. Chiu et al., "Detecting postnatal depression in Chinese women. Validation of the Chinese version of the Edinburgh postnatal depression scale," *British Journal of Psychiatry*, vol. 172, pp. 433–437, 1998.

[24] P. Klainin and D. G. Arthur, "Postpartum depression in Asian cultures: a literature review," *International Journal of Nursing Studies*, vol. 46, no. 10, pp. 1355–1373, 2009.

[25] J. Shao, J. Lou, J. Zhan et al., "Maternal-neonate iron status in over 3,500 Chinese infants," Platform Presentation, Pediatric Academic Societies Meeting E-PAS, 4140.1, Vancouver, Canada, 2010.

[26] W. C. Leung, F. Kung, J. Lam, T. W. Leung, and P. C. Ho, "Domestic violence and postnatal depression in a Chinese community," *International Journal of Gynecology and Obstetrics*, vol. 79, no. 2, pp. 159–166, 2002.

[27] L. L. Gao, S. W. C. Chan, and Q. Mao, "Depression, perceived stress, and social support among first-time Chinese mothers and fathers in the postpartum period," *Research in Nursing and Health*, vol. 32, no. 1, pp. 50–58, 2009.

[28] E. Y. Wan, C. A. Moyer, S. D. Harlow, Z. Fan, Y. Jie, and H. Yang, "Postpartum depression and traditional postpartum care in China: role of Zuoyuezi," *International Journal of Gynecology and Obstetrics*, vol. 104, no. 3, pp. 209–213, 2009.

[29] R. H. Xie, G. He, D. Koszycki, M. Walker, and S. W. Wen, "Prenatal social support, postnatal social support, and postpartum depression," *Annals of Epidemiology*, vol. 19, no. 9, pp. 637–643, 2009.

[30] Q. Mao, L. X. Zhu, and X. Y. Su, "A comparison of postnatal depression and related factors between Chinese new mothers and fathers," *Journal of Clinical Nursing*, vol. 20, no. 5-6, pp. 645–652, 2011.

[31] L. E. Murray-Kolb, "Iron status and neuropsychological consequences in women of reproductive age: what do we know and where are we headed?" *Journal of Nutrition*, vol. 141, no. 4, pp. 747S–755S, 2011.

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 514345, 8 pages
doi:10.1155/2012/514345

Review Article

Oral Iron Prophylaxis in Pregnancy: Not Too Little and Not Too Much!

Nils Milman

Department of Obstetrics, Næstved Hospital, DK-4700 Næstved, Denmark

Correspondence should be addressed to Nils Milman, nils.milman@webspeed.dk

Received 7 May 2012; Accepted 8 June 2012

Academic Editor: Alexander Krafft

An adequate supply of iron is essential for normal development of the fetus and newborn child. Iron deficiency and iron deficiency anemia (IDA) during pregnancy increase the risk of preterm birth and low birth weight. Iron is important for development of the fetal brain and cognitive abilities of the newborn. Children born to iron-deficient mothers will start their lives suffering from iron deficiency or even IDA. Oral iron prophylaxis to pregnant women improves iron status and prevents development of IDA. The Danish National Board of Health has since 1992 recommended prophylactic oral iron supplements to all pregnant women and the currently advocated dose is 40–50 mg ferrous iron taken between meals from 10 weeks gestation to delivery. However, 30–40 mg ferrous iron is probably an adequate dose in most affluent societies. In developed countries, individual iron prophylaxis guided by iron status (serum ferritin) has physiological advantages compared to general iron prophylaxis. In contrast, in most developing countries, general iron prophylaxis is indicated, and higher doses of oral iron, for example, 60 mg ferrous iron or even more should be recommended, according to the present iron status situation in the specific populations of women of fertile age and pregnant women.

1. Introduction

In a global perspective, the most frequent nutritional insufficiency is definitely iron deficiency, which is encountered with a high prevalence in women of fertile age as well as in pregnant and postpartum women [1]. In many developing countries, iron deficiency anemia (IDA) in pregnancy is more the rule than the exception with a prevalence of approximately 52% [2]. In the prosperous western societies, the frequency of IDA is lower due to better nutrition, approximately 25% in pregnant women not taking iron supplements and less than 5% in women taking prophylactic iron supplements of 40–60 mg ferrous iron per day [3, 4]. The World Health Organization (WHO) estimates that the number of anemic pregnant women in the world is ~56 million and the majority of these women (75–80%) have IDA [2]. Of these women, ~7 million are residents in Europe and the Americas and the remaining 49 million in more or less developed countries. In Europe, the number of anemic pregnant women is ~2.5 million.

An adequate body iron status is, among other factors, a prerequisite for a normal and healthy gestation, a normal development of the fetus and a healthy newborn baby. Iron deficiency, even without IDA, reduces the cognitive abilities and physical performance in nonpregnant women [5, 6]. In pregnant women, IDA is associated with preterm delivery, low birth weight of the newborns [7] as well as iron deficiency in the newborns.

Furthermore, untreated iron deficiency and IDA in the third trimester strongly predisposes to postpartum iron deficiency and IDA [8], which are associated with decreased physical abilities and psychic disturbances including emotional instability, depression, stress, and reduced cognitive performance tests [9, 10].

1.1. Dietary Iron Intake Is Inadequate in the Majority of Pregnant Women. In gestation, the total demands for absorbed iron are approximately 1240 mg (Table 1). The demand for absorbed iron increase steadily during pregnancy from 0.8 mg/day in the initial 10 weeks of gestation to 7.5 mg/day in the last 10 weeks of gestation as shown in Figure 1. During the entire gestation period, the average demand for absorbed iron is 4.4 mg/day [11–13].

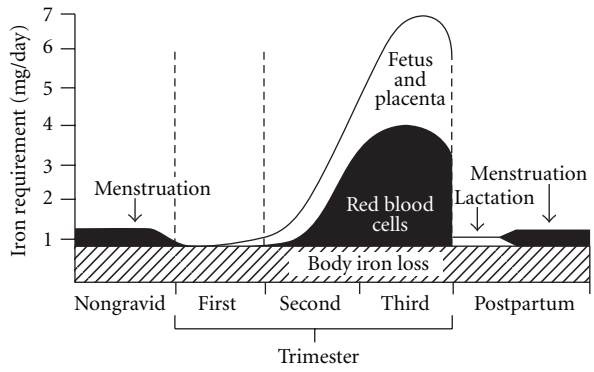


Figure 1: Requirements for absorbed iron in pregnant and lactating women; reproduced with permission [13].

Table 1: Iron balance in normal pregnancy and delivery, approximate figures.

Gross iron demands	
Obligatory iron loss (0.8 mg × 290 days)	230 mg
Increase in red cell mass	450 mg
Newborn baby (weight 3500 g)	270 mg
Placenta and umbilical cord	90 mg
Blood losses at delivery	200 mg
Total gross	1240 mg
Net iron demands	
Menostasia in pregnancy	−160 mg
Postpartum decrease in red cell mass	−450 mg
Total net iron demands	630 mg

Danish women of fertile age have a mean dietary iron intake of 9 mg/day, that is, the majority of the women (more than 90%) have an iron intake which is definitely below the recommended intake of 15–18 mg/day in women of fertile age [14].

In general, women do not make substantial changes in their dietary habits when they become pregnant. In a Norwegian dietary survey, more than 800 women were examined prior to pregnancy as well as in 17 and 33 weeks of gestation. Energy intake and the composition of the diet were similar before and during gestation. Mean energy intake was 8.9 MJ/day at the dietary assessments [15], which corresponds to the energy intake in nonpregnant Danish women. The average distributions of energy derived from protein, fat and carbohydrates were identical, 14, 36, and 50%, respectively. Mean dietary iron intake was 11 mg/day and below 18 mg/day in 96% of the women [15]. Pregnant women in the UK have a mean dietary iron intake of 10 mg/day [16] and pregnant Bavarian women a mean dietary iron intake of 13 mg/day [17], that is, far below the intake of 27–30 mg/day, which is recommended in Germany and USA.

Body iron balance and iron status are influenced by the magnitude of dietary iron intake in combination with the bioavailability of dietary iron. Generally, dietary iron intake is proportional with the energy intake. In the developing countries as well as in the western countries, almost all women have a dietary iron intake, which is inadequate to fulfill the body iron demands in the second and third trimester of pregnancy. The low dietary iron intake is partly due to a low intake of meat, poultry, and fish products and partly due to a low energy intake elicited by the sedentary lifestyle, which has become dominant in many western and some developing countries.

From a nutritional point of view, food iron exists in two main forms, heme iron and nonheme iron. The major part of dietary iron consists of nonheme iron. However, heme iron has a higher bioavailability than nonheme iron, it is more easily absorbed and therefore plays a major role in maintaining a favorable body iron status. Iron absorption is increased by consumption of food items with a high content of iron with a high bioavailability, for example, beef, pork, poultry, fish, and food items containing blood products. Besides heme iron, meat contains a promoter of nonheme iron absorption, the so-called "meat factor". Calf and pork liver have a high content of iron with a good bioavailability, but the Danish Health Authorities advise pregnant women not to consume pork liver and pork liver paté due to the high content of vitamin A, which possibly may cause malformations in the fetus [18]. In regions of the world where the diet is predominantly vegetarian and there is a high consumption of tea, for example, South East Asia, iron status in pregnant women is lower than in regions with a low intake of tea and a higher consumption of meat products (e.g., European countries) [2].

The absorption of iron is inhibited by calcium, which is most abundant in milk and milk products, by polyphenols in tea, coffee, and some wines and by phytates in cereal products, for example, bread. Even under the most favorable conditions, only 30% of dietary iron can be absorbed, corresponding to 3 mg iron/day with an iron intake of 9-10 mg/day, that is, considerably below the average daily iron requirements during pregnancy. In the average Danish diet the bioavailability of iron is approximately 18%. A higher dietary iron intake with a higher bioavailability would imply fundamental changes in nutritional patterns, and it is not realistic to assume that such changes can be implemented in pregnant women. In the Nordic countries, the Nordic Council of Ministers elaborates the common "Nordic Nutrition Recommendations". As a consequence of the fact that dietary iron content is inadequate to fulfil the need for iron in the majority of pregnant women, the Nordic guidelines refrain from giving exact recommendations for dietary iron intake during pregnancy [19]. As mentioned above some countries advocate a dietary iron intake of 27–30 mg/day in pregnancy.

2. Iron Prophylaxis in Pregnancy: A Confusing Situation

There is no consensus in the developed Western countries concerning iron prophylaxis to pregnant women. In fact, each country has their separate recommendation on this

issue. Some countries (e.g., Denmark) advocate iron prophylaxis, while others (e.g., UK, Norway) do not. Some countries (e.g., Germany) have not yet established national guidelines. The European Union in 1993 concluded that "the physiologic solution for covering the high iron requirements in pregnancy is to use iron from stores. The problem, however, is that very few women, if any, have sufficient iron stores of this magnitude, greater than 500 mg. Therefore, daily iron supplements are recommended in the latter half of pregnancy". The European Union sponsors the European Micronutrient Recommendations Aligned (EURRECA) with the intensions of harmonising nutrient recommendations across Europe with special focus on vulnerable groups, including pregnant women. The Nordic Nutrition Recommendations in 2004 stated that "an adequate iron balance during pregnancy demands body iron stores of at least 500 mg. The physiological need for iron in the second half of gestation cannot be covered by dietary intake of iron" [19].

2.1. Iron Is Important for Fetal Development. Iron is essential for a normal development of the fetus, and it is therefore crucial to prevent and avoid iron deficiency during the entire gestation period. A physiological and logical way to obtain this goal is to prevent (or treat if indicated) iron deficiency in the pregnant woman.

The fetus uses the major part of its iron supply to the synthesis of hemoglobin, but iron also plays an important role in the development of several vital organ systems, including the central nervous system where iron containing enzymes are involved in many metabolic processes. The growing brain has a demand for a balanced supply of iron across the blood-brain barrier [20]. In the fetus and newborn babies, iron deficiency may cause permanent damage to the brain, which negatively affects the intelligence, cognitive abilities and behavior during growth and later in life [21].

2.2. Iron Status in the Newborn. To a large extent, the newborn's iron status depends on the woman's iron status during pregnancy. Infants born to mothers who have taken iron supplements during gestation have larger body iron reserves (serum ferritin) than infants born to mothers who have taken placebo [3, 22].

Therefore, infants born to iron supplemented mothers have a smaller risk of developing iron deficiency and IDA in the first years of life [23]. Another factor, which is of importance for the newborn's iron status is the volume of blood, which is transferred from the placenta before the umbilical cord is clamped. In full-term neonates, delayed clamping for a minimum of two minutes following birth is beneficial for hematological status and iron status [24]. It increases the newborn's blood volume by approximately 30% and decreases the risk of iron deficiency during infancy [25].

2.3. Birth Weight Is Influenced by the Mothers Iron Status. Experiences from both developing and developed countries show that IDA in pregnant women increases the risk of preterm birth and low birth weight of the newborn [7, 26–28]. Pregnant Nepal-women, who took daily supplements of 60 mg ferrous iron and 0.4 mg folic acid from 11 weeks gestation gave birth to children with markedly higher birth weight than did non-supplemented women [28]. A study from USA in low-income women showed that IDA during pregnancy doubled the risk of preterm birth and tripled the risk of having a baby with low birth weight; a daily supplement of 65 mg ferrous iron reduced the frequency of preterm birth and low birth weight [7]. In another study, a daily supplement of 30 mg ferrous iron started before 20 weeks gestation induced higher birth weight of the newborn compared to non-supplemented women. These studies also point to the fact that iron supplements should be started in early pregnancy in order to obtain the best effects on the mother's course of gestation, on the development of the fetus and on the newborns birth weight.

3. Iron Supplements in Pregnancy—How Little is Enough?

In healthy women, serum ferritin is a reliable biomarker for mobilizable body iron reserves, that is, iron status. A ferritin concentration below 15–20 μg/L indicates the presence of iron depletion and iron deficiency. When in addition there is low hemoglobin, the criteria for IDA are substantial. Many studies have shown that pregnant women taking iron supplements have higher iron status and higher hemoglobin compared to women not taking supplements [3]. The differences in iron status are recognizable many months after the women have given childbirth [2]. Pregnant women who do not take iron supplements often present with iron deficiency and IDA and in European countries IDA is more frequent among immigrants from the Middle and Far East [29] than in ethnic Europeans.

In Scandinavia approximately 40% of nonpregnant women in the fertile age have a low iron status (i.e., serum ferritin <30 μg/L) and 4% have (unrecognized) IDA [14]. Among healthy ethnic Danish pregnant women, not taking iron supplements, 50% developed iron deficiency and 21% IDA, whereas among women taking 66 mg ferrous iron daily from 14 weeks gestation, 10% developed iron deficiency in late pregnancy but none displayed IDA [3].

Previously, the recommended doses of prophylactic iron supplements in pregnancy were quite high, about 100–200 mg ferrous iron daily [22]. Considering the potential side effects of iron it is important to define the smallest dose of iron, which is effective to fulfill the anticipated goals. A study of Danish pregnant women evaluated the effect of 20, 40, 60, and 80 mg ferrous iron daily from 18 weeks gestation to delivery. It appeared that a dose of 20 mg ferrous iron was inadequate to prevent iron deficiency in a substantial number of women. However, 40 mg ferrous iron prevented IDA in more than 95% of the women. Furthermore, there were no significant differences in iron status between women taking 40, 60, and 80 mg iron (Table 2) [4]. A study has compared the effect of prophylactic oral iron (ferrous sulphate 80 mg/day from ~22 weeks gestation) with prophylactic intravenous iron in repeated doses of 200 mg (iron sucrose total dose 400 or 600 mg). There was no

Table 2: Prevalence of iron deficiency and iron deficiency anemia during pregnancy in Danish women according to ferrous fumarate iron supplements taken between meals from 18 weeks gestation to delivery [4].

	Iron deficiency*			Iron deficiency anemia**		
Gestational week	18	32	39	18	32	39
n=	427 (%)	310 (%)	269 (%)	427 (%)	310 (%)	269 (%)
Ferrous iron (mg/day)						
20	6.1	50.0	28.8	0	1.3	10.0
40	9.0	26.0	11.1	1.9	1.3	4.5
60	6.9	16.9	10.0	0	0	0
80	10.8	13.2	9.0	0	0	1.5
P value***	NS	<0.0001	<0.01	NS	NS	0.02

* Serum ferritin <13 μg/L.
** Pregnancy: ferritin <13 μg/L and hemoglobin <106 g/L (week 18) <105 g/L (week 32) <115 g/L (week 39).
*** NS: nonsignificant.

clinically significant difference in hematological, maternal, and fetal outcomes in the oral iron group compared with the intravenous iron group. However, women taking oral iron had lower serum ferritin prior to delivery than women having 600 mg intravenous iron [30].

Could a daily multivitamin-multimineral supplement especially designed for pregnant women, which in Denmark contains 18–27 mg ferrous iron be used for iron prophylaxis? Unfortunately not, one study has shown that 72% of pregnant women taking a multivitamin-multimineral supplement containing 18 mg ferrous iron develop iron deficiency [31]. The absorption of iron from these tablets has not been adequately investigated but is probably low due to the absorptive interaction of iron with the other divalent metal ions contained in the tablets (zinc, copper, manganese, selenium, chromium, molybdenum, and sometimes calcium). Therefore it appears rational to administer iron supplements in separate tablets, which only contains iron.

