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Journal of Clinical & Experimental Cardiology

Mini Review

Maternal-Fetal Outcomes of Hemochromatosis and Iron Supplementation in Pregnancy

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ABSTRACT

Hemochromatosis, or pathologic iron overload, perpetuates a wide array of clinical manifestations due to cytotoxic iron deposition in various organ systems. The condition develops later in women due to iron loss during menses, pregnancy, and breastfeeding. Iron stores in pregnancy are naturally diluted by blood volume expansion; however, iron overload from genetic predisposition or iron over-supplementation is still possible and carries similar risks to iron deficiency in pregnancy. This mini review examines current understanding of the effects of iron overload in pregnancy on maternal and fetal outcomes. Evolving evidence suggests that adverse maternal outcomes include preeclampsia and gestational diabetes mellitus. Adverse neonatal outcomes include increased risk for neurocognitive deficits and later development of T1DM. These findings call into question the universal recommendations for iron supplementation in pregnancy, especially in pregnant women with iron-sufficiency or predisposition to overload.

Keywords: Hemochromatosis; Pregnancy; Iron-overload; Preeclampsia; Iron supplementation; Maternal outcomes; Neonatal outcomes

INTRODUCTION

Hemochromatosis is a disorder of excess iron storage and pathologic iron deposition into bodily tissues [1]. It is divided into two classes: Acquired-type and the more prevalent Hereditary (primary) Hemochromatosis (HH). HH is commonly derived from mutations in the *HFE* gene (e.g., *C282Y* and *H63D*) [1,2]. The *HFE* gene modulates expression of hepcidin, the key hormone that controls iron metabolism. Hepcidin is typically upregulated in enterocytes and macrophages in response to inflammatory states and increased iron levels to prevent intestinal absorption of iron into the bloodstream [2]. In HH, hepcidin is under-expressed and iron is continually absorbed from the digestive tract despite increasing iron storage, measured by serum ferritin levels [2]. Secondary hemochromatosis is iron excess from repeated blood transfusions, disorders of erythropoiesis, and rarely oral iron over-supplementation. The ability of the human body to accumulate iron is not surprising, given it has no natural excretory mechanism [1]. Clinical manifestations of hemochromatosis are related to free radical production from excess iron in tissue, culminating in end-organ damage [1,2]. The classic triad of manifestations is cirrhosis, diabetes mellitus, and skin pigmentation; the latter two are commonly coined "bronze diabetes". Additional manifestations include arthropathy, cardiomyopathy, hypogonadism, hypothyroidism, and an increased risk of developing certain bacterial infections [1].

Hemochromatosis has long been shown to appear later and with milder manifestations in women due to iron loss during menses, pregnancy, and breastfeeding [3]. In pregnancy, iron stores are diluted because of blood volume expansion for maternal-fetal combined growth [4]. Iron is essential for oxygen transport in red blood cells from the maternal to the feto-placental circulation and supports fetal hematopoiesis, growth, and neurocognitive development [5]. Iron deficiency in pregnancy is associated with preterm labor, increased rates of instrumental or cesarean delivery, postpartum hemorrhage, maternal mortality, and adverse neonatal outcomes [5]. Consequently, the World Health Organization (WHO) recommends weekly iron supplementation throughout pregnancy for all women beginning as early as conception [6]. While pregnancy itself is typically a protective factor

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Received: 21-Feb-2024, Manuscript No. JCEC-24-29699; **Editor assigned:** 23-Feb-2024, PreQC No. JCEC-24-29699 (PQ); **Reviewed:** 08-Mar-2024, QC No. JCEC-24-29699; **Revised:** 15-Mar-2024, Manuscript No. JCEC-24-29699 (R); **Published:** 22-Mar-2024, DOI: 10.35248/2155-9880.24.15.880

Citation: Delahunty M, Sadek B, Yerigeri K (2024) Maternal-Fetal Outcomes of Hemochromatosis and Iron Supplementation in Pregnancy. J Clin Exp Cardiolog. 15:880.

against the later manifestations of hemochromatosis in a predisposed female, it must be emphasized that iron overload in pregnancy is equally as ominous as iron deficiency for both maternal and neonatal outcomes.