During pregnancy, the oxidative stress increases to reach maximum levels at 14–24 weeks gestation [32, 33]. However, in an animal model, IDA *per se* was shown to increase oxidative stress levels in the organs and in placenta as well as hypoxia and inflammation in placenta [34]. However, daily iron supplements may also contribute to an increase in oxidative stress [35] and may induce damage to the intestinal epithelium due to high local concentrations of iron-generated free radicals.

Another concern associated with oral ferrous iron is the possible increase in the plasma concentration of the highly reactive nontransferrin bound iron. The increase in nontransferrin bound iron appears to be related to the iron dose and is most pronounced at high doses [36]. For these reasons the recommended dose of iron should be the smallest to be effective and should preferably be administered in a slow-release formula.

The daily diet contains a number of substances (e.g., calcium, polyphenols, phytates) that inhibit the absorption of iron by approximately 40% [37]. Consequently, ferrous iron supplements should be taken between meals, preferably with fruit juice containing vitamin C [38], which enhances absorption, whereas milk, coffee, and tea inhibit absorption.

4. Side Effects of Oral Iron Supplements

Among women it is a widespread opinion that ferrous iron tablets cause gastrointestinal discomfort. Gastrointestinal side-effects are dose dependent and usually encountered at ferrous iron doses above 100 mg/day [39]. However, controlled studies have shown that the frequencies of gastrointestinal symptoms in pregnant women taking 105 mg ferrous iron daily are not significantly different from women taking placebo [40]. Another study found no difference in gastrointestinal symptoms in pregnant women taking 80 versus 20 mg ferrous iron daily except a slightly higher frequency of constipation at the higher dose [4, 41].

Most ferrous iron formulas contain ferrous sulphate or ferrous fumarate. The iron chelate ferrous bisglycinate (Ferrochel) appears to be very well absorbed [42] and to have fewer gastrointestinal side effects than conventional ferrous iron salts. Also the oral ferric iron polymaltose complex (Maltofer) offers at least equivalent efficacy and a superior safety profile compared to ferrous sulfate for treatment of IDA during pregnancy [43]. Consequently, the anxiety for potential gastrointestinal discomfort does not seem to be justified as an argument against low-dose prophylactic iron supplementation to pregnant women.

4.1. Iron Prophylaxis: General or Individual? In developing countries with sparse health resources, iron prophylaxis in pregnancy should appropriately be recommended as a general prophylaxis given to all women. In developed counties, where ample health resources are available, the question of iron prophylaxis should focus on the advantages/disadvantages of general versus individual prophylaxis. General iron prophylaxis means that all pregnant women are recommended to take iron supplements irrespective of their iron status. Individual prophylaxis indicates that iron supplements are adjusted according to the woman's iron status. From a nutritional and physiological point of view, individual iron prophylaxis is preferable to general iron prophylaxis. Iron supplements may possibly decrease the absorption of other essential divalent metal ions, for example, zinc [44] and increase the oxidative stress both locally in the intestines and generally in the body [35, 45].

Ideally, the prophylactic iron dose should therefore be the lowest possible dose, which is sufficient to prevent iron deficiency and IDA, and this purpose is most adequately obtained by individual prophylaxis.

Iron status can be defined according to the serum ferritin concentration in otherwise healthy women without ongoing inflammation. By analysis of serum ferritin either shortly before pregnancy or in early pregnancy, it is possible to categorize women in three groups: (a) those with low iron status (ferritin <30 μg/L) who either already have or are in overt risk of developing iron deficiency and IDA; (b) those with intermediate iron status (ferritin 30–70 μg/L) and moderate risk of iron deficiency and IDA; (c) those with adequate iron status (ferritin >70–80 μg/L) with minimal or no risk of iron deficiency. Healthy pregnant women having ferritin above 70–80 μg/L appear to be in safe water concerning iron deficiency as their body iron reserves are 500 mg or more, which is adequate to complete a pregnancy without taking iron supplements [19].

Genetic hemochromatosis is a group of disorders/diseases, which are characterized by excessive body iron overload [46, 47]. In populations of northern European ancestry (Iceland, Norway, Sweden, Denmark, United Kingdom, Ireland, northern France, northern Germany) mutations on the *HFE* gene, which cause genetic hemochromatosis type 1 is the most frequent hereditary disorder with a recessive inheritance. In Denmark, 0.4% of the population is homozygotes and 11% are heterozygotes [46]. Homozygous and the majority of heterozygous women will certainly not benefit from iron supplements in a general supplementation program, on the contrary this may increase body iron load and aggravate their disorder.

5. General Iron Prophylaxis

In Denmark, the National Board of Health has since 1992 recommended general iron prophylaxis to pregnant women with 50–70 mg ferrous iron daily from 20 weeks gestation. This recommendation was based on the outcome of a Danish study of iron supplementation during pregnancy, which demonstrated that 66 mg of ferrous iron as fumarate taken between meals was capable of preventing iron deficiency, and IDA [3]. In 2008, according to the results of a subsequent Danish dose response study [4], the guidelines were adjusted towards a lower dose of 40–50 mg ferrous iron daily from 10 weeks gestation until delivery. It is advocated that the iron supplement should be taken separately between meals in order to ensure an optimum absorption. Danish standard multivitamin-multimineral tablets contain 10–14 mg ferrous iron per tablet, while those designed for pregnant women contain 18–27 mg iron. This iron is not included in the calculation of the total iron intake, because it probably is very poorly absorbed (see above) [31], due to competition with the other minerals [44] and components contained in multivitamin-multimineral tablets.

As a guideline, pregnant women in developed countries should be recommended 30–40 mg ferrous iron daily during pregnancy. Iron tablets designed specifically for pregnant women (GraviJern, Ferrosan—a part of Pfizer Inc., Denmark) contain 40 mg ferrous iron as fumarate in a slow release formulation.

In many developing countries, the prevalence of low iron status, iron deficiency, and IDA in women of fertile age and in pregnant women is considerably higher than in the Western countries [2] and consequently the prophylactic iron dose should be higher. The WHO guidelines have recommended that iron is provided to pregnant women during antenatal visits for daily supplementation of 60 mg elemental iron, for 6 months during pregnancy and three months postpartum [48]. Iron supplements of 60 mg ferrous iron daily appear sufficient to produce maximal hemoglobin response [49, 50] and appear to be adequate to prevent IDA in pregnant Danish women [3, 4] as shown in Table 2.

6. Individual Iron Prophylaxis

The serum ferritin concentration should be analyzed when pregnancy is planned or as early in pregnancy as possible, preferably within 10 weeks gestation. Each μg/L of ferritin indicates approximate mobilizable body iron reserves of 7–7.5 mg [51]. Multivitamin-multimineral tablets (preferably without iron) containing 0.4 mg folic acid should be recommended from the time pregnancy is planned.

(1) Ferritin above 70–80 μg/L (~20–25% of pregnant Danish women): body iron reserves are larger than 500 mg and iron supplements are not indicated. If ferritin is above 100–150 μg/L, consider to check for inflammation, kidney disease, liver disease, hereditary hemochromatosis, cancer.

(2) Ferritin in the range of 30–70 μg/L (~40% of women): iron reserves are 200–500 mg. Advocated iron supplements are 30–40 mg ferrous iron daily.

(3) Ferritin below 30 μg/L (~40% of women): iron reserves are small and depleted in those women having values below 15 μg/L: advocated iron supplements are 60–80 mg ferrous iron daily.

Individual iron prophylaxis has since 2002 been advocated by the Danish National Food Institute and since 2005 by the Danish Council of Nutrition. Both institutions conclude that iron supplements should be restricted to women with a clear demand for extra iron [11]. However, the Danish National Board of Health, having the final decisive authority, still needs to approve these recommendations. In Sweden, individual iron prophylaxis has been recommended by the Swedish Society for Obstetrics and Gynaecology since 2008 [52].

6.1. When Should the Women Start on Iron Supplements? Earlier recommendations advocated that the best time to start on prophylactic iron was at 20 weeks gestation. This limit was chosen according to the results of studies showing increasing iron absorption after 20 weeks gestation [53–55]. However, analysis of these reports shows that the majority of the examined women with increased iron absorption had marked iron deficiency! Pregnant women with adequate

iron reserves display a nearly "normal" iron absorption throughout pregnancy [53, 54]. Considering the significance of iron for the fetal brain development, course of pregnancy and birth weight of the newborn, low-dose iron prophylaxis should probably start when pregnancy is planned or as early in pregnancy as possible. In most countries recommending iron prophylaxis, this is initiated at the first visit to the antenatal care clinic, which may vary from 10 to 20 weeks gestation according to the structure of antenatal care in various countries. The Danish National Board of Health has recently changed their recommendation for starting iron prophylaxis from 20 to 10 weeks gestation.

7. What about Iron Supplements in the Lactation Period?

There are no prospective controlled studies concerning iron supplements postpartum. Therefore, in the lactation period, empirical solutions should be activated. In developing countries the WHO guidelines recommend that iron supplementation should be continued 12 weeks after partum [48]. If the woman has taken iron prophylaxis during pregnancy and presents an adequate iron status prior to childbirth and has small or normal blood losses at delivery, iron supplementation is hardly indicated in the lactation period. However, if the woman suffers peripartum blood losses greater than 400–500 mL or presents with acute bleeding anemia after delivery, her iron status should be checked and if low, oral iron treatment with 100 mg ferrous daily should be started and continued for at least 12 weeks after hemoglobin has increased to normal level [56].

If iron deficiency or IDA is present prior to delivery, it will definitely be aggravated postpartum due to blood losses. Therefore, high-dose oral iron treatment is indicated for a prolonged period, and intravenous iron therapy should be considered in women who do not respond adequately to oral iron within a couple of weeks [56].

8. Conclusion

In developing countries, a large fraction of women of fertile age have iron deficiency and IDA. Even in developed countries, this problem is substantial. Pregnancy induces extraordinary high demands for iron in order to increase maternal red blood cell mass and secure a normal development of the fetus. The iron demands cannot be fulfilled solely by dietary iron intake. Therefore, low-dose oral iron supplementation is indicated in the majority of pregnant women (e.g., 60 mg ferrous iron in developing and 30–40 mg in developed countries). In developing countries, general iron prophylaxis is most feasible, while in developed countries, individual iron prophylaxis should be considered. Prophylactic programs should be structured according to the iron status of women of fertile age in the specific regions/countries. In developed countries, even though there exits substantial evidence of the positive effects of iron supplements on so-called "soft values", that is, iron status and hematological status, there is only a small or no effect on the "hard values", that is, maternal and fetal outcome of pregnancy and delivery [50, 57]. This situation fuels the continuing discussion between the supporters and opponents of iron supplementation. However, for the benefit of pregnant women and their children, it is important that a common consensus will be reached in the near future.

9. Effects of Oral Iron Supplements

Beneficial

Pregnant women:

(i) lower prevalence of iron deficiency and IDA,
(ii) improved physical and psychical well-being.

Postpartum women:

(i) higher iron status at delivery,
(ii) lower prevalence of postpartum iron deficiency, and IDA due to peripartum blood losses.

Fetuses and newborns:

(i) beneficial for development of the brain and other organs,
(ii) lower frequency of premature birth,
(iii) decreased prevalence of low birth weight at term and low for gestational age birth weight.

Infants:

(i) larger body iron reserves at birth,
(ii) lower prevalence of iron deficiency and IDA in the initial 2 years of life.

Disadvantageous

Pregnant women:

(i) increased oxidative stress locally in the small intestines,
(ii) increased oxidative stress in the body in general,
(iii) increase in plasma nontransferrin bound iron,
(iv) gastrointestinal side effects at high iron doses,
(v) accelerated body iron overload in women with (nondiagnosed) genetic hemochromatosis.

References

[1] N. Milman, "Anemia—still a major health problem in many parts of the world!," *Annals of Hematology*, vol. 90, no. 4, pp. 369–377, 2011.

[2] World Health Organization, "Worldwide prevalence of anaemia 1993—2005," WHO Global Database on Anaemia, Switzerland, 2008, http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf.

[3] N. Milman, A. O. Agger, and O. J. Nielsen, "Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women," *Danish Medical Bulletin*, vol. 38, no. 6, pp. 471–476, 1991.

[4] N. Milman, T. Bergholt, L. Eriksen et al., "Iron prophylaxis during pregnancy - How much iron is needed? A randomized dose-response study of 20–80 mg ferrous iron daily in pregnant women," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 84, no. 3, pp. 238–247, 2005.

[5] A. B. Bruner, A. Joffe, A. K. Duggan, J. F. Casella, and J. Brandt, "Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls," *The Lancet*, vol. 348, no. 9033, pp. 992–996, 1996.

[6] T. W. Rowland, M. B. Deisroth, G. M. Green, and J. F. Kelleher, "The effect of iron therapy on the exercise capacity of nonanemic iron-deficient adolescent runners," *American Journal of Diseases of Children*, vol. 142, no. 2, pp. 165–169, 1988.

[7] M. E. Cogswell, I. Parvanta, L. Ickes, R. Yip, and G. M. Brittenham, "Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial," *American Journal of Clinical Nutrition*, vol. 78, no. 4, pp. 773–781, 2003.

[8] N. Milman, "Postpartum anemia I: definition, prevalence, causes, and consequences," *Annals of Hematology*, vol. 90, pp. 1247–1253, 2011.

[9] J. L. Beard, M. K. Hendricks, E. M. Perez et al., "Maternal iron deficiency anemia affects postpartum emotions and cognition," *Journal of Nutrition*, vol. 135, no. 2, pp. 267–272, 2005.

[10] E. J. Corwin, L. E. Murray-Kolb, and J. L. Beard, "Low hemoglobin level is a risk factor for postpartum depression," *Journal of Nutrition*, vol. 133, no. 12, pp. 4139–4142, 2003.

[11] N. Milman, "Iron and pregnancy—a delicate balance," *Annals of Hematology*, vol. 85, no. 9, pp. 559–565, 2006.

[12] World Health Organization, "Iron deficiency Anaemia: Assessment, prevention and control", WHO/NHD/01.3, 2001.

[13] T. H. Bothwell, "Iron requirements in pregnancy and strategies to meet them," *American Journal of Clinical Nutrition*, vol. 72, pp. 257S–264S, 2000.

[14] N. Milman, K. E. Byg, and L. Ovesen, "Iron status in Danes 1994: II: prevalence of iron deficiency and iron overload in 1319 Danish women aged 40–70 years. Influence of blood donation, alcohol intake and iron supplementation," *Annals of Hematology*, vol. 79, no. 11, pp. 612–621, 2000.

[15] K. Trygg, K. Lund-Larsen, B. Sandstad, H. J. Hoffman, G. Jacobsen, and L. S. Bakketeig, "Do pregnant smokers eat differently from pregnant non-smokers?" *Paediatric and Perinatal Epidemiology*, vol. 9, no. 3, pp. 307–319, 1995.

[16] N. A. Alwan, D. C. Greenwood, N. A. B. Simpson, H. J. McArdle, K. M. Godfrey, and J. E. Cade, "Dietary iron intake during early pregnancy and birth outcomes in a cohort of British women," *Human Reproduction*, vol. 26, no. 4, pp. 911–919, 2011.

[17] H. Hauner, C. Vollhardt, K. T. M. Schneider, A. Zimmermann, T. Schuster, and U. Amann-Gassner, "The impact of nutritional fatty acids during pregnancy and lactation on early human adipose tissue development: rationale and design of the INFAT study," *Annals of Nutrition and Metabolism*, vol. 54, no. 2, pp. 97–103, 2009.

[18] P. Mastroiacovo, T. Mazzone, A. Addis et al., "High vitamin A intake in early pregnancy and major malformations: a multicenter prospective controlled study," *Teratology*, vol. 59, pp. 7–11, 1999.

[19] Nordic Council of Ministers, *Nordic Nutrition Recommendations 2004*, Copenhagen, Denmark, 2004.

[20] J. Beard, "Iron deficiency alters brain development and functioning," *Journal of Nutrition*, vol. 133, pp. 1468S–1472S, 2003.

[21] S. Grantham-McGregor and C. Ani, "A review of studies on the effect of iron deficiency on cognitive development in children," *Journal of Nutrition*, vol. 131, supplement 2, pp. 649S–666S, 2001.

[22] N. Milman, "Iron prophylaxis in pregnancy—general or individual and in which dose?" *Annals of Hematology*, vol. 85, no. 12, pp. 821–828, 2006.

[23] K. F. Michaelsen, N. Milman, and G. Samuelson, "A longitudinal study of iron status in healthy Danish infants: effects of early iron status, growth velocity and dietary factors," *Acta Paediatrica, International Journal of Paediatrics*, vol. 84, no. 9, pp. 1035–1044, 1995.

[24] E. K. Hutton and E. S. Hassan, "Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials," *Journal of the American Medical Association*, vol. 297, no. 11, pp. 1241–1252, 2007.

[25] N. K. Møller and T. Weber, "Early vs delayed clamping of the umbilical cord in full term, preterm and very preterm infants," *Ugeskr Laeger*, vol. 170, pp. 1919–1921, 2008.

[26] L. H. Allen, "Anemia and iron deficiency: effects on pregnancy outcome," *American Journal of Clinical Nutrition*, vol. 71, pp. 1280S–1284S, 2000.

[27] K. M. Rasmussen and R. J. Stoltzfus, "New evidence that iron supplementation during pregnancy improves birth weight: new scientific questions," *The American Journal of Clinical Nutrition*, vol. 78, no. 4, pp. 673–674, 2003.

[28] U. Ramakrishnan, "Nutrition and low birth weight: from research to practice," *American Journal of Clinical Nutrition*, vol. 79, no. 1, pp. 17–21, 2004.

[29] M. Nybo, L. Friis-Hansen, P. Felding, and N. Milman, "Higher prevalence of anemia among pregnant immigrant women compared to pregnant ethnic Danish women," *Annals of Hematology*, vol. 86, no. 9, pp. 647–651, 2007.

[30] G. Bencaiova, U. von Mandach, and R. Zimmermann, "Iron prophylaxis in pregnancy: intravenous route versus oral route," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 144, no. 2, pp. 135–139, 2009.

[31] J. K. Thomsen, J. C. Prien-Larsen, A. Devantier, and N. Fogh-Andersen, "Low dose iron supplementation does not cover the need for iron during pregnancy," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 72, no. 2, pp. 93–98, 1993.

[32] M. Moretti, M. Phillips, A. Abouzeid, R. N. Cataneo, and J. Greenberg, "Increased breath markers of oxidative stress in normal pregnancy and in preeclampsia," *American Journal of Obstetrics and Gynecology*, vol. 190, no. 5, pp. 1184–1190, 2004.

[33] J. M. Morris, N. K. Gopaul, M. J. R. Endresen et al., "Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia," *British Journal of Obstetrics and Gynaecology*, vol. 105, no. 11, pp. 1195–1199, 1998.

[34] J. E. Toblli, G. Cao, L. Olivieri, and M. Angerosa, "Effects of iron deficiency anemia and its treatment with iron polymaltose complex in pregnant rats, their fetuses and placentas: oxidative stress markers and pregnancy outcome," *Placenta*, vol. 33, pp. 81–87, 2012.

[35] F. E. Viteri, E. Casanueva, M. C. Tolentino, J. Díaz-Francés, and A. B. Erazo, "Antenatal iron supplements consumed daily produce oxidative stress in contrast to weekly supplementation in Mexican non-anemic women," *Reproductive Toxicology*, vol. 34, no. 1, pp. 125–132, 2012.

[36] K. Schümann, S. Kroll, M. E. Romero-Abal et al., "Impact of oral iron challenges on circulating non-transferrin-bound iron in healthy Guatemalan males," *Annals of Nutrition and Metabolism*, vol. 60, pp. 98–107, 2012.

[37] L. Hallberg, L. Rossander, and A. B. Skaanberg, "Phytates and the inhibitory effect of bran on iron absorption in man," *American Journal of Clinical Nutrition*, vol. 45, no. 5, pp. 988–996, 1987.

[38] L. Hallberg, M. Brune, and L. Rossander, "Iron absorption in man: ascorbic acid and dose-dependent inhibition by phytate," *American Journal of Clinical Nutrition*, vol. 49, no. 1, pp. 140–144, 1989.

[39] L. Sölvell, "Oral iron therapy. Side effects," in *Iron Deficiency. Pathogenesis, Clinical Aspects, Therapy*, L. Hallberg, H.-G. Harwerth, and A. Vannotti, Eds., pp. 573–583, Academic, London, UK, 1970.

[40] D. S. Kerr and S. Davidson, "Gastrointestinal intolerance to oral iron preparations," *The Lancet*, vol. 272, no. 7045, pp. 489–492, 1958.

[41] N. Milman, K. E. Byg, T. Bergholt, and L. Eriksen, "Side effects of oral iron prophylaxis in pregnancy—myth or reality?" *Acta Haematologica*, vol. 115, no. 1-2, pp. 53–57, 2006.

[42] M. Layrisse, M. N. García-Casal, L. Solano et al., "Iron bioavailability in humans from breakfasts enriched with iron bis-glycine chelate, phytates and polyphenols," *Journal of Nutrition*, vol. 130, no. 9, pp. 2195–2199, 2000.

[43] R. Ortiz, J. E. Toblli, J. D. Romero et al., "Efficacy and safety of oral iron(III) polymaltose complex versus ferrous sulfate in pregnant women with iron-deficiency anemia: a multicenter, randomized, controlled study," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 24, pp. 1–6, 2011.

[44] M. Olivares, F. Pizarro, M. Ruz, and D. López de Romaña, "Acute inhibition of iron bioavailability by zinc: studies in humans," *Biometals*. In press.

[45] F. E. Viteri, E. Casanueva, M. C. Tolentino, J. Díaz-Francés, and A. B. Erazo, "Antenatal iron supplements consumed daily produce oxidative stress in contrast to weekly supplementation in Mexican non-anemic women," *Reproductive Toxicology*, vol. 34, no. 1, pp. 125–132, 2012.

[46] P. Pedersen, G. V. Melsen, and N. Milman, "Frequencies of the haemochromatosis gene (*HFE*) variants C282Y, H63D and S65C in 6,020 ethnic Danish men," *Annals of Hematology*, vol. 87, no. 9, pp. 735–740, 2008.

[47] A. Pietrangelo, "Non-HFE hepatic iron overload," *Seminars in Liver Disease*, vol. 31, pp. 302–318, 2011.

[48] R. Stoltzfus and M. Dreyfuss, ". Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia," The International Nutritional Anaemia Consultative Group, (INACG/WHO/UNICEF), Washington, DC, USA, 1998.

[49] E. C. Ekström, S. M. Z. Hyder, A. M. R. Chowdhury et al., "Efficacy and trial effectiveness of weekly and daily iron supplementation among pregnant women in rural Bangladesh: disentangling the issues," *American Journal of Clinical Nutrition*, vol. 76, no. 6, pp. 1392–1400, 2002.

[50] N. L. Sloan, E. Jordan, and B. Winikoff, "Effects of iron supplementation on maternal hematologic status in pregnancy," *American Journal of Public Health*, vol. 92, no. 2, pp. 288–293, 2002.

[51] G. O. Walters, F. M. Miller, and M. Worwood, "Serum ferritin concentration and iron stores in normal subjects," *Journal of Clinical Pathology*, vol. 26, no. 10, pp. 770–772, 1973.

[52] H. Strevens, H. Fadl, C. Weatergren, B. Knutson, and P. Ny, "A basic medical program in pregnant women," in *Antenatal Care, Sexual and Reproductive Health*, pp. 47–48, Stockholm, Sweden, 2008, Rapport nr 59.

[53] B. Svanberg, "Absorption of iron in pregnancy," *Acta Obstetricia et Gynecologica Scandinavica, Supplement*, vol. 48, pp. 87–108, 1975.

[54] H. C. Heinrich, H. Bartels, B. Heinisch et al., "Intestinale^{59}Feresorption und prälatenter eisenmangel während der gravidität des menschen," *Klinische Wochenschrift*, vol. 46, no. 4, pp. 199–202, 1968.

[55] J. F. R. Barrett, P. G. Whittaker, J. G. Williams, and T. Lind, "Absorption of non-haem iron from food during normal pregnancy," *British Medical Journal*, vol. 309, no. 6947, pp. 79–82, 1994.

[56] N. Milman, "Postpartum anemia II: prevention and treatment," *Annals of Hematology*, vol. 91, pp. 143–154, 2012.

[57] K. Mahomed, "Iron supplementation in pregnancy," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD000117, 2000.

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 454601, 7 pages
doi:10.1155/2012/454601

Review Article

Preventive Treatments of Iron Deficiency Anaemia in Pregnancy: A Review of Their Effectiveness and Implications for Health System Strengthening

Kayode O. Osungbade[1] and Adeolu O. Oladunjoye[2]

[1] *Department of Health Policy and Management, Faculty of Public Health, College of Medicine and University College Hospital, University of Ibadan, P.M.B. 5017 General Post Office, Ibadan, Nigeria*
[2] *Department of Community Medicine, University College Hospital, P.M.B. 5116 General Post Office, Ibadan, Nigeria*

Correspondence should be addressed to Kayode O. Osungbade, koosungbade@yahoo.com

Received 2 February 2012; Revised 1 May 2012; Accepted 21 May 2012

Academic Editor: Laura Murray-Kolb

Objectives. We conducted a review of effectiveness of preventive treatments of iron deficiency anaemia in pregnancy in developing countries and highlighted their constraints as well as interventions required to strengthen the health services. *Methods*. Literature from Pubmed (MEDLINE), AJOL, Google Scholar, and Cochrane database was reviewed. *Results*. Evidence-based preventive treatment options for iron deficiency anaemia in pregnancy include prophylaxis iron supplements and food fortification with iron. Evidence abounds on their effectiveness in reducing the prevalence of iron deficiency anaemia in pregnancy. However, these prospects are threatened by side effects of iron supplements, low utilization of maternal health service in developing countries, partial implementation of preventive treatments, and weak infrastructure and political commitment to implement mass fortification of local staple foods by national governments. *Conclusion*. Sustainability of effectiveness of preventive treatments of iron deficiency anaemia in pregnancy could be achieved if the identified threats are adequately addressed.

1. Introduction

Iron deficiency anaemia is defined as anaemia accompanied by depleted iron stores and signs of a compromised supply of iron to the tissues [1]. There is variation in haemoglobin levels during pregnancy; at the beginning of a pregnancy, there is a normal reduction in haemoglobin level followed by a slight rise towards the end of pregnancy [2]. The initial reduction has been explained to result from increased red cell mass and demands of the fetus which exceeds iron intake with consequent reduction in iron stores of the woman's body [2]. Thus, the World Health Organization has defined anaemia in pregnancy as a haemoglobin value below 11 g/dL [1, 3].

There are two known factors which contribute to development of iron deficiency anaemia (IDA) in pregnancy; the first is the woman's iron stores at the time of conception and the second is the amount of iron absorbed during gestation. The fact that anaemia frequently does occur in pregnancy among women in developing countries is an indication that preexisting iron stores are often inadequate and physiological adaptations to pregnancy are insufficient to meet the increased requirements [4]. Hence, iron supplementation in pregnancy has become a standard and routine practice as a preventive treatment for iron deficiency anaemia in pregnancy in developing countries. In view of the foregoing, a review of effectiveness of preventive treatments of iron deficiency anaemia in pregnancy was conducted; furthermore, constraints were highlighted and suggestions for improvement were provided.

2. Methods

We conducted a review of literature on evidence-based preventive treatments of iron deficiency anaemia in pregnancy with particular reference to developing countries. The following search terms were used: prevalence, burden, iron

Table 1: A list of randomised and quasi-randomised trials used for review.

	Study	Study site	Subject number	Study question	Study methods	Study outcome
(1)	Zamani et al., 2008 [8]	Iran	152 pregnant women	Twice weekly iron supplementation versus daily regimen	Randomised control trial	Haemoglobin concentration
(2)	Bencaiova et al., 2009 [25]	Switzerland	260 pregnant women	intravenous iron sucrose versus daily oral ferrous sulphate	Randomised control trial	Haemoglobin concentration; iron stores
(3)	Asibey-Berko et al., 2007 [29]	Ghana	184 women	Double-fortified salt versus weekly oral iron supplement versus weekly placebo	Double-blind randomised controlled trial	Haemoglobin concentration
(4)	Hoa et al., 2005 [31]	Vietnam	168 women	Milk fortified with iron versus milk nonfortified with iron versus iron supplementation versus placebo	Quasirandomised trial	Haemoglobin concentration
(5)	Young et al., 2000 [36]	Malawi	413 pregnant women	Daily regimen versus weekly iron supplementation	Randomised controlled trial	Haemoglobin concentration
(6)	Latham et al., 2003 [30]	Tanzania	Pregnant women	Micronutrient dietary supplement versus placebo	Randomised controlled trial	Iron stores

deficiency, anaemia in pregnancy, preventive treatments, and developing countries. Cross-sectional, observational, and randomized control trials' literature on the subject published between 2000 and 2011 served as the main sources of information. These works of literature were obtained from the commonly used medical databases such as PubMed (Medline), AJOL, and Google Scholar; in addition, Cochrane Library was used as source for systematic reviews on the subject matter.

The search generated 27 related articles in the following categories: prevalence—2, treatments—8, reviews—6, interventions/trials—6, dosage—1, and technical reports—4. This paper was limited to the six randomised and quasi-randomised trials (listed in Table 1) on preventive treatments of iron deficiency anaemia in pregnancy, which met at least one of the following inclusion criteria: (i) comparison between daily routine oral supplementation with iron or ironfolic acid and no supplementation/placebo; (ii) comparison between daily routine oral supplementation with iron or ironfolic acid and routine-intermittent (weekly and twice weekly) regimens; (iii) comparison between intermittent oral iron or ironfolic acid supplementation and no supplementation/placebo; (iv) comparison between intravenous route versus oral route of iron supplementation; (v) comparison between food fortification with iron and no fortification/placebo.

3. Results

3.1. Prevalence and Burden of Iron Deficiency Anaemia in Pregnancy in Developing Countries. Worldwide, anemia affects over two billion people and the World Health Organization (WHO) has estimated that half of these are due to iron deficiency [5, 6]. Iron deficiency is not only the most prevalent but also the most neglected nutrient deficiency in the world, particularly among pregnant women and children in developing countries [7]. Presently, over 40 million pregnant women suffer from iron deficiency (ID) and its consequences in developing countries [8].

Iron deficiency is the most common cause of anaemia in pregnancy [2]. Iron deficiency anaemia accounts for 75–95% of cases of anaemia in pregnancy [9]. Iron-deficiency anaemia, the late manifestation of chronic iron deficiency, is thought to be the most common nutrient deficiency among pregnant women [10]. Studies conducted on pregnant women in Zimbabwe, China, India, and Mexico from 1996 to 2008 indicated that between 43% and 73% of the women were iron deficient (usually diagnosed as a low-ferritin concentration); out of these, 7% to 33% had IDA [4].

Among pregnant women, IDA has been associated with increased risks of low birth weight, prematurity, and maternal morbidity [11]. UNICEF has reported deaths of an estimated 50,000 young women per year globally in pregnancy and childbirth due to severe iron deficiency anemia [12]. The high frequency of iron deficiency anaemia in the developing countries has substantial health and economic cost implications. An analysis of 10 developing countries reported $0.32 per head or 0.57% of gross domestic product as a median value of physical productivity loss per year resulting from iron deficiency [13].

3.2. Evidence-Based Preventive Treatment Options

3.2.1. Prophylaxis Iron Supplements. The high physiological requirement for iron in pregnancy is difficult to meet with most diets; this is so especially in developing countries where food requirement is a problem. During pregnancy, iron requirements are not uniform [14]. In the first trimester, daily needs decrease due to the absence of menstruation; thereby saving about 0.56 mg of iron per day, or 160 mg for the pregnancy [15]. In the second trimester, blood volume increases by 45% with an increase in plasma volume of 50%; red cell mass is raised by 35% which amounts to about 450 mg of iron in a 55 kg woman [4]. Fetal demands for iron are maximal during the third trimester and these are estimated at about 270 mg in a 3 kg fetus [16]. Therefore, an average daily dose of 4–6 mg of iron is required in the second and third trimesters of pregnancy [14].

Overall, a woman requires about 2–2.8 mg of iron per day during pregnancy [17]. But she will need to consume much more to obtain this daily requirement (i.e., between 20 and 48 mg of dietary iron) [18]. However, literature has presented different views on iron requirements during pregnancy ranging from 450 to 1,150 mg with a median of 790 mg [14, 19–21]. Since these requirements are difficult to meet through an ordinary diet, especially in developing countries where most diets do not contain adequate bioavailable iron, routine iron supplementation in pregnancy has been found to be of immense benefit [14, 19–21].

Iron deficiency in nonpregnant populations can be measured quite precisely using laboratory tests such as serum ferritin, serum iron, transferrin, transferrin saturation, and transferrin receptors [7]. However, there is a limitation to the use of some of these biochemical indicators of iron status in certain settings and conditions; thus, necessitating caution in their interpretations. For example, serum ferritin level, being an acute-phase protein, is raised in associated underlying infections and long-term diseases; it can therefore give a false normal or high level in a state of iron deficiency. Whereas in pregnancy, serum ferritin levels decline even in women ingesting daily supplements of iron [22–24].

There are different forms of preventive treatment of iron deficiency anaemia in pregnancy. Iron supplements can be given by mouth and parenteral route as intramuscular and intravenous injections; in addition, it can be administered as blood transfusion and recombinant erythropoietin with iron. The first choice in the prophylaxis of iron deficiency anaemia for almost all women is oral iron replacement because of its effectiveness, safety, and low cost [25]. Oral iron, either as iron sulphate or fumarate, is the most commonly used preventive treatment for iron deficiency and iron deficiency anaemia in pregnancy. Direct iron supplementation has been extensively used in most developing countries as an intervention to prevent iron deficiency and consequently anaemia during pregnancy [7]. Thus, preventive treatment with iron supplements has always been given in combination with folic acid and this has been included as part of routine antenatal care provided to pregnant women at every visit in developing countries [26]. The rationale for this combination is to meet increased folic acid requirements in pregnancy brought about by the rapidly dividing cells in the fetus and elevated urinary losses [7].

The International Nutritional Anaemia Consultative Group had recommended a daily dose of 60 mg of iron for pregnant nonanaemic women, if supplementation for more than six months is possible before delivery [27]. An increased daily dose of 120 mg of iron is further suggested if the duration of supplementation in pregnant nonanaemic women is shorter or where the prevalence of iron deficiency in women is high or in settings where pregnant women are generally anaemic [27]. This supplement should include 400 μg of folic acid or lower doses, if this amount is not available [7].

3.2.2. Food Fortification with Iron. Iron fortification involves the addition of iron, usually with folic acid, to an appropriate food vehicle that is made available to the population at large. Food fortification with iron has thus become a promising approach for preventing iron deficiency anaemia in pregnancy in developing countries. Iron fortification of foods might be particularly useful and cost effective in settings where the logistics of oral iron supplementation among pregnant women are highly challenging. In addition, it is found very useful in developing countries where the rate of compliance with preventive treatment of iron is poor [4].

To this end, a variety of food items such as cereal flour (maize or wheat), salt, beverage, milk, sugar, noodles, rice, and fish sauce had been fortified with iron and used successfully as dietary supplements to boost iron stores, and hence improve haemoglobin levels in the population [28–31]. Elemental iron powders are the most widely used iron compound in fortification programmes since about 50 years [32].

3.3. A Review of Effectiveness of Preventive Treatments of Iron Deficiency Anaemia in Pregnancy

3.3.1. Prophylaxis Iron Supplements. The overall impact of interventions on iron supplementation under field conditions has been limited and its effectiveness questioned [33]. These concerns had been attributed to inadequate infrastructure and poor compliance with preventive treatment, among others [34]. Furthermore, the effectiveness of this intervention has been evaluated mostly in terms of improvement in haemoglobin concentration, rather than maternal or infant health [35]. For example, a randomized controlled trial among pregnant women in Switzerland showed that the parenteral route of iron prophylaxis of anaemia has no clinically significant benefit over oral route as there was no significant difference in maternal outcomes and serious adverse events between the two groups [25].

A Cochrane review of a randomized control trial conducted in Pakistan reported that daily iron treatment is better than intermittent iron supplementation in increasing haemoglobin level at delivery among pregnant women in developing countries [2]. Findings from other studies on routine daily or weekly antenatal iron or iron plus folic acid supplementation showed that it may be of benefit, especially where pregestational iron deficiency and anaemia are prevalent [7]. A recently published randomized study found no difference in most pregnancy outcomes between daily and twice weekly iron supplementation regimens, though the daily regimen was found to be more effective than twice weekly regimen in preventing Hb decrement at near term [8]. The timing and dosage of oral iron are also controversial as most studies have focused on preventive treatment from midpregnancy, at or before 20 weeks gestation [4].

Some researchers, on the other hand, believe that both daily and weekly iron supplementation are relatively unsuccessful in the reduction of prevalence of anemia in pregnancy. They opined that sufficient attention should be paid to adolescent girls and women of reproductive age long before pregnancy and suggested intermittent low-dose iron supplements and in some cases, combined with necessary micronutrients [36, 37]. Apart from its effectiveness, it was argued

that intermittent supplementation is more physiological by avoiding mucosal absorption block and excessive pooling of intestinal iron with associated oxidative stress; furthermore, it has logistic advantages of distribution particularly in areas of limited supply and many of the gastrointestinal side effects of daily iron are avoided [4].

Experiences on parenteral iron use are predominantly, but not exclusively, from the developed world as reports of its prophylactic use in pregnancy are scant; this may be related to concerns about adverse reactions associated with its use in parenteral form. However, intravenous iron sucrose in particular has been used in several recent studies and might be highly beneficial in refractory patients or those intolerant of oral iron formulations [4]. Though, because of its immediate bioavailability, it may result in a more rapid rise in haemoglobin level in anaemic patients compared with oral iron; but it probably does not confer an advantage in preventing anaemia in pregnancy [25, 38].

The WHO technical working group on the prevention and the treatment of severe anaemia has documented that parenteral iron therapy produces a rapid and complete correction of iron deficiency, including replacement of iron stores; thereby producing a more rapid erythropoietic response than oral iron replacement [39]. However, its use should be limited to a selected group of patients who are unable to tolerate oral iron and in whom oral iron therapy fails due to noncompliance. It is also indicated in pregnant women whose hemoglobin level is required to be restored rapidly such as those who present too close to term and those who have severe anemia [40].

3.3.2. Food Fortification with Iron. Food fortification with iron has also been shown to be an equally effective strategy of boosting haemoglobin level in the population, including pregnant women. Asibey-Berko et al. in 2007 recorded 19.5% significant increase in the prevalence of anaemia among rural Ghanaian women, who were not exposed to iron-fortified salt [29]. It was also shown that iron fortification of sugar (with mean intake of 4 mg/day) in nonpregnant Guatemalan women over three years resulted in a substantial increase in iron stores, with reserves still increasing by about 40 mg/year after the third year [41]. Furthermore, two Vietnamese studies showed similar improvements in iron stores following ingestion of ironfortified fish sauce for six to 12 months [42, 43]. Comparable results were documented with dietary supplements containing iron and ironfortified milk [30, 31].

3.4. Constraints to Successful Preventive Treatments of Iron Deficiency Anaemia in Pregnancy

3.4.1. Side Effects of Iron Supplements. Gastrointestinal distress is commonly observed in women consuming high levels of supplemental iron on an empty stomach [7]. Thus, occurrence of gastrointestinal symptoms is usually considered as a critical adverse effect on which a tolerable upper intake level for iron is based for an individual. High dose of oral iron supplements is commonly associated with gastrointestinal effects such as constipation, nausea, vomiting, and diarrhea; the frequency and severity of which vary according to the amount of elemental iron released into the stomach. In addition, elevation of "*free iron*" in the plasma and hence lipid peroxidation which is indicative of oxidative stress has been reported [44–46].

Intramuscular or intravenous iron is thought to be associated with allergic reactions and anaphylactic shock; furthermore, parenteral iron is thought to predispose to venous thrombosis and occasionally cardiac arrest and death [2]. Parenteral iron sucrose complex is known to have several advantages because of its low-allergenic properties and consequently, an extremely low incidence of severe side effects such as anaphylactic reactions [47, 48]; however, its use requires caution as it may not be completely devoid of side effect.

Other disadvantages of intravenous iron supplementation include cost and invasiveness of the procedure. However, it is argued that cost benefit of intravenous iron prophylaxis may be large taking into consideration the opportunity costs of erythropoiesis-stimulating agents, blood transfusions, and hospitalization [25].

3.4.2. Low Utilization of Maternal Health Service in Developing Countries. It is well established that antenatal care provides pregnant women with opportunities to receive cost-effective interventions which are beneficial to mother and child; these interventions include preventive treatments of iron deficiency anemia. However, the potentials of antenatal service have not been maximally utilized in developing countries. This is because these settings are characterized by poor maternal health service indicators such as nonutilization of service or delayed antenatal visit.

For example, researchers have reported a common occurrence of unbooked pregnancies [49, 50] and a wide range (60% to 90%) of antenatal care utilization rates (i.e., antenatal care clinic attendance of at least once during most recent pregnancy) [51–53]. In addition, for certain reasons, a substantial proportion (20% to 80%) of pregnant women in these settings make their first antenatal visit in their third trimester [54–56].

3.4.3. Partial Implementation of Preventive Treatments. The success of routine iron and folate supplementation, especially in areas with a high prevalence of anemia, recommended as a component of antenatal care package for all pregnant women by the World Health Organization is threatened by the practice of partial implementation of preventive treatments of health workers. Researchers have persistently reported noncompliance with this recommendation at a given antenatal visit. Van Eijk et al. in 2006 reported that 53% and 44% of pregnant women received iron and folate supplementation, respectively, during last pregnancy [54]. Other studies reported 36–54% iron supplementation [51, 55].

3.4.4. Weak Infrastructure and Political Commitment. The efforts of World Food Programme (WFP) in overcoming micronutrient deficiencies in nutritionally-vulnerable

groups and low-income food-deficit countries continue to be thwarted by challenges such as technical and managerial capacity constraints, the need for systematic compliance with procurement specifications and quality control, clearer policies on micronutrient content labeling, and the need for cash resources to support many aspects associated with local processing and fortification activities [57].

3.5. Recommendations. The World Health Organization has recommended that weekly iron and folic acid supplementation should be considered as a strategy for prevention of iron deficiency in population groups. This is particularly so where the prevalence of anemia is above 20% among women of reproductive age [58]. Since iron tablets induce a high concentration of free radicals in the intestinal milieu, which may damage the intestinal epithelium, the minimal essential iron dose is to be recommended [59]. Therefore, there is a need to establish effective and safe doses of supplemental iron with folic acid either as daily or weekly supplementation; this should take into consideration nutritional and haematological status of women in developing countries. Though compliance with weekly dosage may be better than daily regimen because of reduced side effects, it is desirable to conduct further field randomized controlled trials in order to establish the efficacy of weekly supplementation compared to daily regimen.

Alternatively, an equally effective, safe, and affordable iron compound with little or no side effect can be developed for use especially in public health antenatal supplementation programmes. To this end, we recommend a cue to be taken from new approaches to iron fortification technology development whereby iron-mediated undesirable taste and appearance are prevented while its stability and bioavailability are preserved [60]. While this approach is being pursued, we recommend that appropriate measures be taken to strengthen the existing health systems in dealing with gastro-intestinal and life-threatening side effects of iron supplements.

Thus, clinical skills of local health staff could be improved through targeted trainings such as the WHO training on Life Saving Skills [61] for health workers. Though the training lays emphasis on core midwifery skills, it could be expanded to include cardiopulmonary resuscitation of mothers; furthermore, local health staff should be provided with appropriate state-of-art equipment to work with. Although, laboratories at the health facilities in developing countries usually lack the capacity to conduct quality blood test, they could be strengthened to provide reliable estimations of red blood cell indices such as haemoglobin, haematocrit, mean cell volume, mean cell haemoglobin, and mean cell haemoglobin concentration. Where possible, estimation of serum ferritin level is desirable to adjust the dose of iron supplements [62]. With respect to partial implementation of preventive treatment, local health staff should be encouraged on adherence to the guidelines on antenatal care package at any given antenatal visit so that partial implementation of preventive treatments is minimized.

Mass fortification programme of common local staple foods with iron and folic acid is a long-term goal, which national governments in developing countries should consider as a strategy aimed at reducing the prevalence of iron deficiency anaemia in the general population. Since iron deficiency anaemia in pregnancy is determined by preexisting body iron stores, among other factors, we recommend that the mass fortification programme should be located and implemented within the context of reproductive health services.

4. Conclusions

Iron deficiency remains the most important cause of anaemia in pregnancy in developing countries. Hence, its contribution to increased risks of low birth weight, prematurity, and maternal morbidity cannot be underscored. Prophylaxis iron supplement and food fortification with iron have the prospects of improving maternal and child health, except for the identified constraints. Sustained advocacy in tackling micronutrient deficiencies at national and international policy levels is also a prerequisite to the attainment of Millennium Development Goals 4 and 5.

References

[1] World Health Organization, *Iron Deficiency Anemia Assessment Prevention and Control: A Guide for Program Managers*, World Health Organization, Geneva, Switzerland, 2001.

[2] L. Reveiz, G. M. Gyte, and L. G. Cuervo, "Treatments for iron-deficiency anaemia in pregnancy," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD003094, 2007.

[3] World Health Organization, *The Prevalence of Anaemia in Women: A Tabulation of Available Information (WHO/MCH/MSM/92)*, WHO, Maternal Health and Safe Motherhood Programme, Division of Family Health, Geneva, Switzerland, 1992.

[4] L. P. McMahon, "Iron deficiency in pregnancy," *Obstetric Medicine*, vol. 3, pp. 17–24, 2010.

[5] B. Brabin, "Haematological profiles of the people of rural southern Malawi: an overview," *Annals of Tropical Medicine and Parasitology*, vol. 98, pp. 71–83, 2004.

[6] L. M. Bodnar, A. M. Siega-Riz, L. Arab, K. Chantala, and T. McDonald, "Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women," *Public Health Nutrition*, vol. 7, no. 6, pp. 701–711, 2004.

[7] J. P. Pena-Rosas and F. E. Viteri, "Effects of routine oral iron supplementation with or without folic acid for women during pregnancy," *Cochrane Database of Systematic Reviews*, vol. 3, Article ID CD004736, 2006.

[8] A. R. Zamani, Z. Farajzadegan, A. Ghahiri, M. Khademloo, and P. Golshiri, "Effectiveness of twice weekly iron supplementation compared with daily regimen in reducing anemia and iron deficiency during pregnancy: a randomized trial in Iran," *Journal of Research in Medical Sciences*, vol. 13, no. 5, pp. 230–239, 2008.

[9] S. Halimi, "Oral versus parenteral iron therapy for correction of iron deficiency anaemia in preganancy," *Gomal Journal of Medical Sciences*, vol. 9, no. 1, 2011.

[10] World Health Organization, *The Prevalence of Anaemia in Women: A Tabulation of Available Information*, WHO, Geneva, 1992.

[11] S. R. S. Pasricha, S. C. Flecknoe-Brown, K. J. Allen et al., "Diagnosis and management of iron deficiency anaemia: a clinical update," *Medical Journal of Australia*, vol. 193, no. 9, pp. 525–532, 2010.

[12] D. A. Hussar, "New drugs: pregabalin and omega-3-acid ethyl esters," *Journal of the American Pharmacists Association*, vol. 45, no. 6, pp. 765–767, 2005.

[13] S. Horton and J. Ross, "The economics of iron deficiency," *Food Policy*, vol. 28, no. 1, pp. 51–75, 2003.

[14] T. H. Bothwell, "Iron requirements in pregnancy and strategies to meet them," *American Journal of Clinical Nutrition*, vol. 72, no. 1, pp. 257S–264S, 2000.

[15] L. Hallberg and L. Rossander-Hulten, "Iron requirements in menstruating women," *American Journal of Clinical Nutrition*, vol. 54, no. 6, pp. 1047–1058, 1991.

[16] E. M. Widdowson and C. M. Spray, "Chemical development in utero," *Archives of Disease in Childhood*, vol. 26, no. 127, pp. 205–214, 1951.

[17] J. Mukherji, "Iron deficiency anemia in pregnancy," *Rational Drug Bulletin*, vol. 12, pp. 2–5, 2002.

[18] C. S. Gautam, L. Saha, K. Sekhri, and P. K. Saha, "Iron deficiency in pregnancy and the rationality of iron supplements prescribed during pregnancy," *Medscape General Medicine*, vol. 10, no. 12, article 283, 2008.

[19] N. Milman, T. Bergholt, L. Eriksen et al., "Iron prophylaxis during pregnancy - How much iron is needed? A randomized dose-response study of 20-80 mg ferrous iron daily in pregnant women," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 84, no. 3, pp. 238–247, 2005.

[20] N. Milman, "Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy," *International Journal of Hematology*, vol. 63, no. 2, pp. 103–135, 1996.

[21] L. M. Bodnar, M. E. Cogswell, and K. S. Scanlon, "Low income postpartum women are at risk of iron deficiency," *Journal of Nutrition*, vol. 132, no. 8, pp. 2298–2302, 2002.

[22] J. Puolakka, O. Jänne, A. Pakarinen, P. A. Järvinen, and R. Vihko, "Serum ferritin as a measure of iron stores during and after normal pregnancy with and without iron supplements," *Acta Obstetricia et Gynecologica Scandinavica, Supplement*, vol. 95, pp. 43–51, 1980.

[23] I. Romslo, K. Haram, N. Sagen, and K. Augensen, "Iron requirement in normal pregnancy as assessed by serum ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations," *British Journal of Obstetrics and Gynaecology*, vol. 90, no. 2, pp. 101–107, 1983.

[24] B. Svanberg, B. Arvidsson, A. Norrby, G. Rybo, and L. Sölvell, "Absorption of supplemental iron during pregnancy—a longitudinal study with repeated bone-marrow studies and absorption measurements," *Acta Obstetricia et Gynecologica Scandinavica, Supplement*, no. 48, pp. 87–108, 1975.

[25] G. Bencaiova, U. von Mandach, and R. Zimmermann, "Iron prophylaxis in pregnancy: intravenous route versus oral route," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 144, no. 2, pp. 135–139, 2009.

[26] J. P. Peña-Rosas and F. E. Viteri, "Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD004736, 2009.

[27] R. J. Stoltzfus and M. L. Dreyfuss, *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia*, International Nutritional Anemia Consultative Group/ UNICEF/WHO, Geneva, Switzerland.

[28] UNICEF/UNU/WHO/MI, "Preventing iron deficiency in women and children technical consensus on key issues," in *Technical Workshop, UNICEF*, 1999 International Nutrition Foundation and Micronutrient Initiative Boston, New York, NY, USA, 19991998.

[29] E. Asibey-Berko, S. H. Zlotkin, G. S. Yeung et al., "Dual fortification of salt with iron and iodine in women and children in rural Ghana," *East African Medical Journal*, vol. 84, no. 10, pp. 473–480, 2007.

[30] M. C. Latham, D. M. Ash, D. Makola, S. T. Tatala, G. D. Ndossi, and H. Mehansho, "Efficacy trials of a micronutrient dietary supplement in schoolchildren and pregnant women in Tanzania," *Food and Nutrition Bulletin*, vol. 24, no. 4, pp. S120–S128, 2003.

[31] P. T. Hoa, N. C. Khan, C. van Beusekom, R. Gross, W. L. Conde, and H. D. Khoi, "Milk fortified with iron or iron supplementation to improve nutritional status of pregnant women: an intervention trial from rural Vietnam," *Food and Nutrition Bulletin*, vol. 26, no. 1, pp. 32–38, 2005.

[32] R. Hurrell, T. Bothwell, J. D. Cook et al., "The usefulness of elemental iron for cereal flour fortification: a Sustain Task Force report," *Nutrition Reviews*, vol. 60, no. 12, pp. 391–406, 2002.

[33] G. H. Beaton and G. McCabe, "Efficacy of intermittent iron supplementation in the control of iron deficiency anaemia in developing countries. An analysis of experience," *The Micronutrient Initiative*, 1999.

[34] J. O. Mora, "Iron supplementation: overcoming technical and practical barriers," *Journal of Nutrition*, vol. 132, no. 4, supplement, pp. 853S–855S, 2002.

[35] G. H. Beaton, "Iron needs during pregnancy: do we need to rethink our targets?" *American Journal of Clinical Nutrition*, vol. 72, no. 1, supplement, pp. 265S–271S, 2000.

[36] M. W. Young, E. Lupafya, E. Kapenda, and E. A. Bobrow, "The effectiveness of weekly iron supplementation in pregnant women of rural northern Malawi," *Tropical Doctor*, vol. 30, no. 2, pp. 84–88, 2000.

[37] F. E. Viteri and J. Berger, "Importance of pre-pregnancy and pregnancy iron status: can long-term weekly preventive iron and folic acid supplementation achieve desirable and safe status?" *Nutrition reviews.*, vol. 63, no. 12, pp. S65–76, 2005.

[38] F. Bayoumeu, C. Subiran-Buisset, N. E. Baka, H. Legagneur, P. Monnier-Barbarino, and M. C. Laxenaire, "Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route," *American Journal of Obstetrics and Gynecology*, vol. 186, no. 3, pp. 518–522, 2002.

[39] J. O. Komolafe, O. Kuti, K. T. Ijadunola, and S. O. Ogunniyi, "A comparative study between intramuscular iron dextran and oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy," *Journal of Obstetrics and Gynaecology*, vol. 23, no. 6, pp. 628–631, 2003.

[40] R. Ayub, N. Tariq, M. M. Adil, M. Iqbal, A. Junaid, and T. Jaferry, "Efficacy and safety of Total Dose Infusion of low molecular weight iron dextran in the treatment of iron deficiency anemia during pregnancy," *Journal of the College of Physicians and Surgeons Pakistan*, vol. 18, no. 7, pp. 424–427, 2008.

[41] F. E. Viteri, E. Alvarez, R. Batres et al., "Fortification of sugar with iron sodium ethylenediaminotetraacetate (FeNaEDTA) improves iron status in semirural Guatemalan populations," *American Journal of Clinical Nutrition*, vol. 61, no. 5, pp. 1153–1163, 1995.

[42] P. Van Thuy, J. Berger, L. Davidsson et al., "Regular consumption of NaFeEDTA-fortified fish sauce improves iron status and reduces the prevalence of anemia in anemic Vietnamese

women," *American Journal of Clinical Nutrition*, vol. 78, no. 2, pp. 284–290, 2003.

[43] P. Thuy, J. Berger, and Y. Nakanishi, "Effectiveness of NaFeEDTA fortified fish sauce in controlling iron deficiency in Vietnam," in *Proceedings of the International Nutritional Anemia Group Meeting*, Lima, Peru, 2004.

[44] W. Breuer, A. Ronson, I. N. Slotki, A. Abramov, C. Hershko, and Z. I. Cabantchik, "The assessment of serum nontransferrin-bound iron in chelation therapy and iron supplementation," *Blood*, vol. 95, no. 9, pp. 2975–2982, 2000.

[45] S. Mertz, L. Woodhouse, and C. Donangelo, "Breath ethane excretion rate in young women is increased in daily iron but not in daily zinc supplementation," *The FASEB Journal*, vol. 13, p. A216, 1999.

[46] B. Lachili, I. Hininger, H. Faure et al., "Increased lipid peroxidation in pregnant women after iron and vitamin C supplementation," *Biological Trace Element Research*, vol. 83, no. 2, pp. 103–110, 2001.

[47] B. G. Danielson, T. Salmonson, H. Derendorf, and P. Geisser, "Pharmacokinetics of iron(III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers," *Arzneimittel-Forschung*, vol. 46, no. 6, pp. 615–621, 1996.

[48] B. Danielson, "Intravenous iron therapy-efficacy and safety of iron sucrose," in *In Prevention and Management of Anaemia in Pregnancy and Postpartum Haemorrhage*, pp. 93–106, 1998.

[49] B. Chigbu, S. Onwere, C. I. Kamanu, C. Aluka, O. Okoro, and E. Adibe, "Pregnancy outcome in booked and unbooked mothers in South Eastern Nigeria," *East African Medical Journal*, vol. 86, no. 6, pp. 267–271, 2009.

[50] A. T. Owolabi, A. O. Fatusi, O. Kuti, A. Adeyemi, S. O. Faturoti, and P. O. Obiajuwa, "Maternal complications and perinatal outcomes in booked and unbooked Nigerian mothers," *Singapore Medical Journal*, vol. 49, no. 7, pp. 526–531, 2008.

[51] National Population Commission [Nigeria] and ICF Macro, *Nigeria Demographic and Health Survey 2008*, National Population Commission and ICF Macro, Abuja, Nigeria, 2009.

[52] Ghana Statistical Service, *Ghana Demographic and Health Survey 2008*, Ghana Health Service, and ICF Macro, Accra, Ghana, 2009.

[53] S. Babalola and A. Fatusi, "Determinants of use of maternal health services in Nigeria - Looking beyond individual and household factors," *BMC Pregnancy and Childbirth*, vol. 9, article 1471, p. 43, 2009.

[54] A. M. Van Eijk, H. M. Bles, F. Odhiambo et al., "Use of antenatal services and delivery care among women in rural western Kenya: a community based survey," *Reproductive Health*, vol. 3, article 2, 2006.

[55] K. Osungbade, S. Oginni, and A. Olumide, "Content of antenatal care services in secondary health care facilities in Nigeria: implication for quality of maternal health care," *International Journal for Quality in Health Care*, vol. 20, no. 5, pp. 346–351, 2008.

[56] K. O. Osungbade, V. N. Shaahu, and O. C. Uchendu, "Clinical audit of antenatal service provision in Nigeria," *Health Care for Women International*, vol. 32, no. 5, pp. 441–452, 2011.

[57] Nutrition Service of the World Food Program, "Micronutrient fortification: WFP experiences and ways forward," *Food and Nutrition Bulletin*, vol. 27, no. 1, pp. 67–75, 2006.

[58] M. Y. Yakoob and Z. A. Bhutta, "Effect of routine iron supplementation with or without folic acid on anemia during pregnancy," *BMC Public Health*, vol. 11, no. 3, article S21, 2011.

[59] E. K. Lund, S. G. Wharf, S. J. Fairweather-Tait, and I. T. Johnson, "Oral ferrous sulfate supplements increase the free radical-generating capacity of feces from healthy volunteers," *American Journal of Clinical Nutrition*, vol. 69, no. 2, pp. 250–255, 1999.

[60] H. Mehansho, "Iron fortification technology development: new approaches," *Journal of Nutrition*, vol. 136, no. 4, pp. 1059–1063, 2006.

[61] World Health Organization, "Making pregnancy safer: the critical role of the skilled attendant. A joint statement by WHO, ICM and FIGO," 2004, http://www.who.int/reproductive-health/publications/2004/skilled_attendant.pdf.

[62] N. Milman, "Iron prophylaxis in pregnancy—general or individual and in which dose?" *Annals of Hematology*, vol. 85, no. 12, pp. 821–828, 2006.

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 630519, 10 pages
doi:10.1155/2012/630519

Review Article

Iron Deficiency Anaemia in Pregnancy and Postpartum: Pathophysiology and Effect of Oral versus Intravenous Iron Therapy

Alhossain A. Khalafallah[1,2] and Amanda E. Dennis[2,3]

[1] *Department of Haematology, Launceston General Hospital, Launceston, Tasmania 7250, Australia*
[2] *School of Human Life Sciences, University of Tasmania, Australia*
[3] *Department of Obstetrics and Gynaecology, Launceston General Hospital, Tasmania 7250, Australia*

Correspondence should be addressed to Alhossain A. Khalafallah, alhossain@yahoo.com

Received 3 February 2012; Revised 4 April 2012; Accepted 18 April 2012

Academic Editor: Nils Milman

Nutritional iron-deficiency anaemia (IDA) is the most common disorder in the world, affecting more than two billion people. The World Health Organization's global database on anaemia has estimated a prevalence of 14% based on a regression-based analysis. Recent data show that the prevalence of IDA in pregnant women in industrialized countries is 17.4% while the incidence of IDA in developing countries increases significantly up to 56%. Although oral iron supplementation is widely used for the treatment of IDA, not all patients respond adequately to oral iron therapy. This is due to several factors including the side effects of oral iron which lead to poor compliance and lack of efficacy. The side effects, predominantly gastrointestinal discomfort, occur in a large cohort of patients taking oral iron preparations. Previously, the use of intravenous iron had been associated with undesirable and sometimes serious side effects and therefore was underutilised. However, in recent years, new type II and III iron complexes have been developed, which offer better compliance and toleration as well as high efficacy with a good safety profile. In summary, intravenous iron can be used safely for a rapid repletion of iron stores and correction of anaemia during and after pregnancy.

1. Iron Deficiency in Women

Nutritional iron deficiency is the most common deficiency disorder in the world, affecting more than two billion people worldwide, with pregnant women at particular risk [1–3]. World Health Organization (WHO) data show that iron deficiency anaemia (IDA) in pregnancy is a significant problem throughout the world with a prevalence ranging from an average of 14% of pregnant women in industrialized countries to an average of 56% (range 35–75%) in developing countries [2, 3].

Furthermore, IDA not only affects a large number of women and children in the developing world, but is also considered the only nutrient deficiency that is significantly prevalent in the developed world also. The number of patients with ID and IDA is overwhelming as more than 2 billion people, approximately 30% of the world's population, are iron deficient with variable prevalence, distribution, and contributing factors in different parts of the world [1–3].

Iron deficiency affects more women than any other condition, constituting an epidemic public health crisis. It is usually present with subtle manifestations and should be considered as a chronic slowly progressing disease that is often underestimated and untreated worldwide despite several warnings and awareness campaigned by the WHO [1–3].

The high prevalence of IDA in women has substantial health consequences with subsequent socioeconomic hazards, including poor pregnancy outcome, impaired educational performance, and decreased work capacity and productivity [1, 4].

Because of the magnitude and consequences of iron deficiency anaemia in the world, especially in women in their childbearing period, several international conferences

on nutrition have addressed this issue in order to reduce the prevalence of iron deficiency in women of childbearing age without major success [1–6]. The consequences of IDA have been widely studied [7–10]. However, there remains a lack of data about its effects on patient's wellbeing.

Targeted iron supplementation, an iron-rich diet, or both, can improve iron deficiency. However, the variability of bioavailable iron compounds limits its value against nutritional iron deficiency. Therefore, laboratory measures of iron stores should be utilised to determine iron deficiency and monitor therapy [3–6].

This review highlights the importance of IDA in pregnancy and discusses appropriate treatment in order to avoid serious complications of anaemia.

2. Iron Metabolism

The balance of iron metabolism in healthy individuals predominantly reflects three variables: nutritional intake, iron loss, and current demand. The nutritional iron intake relates to the amount of digested iron in food and the ability to absorb iron from the digestive tract [4]. The amount of iron absorbed depends largely on the presence or absence of pathology of the gastrointestinal tract or a comorbidity (such as chronic inflammatory diseases) that may result in expression of the iron regulatory proteins and a peptide called hepcidin, which ultimately blocks iron absorption [11–13].

The main source of iron in humans comes from the destruction of erythrocytes by macrophages of the reticuloendothelial system including the spleen or in other words, a recycled internal iron supply. Recent studies have shown how the human body up- and downregulates iron absorption in response to changing iron status via intestinal and hepatic proteins [12–15].

2.1. Iron Metabolism in Pregnancy. During pregnancy, fetal hepcidin controls the placental transfer of iron from maternal plasma to the fetal circulation. When hepcidin concentrations are low, iron enters blood plasma at a high rate. When hepcidin concentrations are high, ferroportin is internalized, and iron is trapped in enterocytes, macrophages, and hepatocytes [11, 15]. The daily requirement of external iron remains as little as between 1 to 8 mg daily [16]. However, more external iron is required to balance increased demand for iron especially with physiological requirements during growth, pregnancy, and lactation [16, 17]. This significant increased demand for iron is required to develop the fetus and placenta in addition to support mother's blood volume. Furthermore, pregnant women are subject to iron loss during and after delivery [16–18].

The total iron loss associated with pregnancy and lactation is approximately 1000 mg [16, 17]. Therefore the recommended daily dietary allowance for iron in pregnancy is 27 mg instead of 8 mg in the adult nonpregnant population. Lactation requires a daily dietary allowance of 10 mg [16–18].

3. Laboratory Markers for Iron Status

3.1. Definition of Anaemia in IDA in Pregnant and Nonpregnant Women. Anaemia of pregnancy is generally defined as Hb <110 g/L or <115 g/L in some clinical practice guidelines with a slight variation according to the trimester of pregnancy. However, a haemoglobin level <100 g/L indicates anaemia at any stage during pregnancy that should initiate investigations and treatment because of potentially serious consequences for the mother and her baby, with an increased risk of intrauterine growth retardation and premature birth. In the meantime, anaemia in women of reproductive age is defined as Hb <120 g/L or in some studies <115 g/L as this is laboratory and population specific [7–10].

3.2. Definition of Iron Deficiency (ID). Iron deficiency can be classified as severe ID when the serum ferritin level is below 20–30 μg/L and mild-moderate ID if the serum ferritin level is below 70–100 μg/L. Ferritin level is considered the surrogate marker for ID. However, serum ferritin is an acute phase reactant and may be raised in cases of inflammation or infection, therefore a concurrent test for inflammatory markers is advisable in cases of anaemia with raised ferritin to exclude reactive causes. ID is most likely not present if the ferritin level is above 100 μg/L [10].

Although a study of bone marrow iron stores is generally regarded as the definitive marker of iron deficiency, it remains an impractical and invasive procedure to apply for most patients. Measurement of both soluble transferrin receptor and serum ferritin provides a tool for accurate diagnosis of IDA [19–21]. However, transferrin receptor is not a well-standardized test that can be reliably reproduced with high precision in most laboratories worldwide [21].

In the meantime, ferritin estimation is an easy automated test to perform in most laboratories in the world; however, its use is limited in cases of inflammation or infection as it is considered to be influenced by acute phase responses and hence negatively influences its value in clinical interpretation of the test results [19, 20]. The commonly available laboratory tests that determine iron status, namely, serum iron, transferrin, total iron-binding capacity (TIBC), transferrin saturation, and ferritin are widely used in worldwide clinical practice [19, 20].

Soluble TfR (sTfR) is present in human plasma and is considered as a truncated form of the tissue receptor that exists as a transferrin-receptor complex and therefore it reflects tissue iron deficiency [21]. Another protein that plays a crucial role in iron metabolism is hepcidin, which is primarily made by hepatocytes and secreted into the blood circulation. Hepcidin is a small-sized molecule composed of 25-amino acid peptide, which is renally excreted and therefore can be detected and measured in urine [14, 15]. Furthermore, hepcidins rapid excretion suggests that it is regulation triggered at the level of production sites. Hepcidin circulates in the ferroportins plasma and responds to various stimuli that regulate iron stores and serum iron [15].

Recent studies demonstrate that hepcidin levels are reduced in iron deficiency [14, 15]. Measurement of blood or urine hepcidin levels can be achieved by mass spectrometry

and immunoassays in serum, plasma, and urine [22]. However, the diagnostic utility of serum hepcidin in iron deficiency has not yet been defined in clinical application [23]. Nevertheless, hepcidin estimation seems a potentially accurate test that reflects the actual iron status with less limitations.

Altogether, new technology such as hypochromic reticulocytes and reticulocyte haemoglobin testing, sTfR, and hepcidin have reportedly been developed with higher sensitivity, specificity, reproducibility, and cost effectiveness [19–24]. This may offer a reliable screening tool for iron deficiency in the future. It is worth noting that there are no specific data addressing the difference of these markers in the pregnant versus nonpregnant population. However, in principle, no essential change should occur in iron metabolism in the pregnant versus non-pregnant population except for the increased iron demand as discussed before.

3.3. Current Strategy to Assess Iron Deficiency during Pregnancy. Full blood count and MCV value allowing the diagnosis of microcytic anaemia is considered a good screening tool for IDA. However, in areas of the world where haemoglobinopathies are prevalent and these may be associated with microcytosis, iron studies, in particular ferritin level remains the surrogate marker for IDA. According to the ferritin level, iron deficiency can be classified as severe ID when the ferritin level is $<30\,\mu$g/L or mild-moderate ID if ferritin $<100\,\mu$g/L and $>30\,\mu$g/L (there is a wide normal range between 20 and 464 and is laboratory and method specific) [8]. In cases of elevated ferritin $>100\,\mu$g/L with a concurrent anaemia, a reactive common cause such as infection should be excluded and other causes of anaemia should be examined accordingly. Other complementary tests in iron studies such as serum iron, iron binding capacity, and transferrin saturation are helpful in confirming the diagnosis of IDA.

4. Oral versus Intravenous Iron for Treatment of Iron Deficiency in Women of Reproductive Age and Pregnancy

Oral iron therapy is the most widely prescribed treatment for iron deficiency anaemia, however, there are many issues that may prevent oral iron supplementation from successfully managing IDA. For instance, many patients do not respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects. Side effects may play a significant role in rates of compliance [25, 26]. Furthermore, the presence of bowel disease may affect the absorption of iron and thereby minimize the benefit received from oral iron therapy [27–29].

The side effects of oral iron therapy include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhoea, and/or constipation, and occur in about 50% of patients taking iron preparations [13, 27–29].

Furthermore, the most widely prescribed oral iron is mainly composed of ferrous salts [25–27]. Ferrous salt is characterized by low and variable absorption rates. Its absorption can be limited by ingestion of certain foods as well as mucosal luminal damage [27–29]. Therefore, ferric compounds were introduced to avoid such obstacles. However, these compounds are generally less soluble and have poor bioavailability [29].

The usual recommended oral iron sulphate dose for the treatment of iron deficiency is at least 80 mg daily of elemental iron, which is equivalent to 250 mg of oral iron sulphate tablets (Abbott, Australasia Pty Ltd.).

Iron absorption requires an acidic medium, therefore its absorption may be decreased by intake of antacids or proton pump inhibitors and histamine receptor antagonists. Interference of iron absorption may occur with the intake of certain medications, which thereby minimises the benefit received from oral iron treatment [29].

The major challenges in the management of IDA are related to the tolerability and side effects of iron therapy in its different forms. Therefore, it is crucial to determine the most appropriate form and dose of iron as well as duration of treatment in order to successfully replenish iron stores. Although oral iron is widely used worldwide, the effectiveness of oral iron is largely compromised by lack of absorption, poor compliance, increased adverse effects (up to 56%), and discontinuation of treatment (up to 20%) [4, 26, 29].

Therefore, parenteral iron is seen to be an attractive option in the treatment of IDA and is likely to be more popular due to the introduction of new intravenous iron preparations, which allow high doses of iron to be administered rapidly in a single treatment [30–32].

4.1. Side Effects of IV Iron. In the past, intravenous iron had been associated with undesirable and sometimes serious side effects and was therefore limited in use [33, 34]. However, in recent years, new type II and III iron complexes have been developed which are better tolerated and can be used for rapid repletion of iron stores [34, 35]. Despite the increasing evidence of the safety of the newer preparations, both in pregnant and general populations, intravenous iron continues to be underutilised because of previous concerns with tolerability of older intravenous iron preparations [7, 8, 30].

Review of infusions of iron dextran among 481 patients of both sexes revealed that about 25% of patients had mild side effects, which were self-limiting. However, about 2% experienced severe allergic reactions and about 0.6% were considered as anaphylactic reactions. Most of these reactions occurred immediately during the infusion of the test dose [36].

Iron gluconate is considered to have a lower reaction rate and therefore a test dose is not recommended with only 3.3 allergic events per million doses per year with iron gluconate reported [37]. There were no life-threatening reactions recorded as a result of iron gluconate infusion. On the other hand, there were 31 fatalities among 196 allergic/anaphylactic reactions, which were reported for iron dextran [37].

The high incidence of adverse reactions to iron dextran, including serious adverse events have limited its application

in pregnancy [38–40, 43]. Whilst the application of iron gluconate is considered safe, it remains impractical in theory as it requires multiple infusions with huge implications on the often limited health system resources as well as on patients' compliance.

More recently new forms of intravenous iron that have been developed and are available, are permitting treating physicians to safely administer relatively high doses of iron in a single dose treatment.

4.2. Intravenous versus Oral Iron Therapy in Pregnancy. Intravenous iron, including iron sucrose, was employed in randomised controlled trials with improved effectiveness of intravenous iron only or in combination with oral iron, compared to oral iron only, based on Hb levels [41–43].

A single IV iron sucrose dose has been reported to be associated with an increased incidence of thrombosis (9/41, 22%) [43]. In contrast, 6 small doses of intravenous iron sucrose administered over a three-week period were without infusion-associated thrombosis, with intravenous iron sucrose administered in 5 daily doses to 45 pregnant women, also well tolerated [41]. In the first study utilising intravenous iron sucrose, there was no significant difference in Hb levels at any time measured at days 8, 15, 21, and 30 and at delivery [42] between intravenous iron sucrose or oral iron sulphate. In contrast, in another trial, with 6 small doses of iron sucrose, there was a significant difference in Hb levels in favour of the intravenous iron sucrose group as measured at 2 and 4 weeks after administration of IV iron and at delivery [41]. However, both trials administered IV iron sucrose at the expense of a vastly greater effort from the patients to present to the hospital for 6 infusions in a short period of time as well as the extra demands on hospital resources [41, 42].

Furthermore, relatively older and established iron preparations such as intravenous iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) demonstrated a high safety profile in the treatment of IDA in both obstetric and general populations without a maximum dose of treatment [30]. The total dose of IV iron polymaltose is calculated according to the patient's body weight and entry Hb level with reference to the product guidelines as follows: iron dose in mg (50 mg per 1 mL) = body weight in kg (maximum 90) × target Hb (120 g/L) − actual Hb in g/L × constant factor (0.24) + iron depot (500). Iron polymaltose infusion showed high efficacy and safety profile during pregnancy in the largest, recently published trial [30].

In this study, two hundred Caucasian pregnant women aged 18 years or above were identified with moderate IDA, defined as Hb ≤115 g/L (reference range (RR) 120–160 g/L) and low iron stores based on a serum ferritin level <30 μg/L (RR 30–440 μg/L). The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after antennal clinic booking, usually after 12 weeks of gestation, followed by oral maintenance therapy. IV iron was commenced during the 2nd and 3rd trimesters only. The oral treatment arm comprised iron sulphate 250 mg tablets (elemental iron 80 mg, Abbott, Australasia Pty Ltd.) to be taken daily within two days after booking until delivery [30]. At preenrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based on a specially designed questionnaire addressing these issues. The participants were followed up during the pregnancy and at a postdelivery median follow-up period of 32 months (range 26–42). Iron status and haemoglobin were determined at time of entry in the study as a baseline, then prior to delivery and thereafter 4 weeks after delivery [30].

As reported in the original study, at delivery the proportion of women with lower than normal ferritin levels was 79% for women who were treated with oral iron as compared to 4.5% for women who received IV iron ($P < 0.001$) [30]. The percentage of women at delivery with Hb level <116 g/L was 29% in the oral iron group versus 16% in the IV iron group ($P = 0.04$) [30].

As a common practice at our institution, we have performed more than 1000 IV iron polymaltose infusions for the treatment of IDA in pregnancy during the last 5 years. Most of the women tolerated the IV iron polymaltose well without major side effects. There was no recorded anaphylaxis or mortality secondary to IV iron in this cohort of patients.

In unpublished data collected as a follow-up study of the original trial [30], there was a significant improvement in the general health of women who received IV iron polymaltose versus oral iron ($P < 0.001$). The duration of breast feeding was longer ($P = 0.04$) in those women who had received IV iron polymaltose versus oral iron. Women with better iron status were less downhearted ($P = 0.005$) and less likely to develop postnatal clinical depression ($P = 0.003$).

This would indicate that it is worthwhile considering the Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy but also during the postnatal period. However, further studies are warranted to confirm and extend these findings.

Furthermore, recent reports demonstrate the feasibility of rapid iron polymaltose infusion over 2 hours [30, 44, 45]. However, a test dose of iron polymaltose (100 mg) should be first administered over 30 minutes, and premedication with antihistamine and/or low-dose steroids is recommended prior to iron treatment for better toleration [44, 45].

A recent comprehensive meta-analysis and review by Reveiz et al. [7] of the literature between 1970 till present on different treatments for IDA of pregnancy showed paucity of good quality trials assessing clinical maternal and neonatal effects of iron administration in women with IDA in spite of the high incidence and burden of disease associated with IDA. During this period, there was only one prospective randomized trial of the effect of IV iron versus oral iron in the treatment of IDA during pregnancy that fulfils the stringent independent reviewer quality criteria [7, 30].

5. Recent Data on Treatment of IDA in the Postpartum Period

The new preparations of intravenous iron (Table 1) are seeking approval for use during pregnancy in phase II and

III clinical trials from the authorised organisational bodies in Europe and the USA. Nevertheless, they can be potentially used currently in the non-pregnant female population for the treatment of postpartum, pre-, and postmenopausal iron deficiency anaemia according to the regional health authority approval.

In a randomised trial to assess safety and efficacy of intravenous ferric carboxymaltose in the treatment of postpartum IDA, 227 women were assigned to IV ferric carboxymaltose with 1000 mg maximum dose (up to 3 weekly doses) versus 117 women who received oral ferrous sulphate 100 mg twice daily [52]. Intravenous iron carboxymaltose was as effective as oral ferrous sulfate with no statistically significant differences between groups at any time point despite the shorter treatment period and a lower total dose of iron (mean 1.3 g IV iron versus 16.8 g oral iron). Furthermore, in the IV iron carboxymaltose group, the increases in ferritin levels were significantly greater than in the ferrous sulphate ($P < 0.0001$) indicating a successful repletion of iron stores and accessibility for erythropoiesis [52].

In a multicenter randomized, controlled study, 291 women directly after delivery with haemoglobin ≤100 g/L were randomized to receive 1000 mg IV iron carboxymaltose (143 women), repeated weekly to a calculated replacement dose (maximum dose 2.5 g), or ferrous sulfate (148 women) 325 mg orally three times daily for 6 weeks (total dose 40.9 g) [53]. Ferric carboxymaltose-treated women achieved a haemoglobin >120 g/L in a shorter period of time with a sustained haemoglobin >120 g/L at day 42. Furthermore, the achieved haemoglobin rise of ≥30 g/L was significantly more rapid in the IV iron group than the oral group in achieving higher serum ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose [53].

In a phase 3 randomised trial 174 women who received IV ferric carboxymaltose with a mean total dose of 1.4 g versus 178 women who received 325 mg ferrous sulfate three times daily for 6 weeks (total dose 40.9 g) were assessed [54]. Patients assigned to IV ferric carboxymaltose achieved a haemoglobin rise >20 g/L faster than the oral iron group (7 days compared with 14 days in the oral iron group, $P < 0.001$). The IV iron group significantly achieved a haemoglobin rise >30 g/L at any time (86.3% compared with 60.4% in the oral iron group, $P < 0.001$), and were more likely to achieve a haemoglobin >120 g/L (90.5% compared with 68.6%, $P < 0.001$). In the meantime, there were no serious adverse drug reactions in both groups [54].

In a large randomized, controlled phase 3 multicentre trial, 477 women with IDA and heavy uterine bleeding were assigned to receive either IV ferric carboxymaltose (230 women) with a maximum dose of 1000 mg repeated weekly to achieve a total calculated replacement dose, or 325 mg of oral ferrous sulphate (65 mg elemental iron) three times daily for 6 weeks with a total dose of 40.9 g in 226 women [55]. Twenty-one patients did not receive the assigned treatment in this study.

About 82% of the IV iron arm achieved haemoglobin rise ≥20 g/L versus 62% in the oral iron $P < 0.001$. Women who achieved a haemoglobin rise ≥30 g/L were 53% in the IV iron group versus 36% in the oral iron group ($P < 0.001$). Also, more women (73%) achieved normal haemoglobin >120 g/L in the IV iron group compared to 50% in the oral iron group ($P < 0.001$). There were no serious adverse drug events. This trial demonstrated that patients with IDA due to heavy uterine bleeding who received IV iron carboxymaltose, are more likely to have normal haemoglobin with replenished iron stores [55].

Altogether, the new intravenous iron preparations represent a medical revolution in effective, rapid, and safe iron repletion in the management of iron deficiency anaemia [46–55]. This will positively reflect on the treatment of IDA in different populations by application of a single high-dose intravenous iron treatment with effective subsequent repletion of iron stores and hence improvement of subjective and objective outcomes of the IDA. Although iron deficiency is a precursor of IDA, many clinical studies treat it similarly to IDA.

6. Cost Effectiveness

The cost of one iron sulphate tablet is approximately USD $0.3, so the average cost throughout one pregnancy is calculated to be between $54 and $89. The cost of iron polymaltose containing 500 mg is $50, so the average treatment cost is $100. In Australia, the cost of the outpatient hospital visit and nursing time for the IV iron adds approximately $60–$100 to the drug cost subject to variations according to different health systems. The cost of the new iron preparation ferric carboxymaltose is approximately $272 per average 1000 mg total dose compared to $280 for 1000 mg of iron sucrose (Table 2). This cost analysis is subject to change according to different health systems and countries.

7. Avoiding Blood Transfusion

In the case of severe IDA, a blood transfusion has been the traditional efficient approach to correct anaemia, especially if patients did not respond to oral iron therapy or when a rapid correction of anaemia is clinically required. Although there is a lack of data regarding the avoidance of blood transfusion during pregnancy, a recent trial investigating treatment of IDA with oral versus IV iron in pregnancy demonstrated that none of both treatment arm participants received blood transfusion for correction of anaemia during pregnancy. However two patients (0.9%) in the oral iron arm received blood transfusion in the postpartum period [30].

Currently, the development of new intravenous iron formulations that offer higher doses in a single administration has provided the treating physicians with the opportunity to employ intravenous iron as an effective, rapid, and safe treatment for IDA [46–55], avoiding the use of blood transfusion with its known hazards [56]. There is increasing evidence-based research that supports the safety and efficacy of IV iron in IDA. There is also increasing evidence for inadequacy of oral iron in terms of adverse effects, lack of compliance as well as lack of absorption and slow and often questionable effect in IDA patients [34, 35, 42].

Table 1: Recently available intravenous (IV) iron preparations.

Name of the IV iron preparation	Status of registration	Indications	Test dose	Duration of infusion	Max dose in single infusion	Reference
*Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc., USA)	FDA approved	Treatment of iron-deficiency anaemia in adult patients with CKD**	None	1 minute	510 mg	[46, 47]
*Ferric carboxymaltose (Ferinject, Vifor Pharma, Glattbrugg, Switzerland)	Approved in Europe,FDA-approval is sought	Treatment of iron-deficiency anaemia in adult patients	None	15 minutes	20 mg/kg with max dose of 1000 mg	[48, 49]
*Iron isomaltoside (MonoFer, Pharmacosmos A/S, Holbaek, Denmark)	Approved in Europe FDA-approval is sought	Treatment of iron-deficiency anaemia in adult patients with CKD**	None	60 minutes	No max dose given at rate of 20 mg/kg	[50, 51]

FDA, Food and Drug Administration; CKD, chronic kidney disease; Max, maximum. *No available data in pregnancy; however, if the benefit of treatment is judged to outweigh the potential risk to the fetus, the treatment should be confined to second and third trimester of pregnancy. **Extended approval is sought.

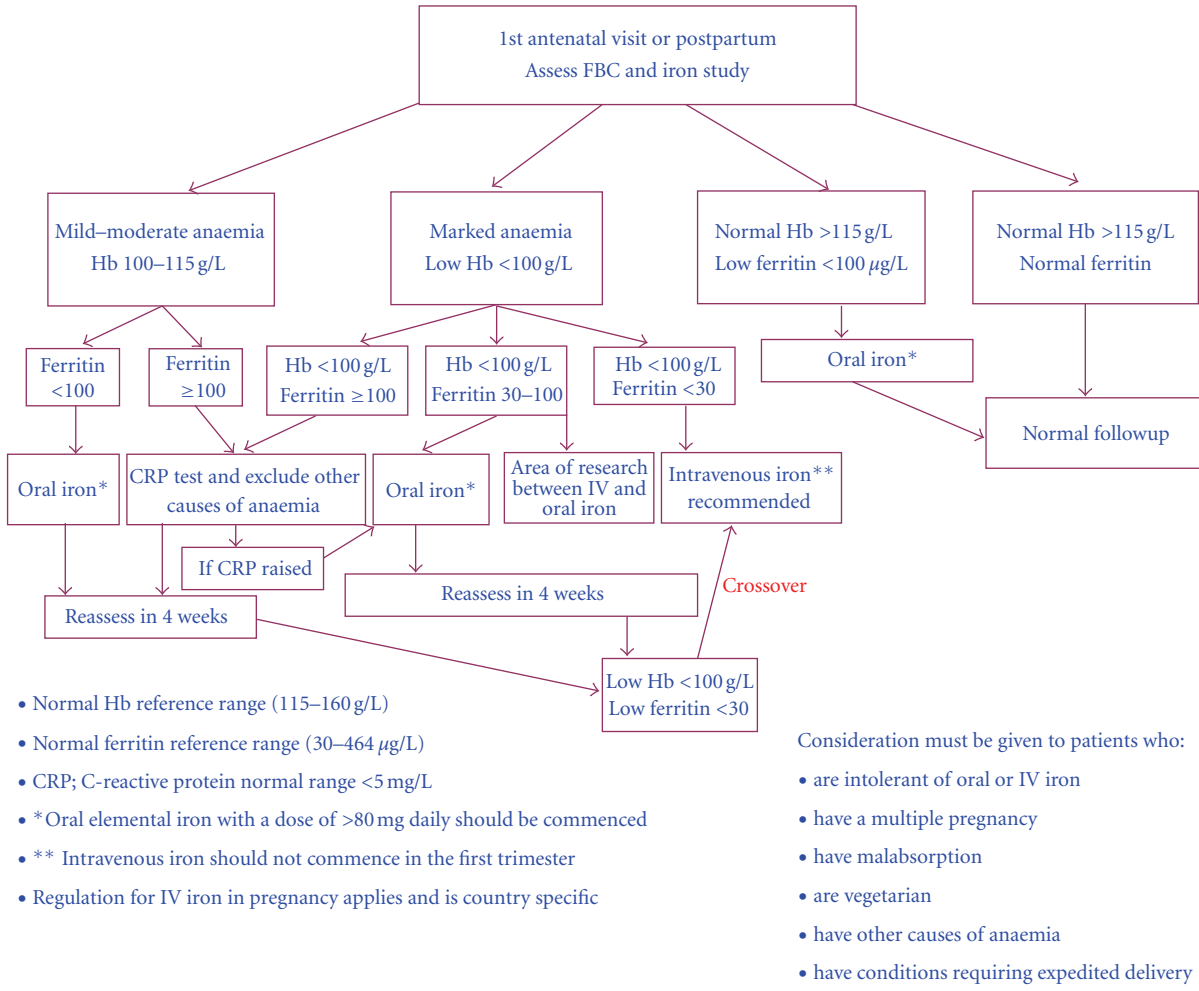


Figure 1: Proposed treatment for anaemia in pregnancy and postpartum period based on different randomized and non-randomized trials [7, 25, 30, 41, 42, 52–55].

Table 2: Comparison of costs of different oral and IV iron preparations.

Product /manufacturer	Scientific name	Route of administration	Elemental iron/ recommended dose	Approximate cost
Ferro-Liquid (AFT Pharmaceuticals)	Ferrous sulphate	Oral liquid 250 mL (30 mg/5 mL)	90 mg/15 mL/day	$19.35 per bottle Total cost per pregnancy $309
Ferro-Tab (AFT Pharmaceuticals)	Ferrous fumarate200 mg	Oral tablet 60 tabs	67.5 mg/day	$11.62 per package Cost per tablet $0.2 Total cost per pregnancy $54
FGF (Abbott)	Ferrous sulfate 250 mg (+ folic acid)	Oral tablet 30 tabs	80 mg/day	$7 per package Cost per tablet $0.23 Total cost per pregnancy $62
Fefol (Pharmacare Laboratories)	Ferrous sulfate 270 mg (+ folic acid)	Oral tablet 30 tabs	87 mg/day	$9.95 per package Cost per tablet $0.33 Total cost per pregnancy $89
Ferro-F-Tab (AFT Pharmaceuticals)	Ferrous fumarate 310 mg (+ folic acid)	Oral tablet 60 tabs	100 mg/day	$12.79 per package Cost per tablet $0.21 Total cost per pregnancy $57
Ferrograd C (Abbott)	Ferrous sulfate 325 mg	Oral tablet 30 tabs	105 mg/day	$8.16 per package Cost per tablet $0.27 Total cost per pregnancy $73
Ferro-gradumet (Abbott)	Ferrous sulfate 325 mg	Oral tablet 30 tabs	105 mg/day	$6.56 per package Cost per tablet $0.21 Total cost per pregnancy $57
		Intravenous iron		
Ferrum-H (Vifor Pharma Pty Ltd)	Iron polymaltose	IV 100 mg ampule package 5 amps	No maximum (Max) dose at a single administration	$49.57 for 5 × 100 mg
Ferrosig (Sigma Pharmaceuticals)	Iron polymaltose 100 mg ampoule	IV 100 mg ampoule package 5 amps	No max dose at a single administration	$49.57 for 5 × 100 mg
Venofer (Aspen Pharmacare)	Iron sucrose	IV 100 mg ampule package 5 amps	Max single dose 300 mg	$139.48 for 5 × 100 mg
Ferinject (Vifor)	Ferric carboxymaltose	IV 100 mg and 500 mg ampules	Max single dose 1000 mg	100 mg: $35/vial 500 mg: $136/vial
MonoFer, (Pharmacosmos)	Iron isomaltoside	IV 100 mg ampule	No max dose at a single administration	Not available
Feraheme, (AMAG Pharmaceuticals, Inc.)	Ferumoxytol	IV 100 mg ampule	Max single dose 510 mg	Not available

Cost is based on Pharmaceutical Benefit Scheme (PBS) listing price in Australia in AUD which is equivalent to USD (1:1) at the time of analysis. However the prices are only approximate as there is considerable variability depending on purchasing situation or country of origin.

A common requirement across the range of clinical situations is the need for safe, effective, higher, and less frequent doses to achieve optimal clinical outcomes. The major goals of such strategies include overall cost reduction, relief to overstretched health system(s), improved patient convenience, improved compliance, preservation of venous access, and reduced blood transfusion [34, 56, 57]. This will ultimately reduce the demand for blood transfusions, especially in the case of short supply. Furthermore, some of the new iron preparations such as ferric carboxymaltose and iron isomaltoside do not require a test dose and therefore, ease the application of intravenous iron in a timely and cost-effective fashion. This certainly will enhance the use of intravenous iron in clinical practice.

8. Summary

The WHO has recognised the problem of IDA in the general population as the most debilitating nutritional deficiency worldwide in the twenty-first century, noting women to be at particularly high risk. Such a problem, if ignored and not addressed properly, can have a devastating effect on entire populations with serious consequences. Therefore, the use of intravenous iron should be considered as an effective, rapid, and safe treatment option in some clinical situations. An algorithm for the treatment of iron deficiency anaemia in pregnancy and postpartum period based on different prospective randomised trials is proposed in Figure 1 [7, 25, 30, 41, 42]. The intravenous iron is increasingly employed to avoid or reduce the demand for blood transfusions or for effective rapid repletion of iron stores. Treatment options for IDA should consider the recently developed intravenous iron formulations, which are considered a milestone in the management of IDA (Figure 1).

Overall, the developing world is most vulnerable, especially the poorest and the least educated populations that are disproportionately affected by iron deficiency, and therefore have the most to gain by eradication of IDA. Furthermore, awareness of the magnitude and scale of the IDA problem during pregnancy and also in the non-pregnant female population will help health practitioners in recognising the most appropriate methods of diagnosis and treatment, which are crucial in overcoming such a devastating health problem. A consensus guideline set by world experts in managing IDA in women and in the general population, incorporating new intravenous iron therapies with a global approach of the health and economy aspects of IDA, should be considered. It is worthwhile considering a universal comprehensive IDA management algorithm that offers different evidence-based treatment options and addresses local conditions. However, developing countries with prevalent IDA often have lack of resources. Therefore, it is crucial to adapt a viable programme with the aim of utilising the local available resources effectively. Perhaps prioritising the treatment of IDA and increasing the awareness among the community of such a chronic devastating problem of paramount importance is the key for success and sustainability of such a programme. Certainly, successful eradication of IDA will result in huge benefits for community health and productivity with a major health saving not only in the developing world but also in developed nations.

Conflict of Interests

The authors declare no conflict of interests in relation to this research. There are nonfinancial associations that may be relevant or seen as relevant to the submitted paper.

Acknowledgments

The authors would like to acknowledge the enormous help of Mrs. Mary Sexton, Pathology Department, Launceston General Hospital, and Mrs. Yvonne Hablutzel, Pharmacy Department, Launceston General Hospital in preparing the manuscript.

References

[1] D. de Benoist, E. McLean, I. Egli, and M. Cogswell, "Worldwide prevalence of anaemia 1993–2005," 2008.

[2] World Health Organization [WHO], "The Prevalence of Anaemia in Women: a tabulation of available information," Division of Family Health, Maternal Health and Safe Motherhood Programme, Division of Health Protection and Promotion, Nutrition Programme; WHO, 2nd ed. World Health Organization, Geneva, Switzerland, 1992.

[3] ACC/SCN (United Nations Administrative Committee on Coordination/Standing Committee on Nutrition), "Fifth report on the world nutrition situation: Nutrition for improved development outcomes," Geneva, Switzerland, acc-scn@who.org, 2004.

[4] M. B. Zimmermann and R. F. Hurrell, "Nutritional iron deficiency," *Lancet*, vol. 370, no. 9586, pp. 511–520, 2007.

[5] G. F. Maberly, F. L. Trowbridge, R. Yip, K. M. Sullivan, and C. E. West, "Programs against micronutrient malnutrition: ending hidden hunger," *Annual Review of Public Health*, vol. 15, pp. 277–301, 1994.

[6] "Iron deficiency anaemia: assessment, prevention and control," World Health Organization Publication WHO/NHD/01.3, 2001.

[7] L. Reveiz, G. M. Gyte, L. G. Cuervo, and A. Casasbuenas, "Treatments for iron-deficiency anaemia in pregnancy," *Cochrane Database of Systematic Reviews*, no. 10, Article ID CD003094, 2011.

[8] A. Khalafallah and M. Mohamed, "Nutritional iron deficiency," in *Anemia*, InTech, Rijeka, Croatia, 2012.

[9] A. C. Looker, P. R. Dallman, M. D. Carroll, E. W. Gunter, and C. L. Johnson, "Prevalence of iron deficiency in the United States," *Journal of the American Medical Association*, vol. 277, no. 12, pp. 973–976, 1997.

[10] A. F. Goddard, M. W. James, A. S. McIntyre, and B. B. Scott, "Guidelines for the management of iron deficiency anaemia," *Gut*, vol. 46, pp. 1–5, 2000.

[11] E. V. Valore and T. Ganz, "Posttranslational processing of hepcidin in human hepatocytes is mediated by the prohormone convertase furin," *Blood Cells, Molecules, and Diseases*, vol. 40, no. 1, pp. 132–138, 2008.

[12] E. G. Meyron-Holtz, S. Moshe-Belizowski, and L. A. Cohen, "A possible role for secreted ferritin in tissue iron distribution," *Journal of Neural Transmission*, vol. 118, pp. 337–347, 2011.

[13] B. Galy, D. Ferring-Appel, S. W. Sauer et al., "Iron regulatory proteins secure mitochondrial iron sufficiency and function," *Cell Metabolism*, vol. 12, pp. 194–201, 2010.

[14] D. A. Weinstein, C. N. Roy, M. D. Fleming, M. F. Loda, J. I. Wolfsdorf, and N. C. Andrews, "Inappropriate expression of hepcidin is associated with iron refractory anemia: implications for the anemia of chronic disease," *Blood*, vol. 100, no. 10, pp. 3776–3781, 2002.

[15] E. Nemeth and T. Ganz, "The role of hepcidin in iron metabolism," *Acta Haematologica*, vol. 122, no. 2-3, pp. 78–86, 2009.

[16] Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine—National Academy of Sciences. Dietary reference intakes: recommended intakes for individuals, vitamins, 2001.

[17] "Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc," pp. 772–773, National Academy Press, Washington, DC, USA.

[18] Institute of Medicine, "Dietary Reference Intakes (DRIs) for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc," National Academy Press, Washington, DC, USA, 2002.

[19] G. H. Guyatt, A. D. Oxman, M. Ali, A. Willan, W. McIlroy, and C. Patterson, "Laboratory diagnosis of iron-deficiency anemia: an overview," *Journal of General Internal Medicine*, vol. 7, no. 2, pp. 145–153, 1992.

[20] T. M. Hansen and N. E. Hansen, "Serum ferritin as indicator of iron responsive anaemia in patients with rheumatoid arthritis," *Annals of the Rheumatic Diseases*, vol. 45, no. 7, pp. 596–602, 1986.

[21] K. Punnonen, K. Irjala, and A. Rajamäki, "Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency," *Blood*, vol. 89, no. 3, pp. 1052–1057, 1997.

[22] E. H. J. M. Kemna, H. Tjalsma, V. N. Podust, and D. W. Swinkels, "Mass spectrometry-based hepcidin measurements in serum and urine: analytical aspects and clinical implications," *Clinical Chemistry*, vol. 53, no. 4, pp. 620–628, 2007.

[23] S. R. Pasricha, Z. McQuilten, M. Westerman et al., "Serum hepcidin as a diagnostic test of iron deficiency in premenopausal female blood donors," *Haematologica*, vol. 96, no. 8, pp. 1099–1105, 2011.

[24] G. Zini, A. Di Mario, M. Garzia, M. Bianchi, and G. D'Onofrio, "Reticulocyte population data in different erythropoietic states," *Journal of Clinical Pathology*, vol. 64, no. 2, pp. 159–163, 2011.

[25] A. Kumar, S. Jain, N. P. Singh, and T. Singh, "Oral versus high dose parenteral iron supplementation in pregnancy," *International Journal of Gynecology and Obstetrics*, vol. 89, no. 1, pp. 7–13, 2005.

[26] P. Jacobs, G. Johnson, and L. Wood, "Oral iron therapy in human subjects, comparative absorption between ferrous salts and iron polymaltose," *Journal of Medicine*, vol. 15, no. 5-6, pp. 367–377, 1984.

[27] D. G. Maxton, R. P. H. Thompson, and R. C. Hider, "Absorption of iron from ferric hydroxypyranone complexes," *British Journal of Nutrition*, vol. 71, no. 2, pp. 203–207, 1994.

[28] N. Sharma, "Iron absorption: IPC therapy is superior to conventional iron salts," *Obstetrics & Gynecology*, pp. 515–519, 2001.

[29] P. Geisser, "In vitro studies on interactions of iron salts and complexes with food-stuffs and medicaments," *Arzneimittel-Forschung*, vol. 40, no. 7, pp. 754–760, 1990.

[30] A. Khalafallah, A. Dennis, J. Bates et al., "A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy," *Journal of Internal Medicine*, vol. 268, no. 3, pp. 286–295, 2010.

[31] M. Auerbach, H. Ballard, and J. Glaspy, "Clinical update: intravenous iron for anaemia," *Lancet*, vol. 369, no. 9572, pp. 1502–1504, 2007.

[32] A. Jenkins, "Using iron dextran to treat iron-deficiency anaemia," *Hospital Pharmacist*, vol. 12, no. 6, pp. 224–225, 2005.

[33] R. Lawrence and M. Helenek, "Development and comparison of iron dextran products," *PDA Journal of Pharmaceutical Science and Technology*, vol. 52, no. 5, pp. 190–197, 1998.

[34] M. Auerbach, L. T. Goodnough, D. Picard, and A. Maniatis, "The role of intravenous iron in anemia management and transfusion avoidance," *Transfusion*, vol. 48, no. 5, pp. 988–1000, 2008.

[35] M. Auerbach and G. M. Rodgers, "Intravenous iron," *New England Journal of Medicine*, vol. 357, no. 1, pp. 93–94, 2007.

[36] R. D. Hamstra, M. H. Block, and A. L. Schocket, "Intravenous iron dextran in clinical medicine," *Journal of the American Medical Association*, vol. 243, no. 17, pp. 1726–1731, 1980.

[37] G. Faich, J. Strobos, and G. R. Matzke, "Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans," *American Journal of Kidney Diseases*, vol. 33, no. 3, pp. 464–597, 1999.

[38] D. L. Burns and J. J. Pomposelli, "Toxicity of parenteral iron dextran therapy," *Kidney International, Supplement*, vol. 55, no. 69, pp. S119–S124, 1999.

[39] B. Michael, D. W. Coyne, S. Fishbane et al., "Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran," *Kidney International*, vol. 61, no. 5, pp. 1830–1839, 2002.

[40] S. Fishbone and E. A. Kowalski, "The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate," *Seminars in Dialysis*, vol. 13, no. 6, pp. 381–384, 2000.

[41] F. Bayoumeu, C. Subiran-Buisset, N. E. Baka, H. Legagneur, P. Monnier-Barbarino, and M. C. Laxenaire, "Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route," *American Journal of Obstetrics and Gynecology*, vol. 186, no. 3, pp. 518–522, 2002.

[42] R. A. Al, E. Unlubilgin, O. Kandemir, S. Yalvac, L. Cakir, and A. Haberal, "Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial," *Obstetrics and Gynecology*, vol. 106, no. 6, pp. 1335–1340, 2005.

[43] L. Reveiz, G. M. Gyte, and L. G. Cuervo, "Treatments for iron-deficiency anaemia in pregnancy," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD003094, 2007.

[44] M. Garg, G. Morrison, A. Friedman, A. Lau, D. Lau, and P. R. Gibson, "A rapid infusion protocol is safe for total dose iron polymaltose: time for change," *Internal Medicine Journal*, vol. 41, no. 7, pp. 548–554, 2011.

[45] A. Manoharan, R. Ramakrishna, and B. Pereira, "Delayed adverse reactions to total-dose intravenous iron polymaltose," *Internal Medicine Journal*, vol. 39, no. 12, p. 857, 2009.

[46] Monograph ferumoxytol (Feraheme). AMAG Pharmaceuticals Inc., 2009.

[47] M. H. Rosner and M. Auerbach, "Ferumoxytol for the treatment of iron deficiency," *Expert Review of Hematology*, vol. 4, no. 4, pp. 399–406, 2011.

[48] S. Kulnigg, S. Stoinov, V. Simanenkov et al., "A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT®) randomized controlled trial," *American Journal of Gastroenterology*, vol. 103, no. 5, pp. 1182–1192, 2008.

[49] W. Qunibi, Q. Dinh, and J. Benjamin, "Safety and tolerability profile of ferric carboxymaltose (FCM) a new high dose intravenous iron, across ten multi-center trials," *Journal of the American Society of Nephrology*, vol. 18, SU-PO1029, 2007.

[50] P. A. Kalra, "Introducing iron isomaltoside 1000 (Monofer®) development rationale and clinical experience," *NDT Plus*, vol. 4, no. 1, pp. i10–i13, 2011.

[51] M. R. Jahn, H. B. Andreasen, S. Fütterer et al., "A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 78, no. 3, pp. 480–491, 2011.

[52] C. Breymann, F. Gliga, C. Bejenariu, and N. Strizhova, "Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia," *International Journal of Gynecology and Obstetrics*, vol. 101, no. 1, pp. 67–73, 2008.

[53] M. H. Seid, R. J. Derman, J. B. Baker, W. Banach, C. Goldberg, and R. Rogers, "Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial," *American Journal of Obstetrics and Gynecology*, vol. 199, no. 4, pp. 435.e1–435.e7, 2008.

[54] D. B. Van Wyck, M. G. Martens, M. H. Seid, J. B. Baker, and A. Mangione, "Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial," *Obstetrics and Gynecology*, vol. 110, no. 2 I, pp. 267–278, 2007.

[55] L. T. Goodnough, D. B. Van Wyck, A. Mangione, J. Morrison, P. E. Hadley, and J. A. Jehle, "Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial," *Transfusion*, vol. 49, no. 12, pp. 2719–2728, 2009.

[56] J. P. Isbister, A. Shander, D. R. Spahn, J. Erhard, S. L. Farmer, and A. Hofmann, "Adverse blood transfusion outcomes: establishing causation," *Transfusion Medicine Reviews*, vol. 25, no. 2, pp. 89–101, 2011.

[57] M. Aickin and H. Gensler, "Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods," *American Journal of Public Health*, vol. 86, no. 5, pp. 726–728, 1996.

Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 635683, 4 pages
doi:10.1155/2012/635683

Clinical Study

Uterine Healing after Therapeutic Intrauterine Administration of TachoSil (Hemostatic Fleece) in Cesarean Section with Postpartum Hemorrhage Caused by Placenta Previa

Katrine Fuglsang,[1] Margit Dueholm,[1] Estrid Stæhr-Hansen,[2] and Lone Kjeld Petersen[1]

[1] *Department of Gynecology and Obstetrics, University Hospital of Aarhus, Skejby Sygehus, 8200 Aarhus N, Denmark*
[2] *Institute of Pathology, University Hospital of Aarhus, Nørrebrogade, 8000 Aarhus C, Denmark*

Correspondence should be addressed to Katrine Fuglsang, katrfugl@rm.dk

Received 4 January 2012; Accepted 1 March 2012

Academic Editor: Alexander Krafft

Background. Application of hemostatic fleece (TachoSil) directly onto the bleeding surfaces of the lower uterine segment has been used to obtain hemostasis during cesarean section caused by placenta previa. *Methods*. Eleven of 15 patients treated with TachoSil for excessive postpartum haemorrhage due to placenta previa were enrolled. An evaluation of the cesarean section scar by transvaginal ultrasound, the uterine cavity and endometrium by hysteroscopy, and the endometrium by biopsy were made. The main outcome measures were intrauterine adhesions, recovery of endometrium at the site of TachoSil application, visible remnants of TachoSil, and scar healing. *Results*. Eight patients had small remnants of TachoSil in the uterine cavity together with signs of resorption. All had a normal endometrial mucosa, and none had adhesions in the uterine cavity. All cesarean section scars were healed without defects. *Conclusion*. TachoSil did not seem to impair healing of the endometrium or scar formation in the uterus after intrauterine application. Resorption of TachoSil seems to progress individually. Intrauterine treatment with TachoSil is a valuable supplement to the traditional treatment of post partum haemorrhage and may help retain reproductive capability. This is a small study, and it will require more studies to confirm the reproducibility.

1. Introduction

The incidence of postpartum hysterectomy varies from 0.2 to 1.74/1000 deliveries. The most common indication for postpartum hysterectomy is abnormally adherent placenta (59%), 41% of which are due to placenta previa [1]. Delivery of patients with placenta previa is associated with the risk of excessive bleeding. Hysterectomy is a lifesaving procedure in the treatment of excessive bleeding due to placenta previa, but it deprives the woman of her ability for further reproduction [2]. In patients with placenta previa, traditionally methods, such as uterotonics, for reducing the blood loss [3] may be insufficient probably because of less muscular activity in the lower uterine segment [4]. Other methods are needed as alternatives to hysterectomy.

Application of TachoSil in the peritoneal cavity is a well-documented treatment, and studies show that the fleece is absorbed [5, 6]. Intrauterine treatment with TachoSil is a new technique with obvious short-term benefits to the patients, but its potential effects on uterine heeling are unknown, and insufficient healing and adhesions could impair the menstrual flow and decrease the ability to achieve future pregnancy. Moreover, the resorption of TachoSil in the uterine cavity is unknown.

The purpose of this study was to evaluate the potential side effects of the application of TachoSil in the uterine cavity.

We studied the healing of cesarean section scars, resorption of TachoSil, recovery of the endometrium at the site of TachoSil and formation of adhesion in the uterine cavity.

In this study, TachoSil was applied when the surgeon assessed the haemorrhage to be unacceptable despite uterotonics. We noted a trend toward faster use of TachoSil from the first patient to the last patient. Thus blood loss and the use of uterotonics and operative procedures to control haemorrhage were reduced [7].

2. Materials and Methods

Fifteen patients treated with TachoSil for excessive postpartum haemorrhage due to placenta previa in the period from January 1, 2007, to January 31, 2009, at the Department of Gynecology and Obstetrics, University Hospital of Aarhus, Skejby Sygehus, were invited for follow-up.

All had been diagnosed with partial or total placenta previa via ultrasound examination in gestational week 32. During their cesarean section, whether acute or elective, traditional uterotonics could not control the bleeding and the surgeon applied TachoSil, after which the hemorrhage was controlled.

The fifteen patients were offered an intrauterine examination and a check of their past gynecologic history. We were able to contact all 15: 11 agreed to participate and 3 declined because of ongoing pregnancy. The patients underwent a transvaginal ultrasound examination performed on a Voluson E8 Expert BT06 with a 12 MHz 3D/4D transvaginal transducer (GE Healthcare, USA). We evaluated the thickness of the endometrium, healing of the cesarean scar with presence of large uterine scars (<2.5 mm of remaining myometrium), and evidence of any remnants of the TachoSil. Hysteroscopy was performed with saline for distension and a 5 mm continuous flow office mini-hysteroscope (Bettocchi office hysteroscope, Karl Storz, Tuttlingen, Germany). Cervical canal, intrauterine cesarean section scar healing, and the endometrial mucus membrane were evaluated. Any remnants of the TachoSil and/or agglutination in the uterine cavity were also described. During the hysteroscopy, biopsies were obtained with a grasping forceps from the endometrium covering the lower uterine segment. One investigator with more than 10 years experience in ultrasound and hysteroscopy did all the examinations.

Two years after the clinical evaluation, a review of the 15 patients' hospital records was made to evaluate their number of pregnancies after treatment with TachoSil.

3. Results

Eleven patients participated in the study, and none experienced complications. Their mean age at delivery was 33.6 years (range 29–41). The mean time from the cesarean section to the examination was 11 months (range 5–25).

There was an individual variation in the length of menostasia (1–8 months), but all had resumed menstruation (Table 1).

Six were primigravida and had not undergone any operative gynecological procedures. Five women had a history of previously cesarean section. In this group the mean number of pregnancies was 3.6 (range 2–6) and the mean number of cesarean sections was 2.6 (range 2–4). One patient had a previous D&C, and one patient had been operated on twice for ectopic pregnancy.

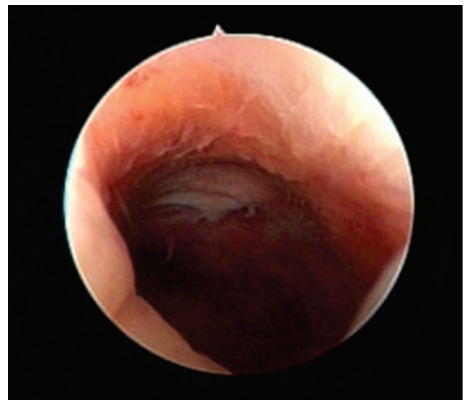


Figure 1: Intrauterine remnant of TachoSil (hemostatic fleece) visualized by hysteroscopy.

The ultrasound examinations visualized the incisional area after cesarean section in the anterior wall of the myometrium in all patients. The endometrium was described as thin at this location compared to the rest of the uterine cavity. In five of the patients, an echogenic density (punctate to 4 mm in diameter) gave the impression of a TachoSil remnant. In these patients, the mean time from cesarean section to the examination was 9.4 months (range 7–13) (Table 1).

The hysteroscopy showed covering of the endometrium in the lower segment in all patients, and no adhesions were seen in the uterine cavity. In eight of the patients, TachoSil remnants were found (Figure 1). The size was described from punctate to 1.5 cm, and the size range was not consistent with the time from cesarean section to the examination (Table 1).

If TachoSil remnants were found during the hysteroscopy, a biopsy was taken from this area, but otherwise random biopsies were taken. Unfortunately the biopsies were not useful for diagnostic purposes due to the size of the sample provided by the office hysteroscope.

Six of the fifteen have spontaneously become pregnant (Table 1). Five have delivered at term and one is pregnant in gestational week 20 (Table 2).

4. Discussion

Application of TachoSil at the lower intrauterine segment at cesarean section did not compromise the healing of the uterine scar or regeneration of the normal endometrium in the uterine cavity as evaluated by ultrasound or hysteroscopy.

Application of TachoSil is a simple, efficient, and rapid-onset treatment, giving control of bleeding. Consequently, none of the patients given TachoSil needed reoperation or developed post-partum endometritis [7]. Application of TachoSil to the lower segment does not give rise to formation of adhesions in the uterine cavity. Six patients became pregnant spontaneously, and all study patients examined had

Table 1: Results of clinical control and overview of pregnancies after treatment with TachoSil application in the uterine cavity.

Patient	Pregnancy	Cesarean section	Age	Menostasia	Time since delivery	Ultrasound		Hysteroscopy	Pathology	
				Month[a]	Month	Scar	TachoSil (mm)	TachoSil (mm)	Endometrium	TachoSil
No pregnancy after application of TachoSil in the uterine cavity										
2	6	2	41	Mens	25	Visible	no	no		
5	2	1	38	3	13	Visible	yes 2×1	yes punctual		
6	4	3	32	Mens	13	Visible	no	yes 0 15×1	no	no
9	2	1	37	Mens	7	Visible	yes 3×3	yes 3×3		
10	1	0	34	6	7	Visible	yes 4×2	yes 4×2	yes	no
12	1	0	31	1	9	Visible	yes punctuate	yes punctuate	yes	yes
15	4	1	29	Mens	5	Visible	no	yes 0 10×1	yes	yes
Pregnancy after application of TachoSil in the uterine cavity										
3	1	0	31				†			
4	1	0	35	8	19	Visible	no	no	yes	yes
7	1	0	31	2	9	Visible	no	no		
8	1	0	30	1	11	Visible	yes 3×3	yes 3×3	yes	yes
11	1	0	32	3	6	Visible	no	yes punctuate	yes	no
13	1	0	31				†			

[a] Mens: menstruation was regained approximately two to three months postpartum, but they did not remember the exact time interval for menostasia.
† Did not attend the clinical control due to pregnancy.

Table 2: Outcome of pregnancies two years after clinical control.

Patient	Pregnancy	Outcome
3	1	Spontaneous vaginal delivery at term
4	1	Spontaneous vaginal delivery at term
7	1	Cesarean section at term due to previosly cesarean section with placenta accreta and previa
8	1	Cesarean section at gestational week 41+5
11	1	Spontaneous vaginal delivery at term
13	3	Abortus inhibitus Abortus provocatus Ongoing pregnancy in gestational week 20

resumed menstruation and showed no signs of adhesion on hysteroscopy.

Delivery of patients with placenta previa may be difficult, and the associated risk of excessive bleeding can cause maternal death [8].

Using TachoSil to reduce the volume of haemorrhage during cesarean section due to placenta previa has demonstrated potential benefits. Thus this new method may control the heavy bleeding and save life without dramatic consequences for the woman giving birth. Therefore it seemed rational to introduce the procedure of applying TachoSil to the lower uterine segment in the presence of uncontrolled hemorrhage in spite of given uterotonics and before B-lynch suture or ligation of internal illiac artery was performed [7].

TachoSil consists of equine collagen, human thrombin, and fibrinogen. TachoComb, a predecessor to this product, is very similar, consisting of equine collagen, bovine thrombin, human fibrinogen, and bovine aprotinin. It is degraded intraperitoneally within 12 weeks in the majority of patients [5]. In a rabbit model, administration of TachoComb prevents adhesions compared to no treatment after operative procedures. Furthermore, histological investigations reveal that the outer surface of the applied TachoComb patch was completely covered by a new serosal layer 2 weeks after

the operation [6]. These studies support the intrauterine appliance of TachoSil to avoid postpartum hysterectomy and preserve a woman's ability to become pregnant.

However, more studies are needed on the effect of TachoSil application in the uterine cavity; especially needed is an evaluation of the use of TachoSil in the corpus of the uterine cavity for placenta site bleeding after childbirth.

In four patients, there were no visible remnants of the TachoSil. In eight of the patients traces of TachoSil were found in the uterine cavity. Based on visual impression there were no endometrial reactions or signs of inflammation related to these remnants. The size of the TachoSil swab applied was 3.0×2.5 cm. Remnants varied from punctate to 1.5×1 cm, but our impression was that TachoSil was in the process of being resorbed in all patients. The largest remnant was found in patient 6, although TachoSil had been applied 13 months previously, confirming the individual variation in the time of resorption. The cesarean sectional scar healed without large scar defects. TachoSil has been used for the sealing of anastomoses [9] and in hernia repair [10], and, as evidenced by other studies, it does not seem to compromise scar formation.

5. Conclusion

Application of TachoSil to the lower uterine segment is an efficient haemostatic procedure to control excessive haemorrhage due to placenta previa. Technically the procedure is an easy and safe procedure and can be performed in all surgical wards. We did not find endothelial defects at the site of TachoSil application or the formation of adhesions in the uterine cavity. The fact that six of the patients became pregnant spontaneously supports this theory. Even though we found TachoSil remnants in eight of the patients, the size of these remnants supports the fact that the speed of resorption varies from patient to patient. Furthermore, this variation had no consequence for the women's reproductive ability, because all had resumed menstruation.

References

[1] M. Roethlisberger, I. Womastek, M. Posch, P. Husslein, N. Pateisky, and R. Lehner, "Early postpartum hysterectomy: incidence and risk factors," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 89, no. 8, pp. 1040–1044, 2010.

[2] E. F. Magann, S. Evans, M. Hutchinson, R. Collins, G. Lanneau, and J. C. Morrison, "Postpartum hemorrhage after cesarean delivery: an analysis of risk factors," *Southern Medical Journal*, vol. 98, no. 7, pp. 681–685, 2005.

[3] F. J. Mercier and M. van de Velde, "Major obstetric hemorrhage," *Anesthesiology Clinics*, vol. 26, no. 1, pp. 53–66, 2008.

[4] L. K. Petersen, H. Oxlund, N. Uldbjerg, and A. Forman, "*In vitro* analysis of muscular contractile ability and passive biomechanical properties of uterine cervical samples from nonpregnant women," *Obstetrics and Gynecology*, vol. 77, no. 5, pp. 772–776, 1991.

[5] H. Osada, H. Tanaka, T. K. Fujii, I. Tsunoda, T. Yoshida, and K. Satoh, "Clinical evaluation of a haemostatic and anti-adhesion preparation used to prevent post-surgical adhesion," *Journal of International Medical Research*, vol. 27, no. 5, pp. 247–252, 1999.

[6] G. Dickneite, U. Rolle, and D. Rosenthal, "Prevention of gynaecological adhesions using haemostatic fleece in a rabbit model," *Journal of International Medical Research*, vol. 34, no. 5, pp. 505–513, 2006.

[7] K. Fuglsang and L. K. Petersen, "New local hemostatic treatment for postpartum hemorrhage caused by placenta previa at cesarean section," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 89, no. 10, pp. 1346–1349, 2010.

[8] M. Tikkanen, M. Gissler, M. Metsäranta et al., "Maternal deaths in Finland: focus on placental abruption," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 88, no. 10, pp. 1124–1127, 2009.

[9] T. P. van Doormaal, A. van der Zwan, B. H. Verweij, M. Biesbroek, L. Regli, and C. A. Tulleken, "Experimental simplification of the excimer laser-assisted nonocclusive anastomosis (ELANA) technique," *Neurosurgery*, vol. 67, no. 3, pp. ons283–ons290, 2010.

[10] N. Arslani, L. Patrtj, M. Kopljar et al., "Advantages of new materials in fascia transversalis reinforcement for inguinal hernia repair," *Hernia*, vol. 14, no. 6, pp. 617–621, 2010.