LITERATURE REVIEW

The effects of iron overload on maternal outcomes

The role of hemochromatosis in perpetuating hypertensive disorders of pregnancy (e.g., preeclampsia) is not an inherently obvious concept; however, a multitude of studies have shown that serum iron and ferritin levels are significantly higher in preeclamptic women than non-preeclamptic women [7,8]. Recent evidence has attributed the role of iron overload in preeclampsia to "ferroptosis" or programmed cell death in response to iron-induced lipid peroxidation of cell membranes [9]. In women who are iron-overloaded, there is increased ferroptosis of Extra-Villous Cytotrophoblastic (EVCT) cells at the materno-fetal junction leading to incomplete penetration and poor development of maternal spiral arteries during weeks 8-18 of gestation [9,10]. This abnormal pattern of placentation is characteristic of preeclampsia and results in tissue hypoxia, free radical release, endothelial dysfunction, and life-threatening hypertension [10]. Another potential mechanism for the role of excess iron in preeclampsia is production of excess hemoglobin and increased blood viscosity, which may lead to poor perfusion and maladaptive development of the spiral arteries [9]. Specific to females with HH, the *HFE* gene mutation plays an additional role in increased absorption of lead in addition to iron. This is due to upregulation of DMT-1, a divalent metal transporter modified by *HFE*, in both the duodenum and placenta [11]. Even when women with HH limit lead exposure, there remains a high risk for fetal lead toxicity. Lead, which shares a similar pathophysiology with iron, has been significantly and substantially implicated in the development of gestational hypertension and preeclampsia [11].

In accordance with these findings, many studies have explored the predictive capacity of maternal serum hepcidin levels for the development of preeclampsia. In a non-preeclamptic pregnancy, maternal hepcidin production is gradually suppressed in response to increased placental demand for iron, with the lowest concentrations in the third trimester [12]. In contrast, multiple studies have shown that maternal third trimester serum hepcidin is significantly elevated in preeclamptic pregnancies compared to controls despite elevated serum ferritin [13]. The inappropriate rise in serum hepcidin in these preeclamptic patients is likely a reflection of the body's innate defense mechanisms against iron overload and cytotoxicity.

Further maternal complications because of iron excess in pregnancy include development of Gestational Diabetes Mellitus (GDM). A meta-analysis of 10 studies performed by Sun et al found an association between elevated maternal ferritin levels and development of GDM [14]. The suspected pathogenesis of this phenomenon is similar to that of the diabetes mellitus caused by hemochromatosis; excess iron deposits in the pancreas and peripheral tissues, leading to B-cell toxicity and decreased insulin secretion as well as insulin resistance throughout the body [15]. The risk for the development of diabetes with iron excess is compounded by the fact that the maternal body is predisposed to the development of insulin resistance *via* a series of hormones (e.g., placental lactogen) which work together to elevate blood glucose so that it is readily transported across the placenta to the growing fetus [16]. GDM is associated with adverse maternal and neonatal outcomes including maternal development of long-term type II diabetes mellitus, fetal macrosomia, preterm birth, and preeclampsia.

The effects of iron overload on neonatal outcomes

Iron deficiency in pregnancy is associated with adverse neonatal outcomes such as low birth weight, preterm birth, Intrauterine Growth Restriction (IUGR), and neurocognitive deficits of the infant that may extend into adulthood [5]. Although less studied, iron excess in pregnancy has been associated with a multitude of equally poor neonatal outcomes, notably neurocognitive deficits. Iron excess in the fetal/neonatal brain (which lacks complete antioxidant capacity) generates reactive oxygen species that may lead to ferroptosis and/or iron deposition in developing brain structures [17]. In mothers with HH, increased lead absorption as a function of the *HFE* mutation may also compound neurocognitive deficits in the developing fetus due to excess lead deposition [11]. A study by Samallahti et al found that children exposed to high maternal iron had 16.02 cm^3 smaller total brain volume and a 2.5 point lower IQ than children exposed to average levels of maternal ferritin [18]. Another study conducted in Norway by Størdal et al., suggested that both fetal exposure to excess iron secondary to maternal HH and maternal iron supplementation during pregnancy is a risk factor for later development of type 1 diabetes regardless of their *HFE* genotype status [19]. Preeclampsia itself is also a risk factor for preterm birth (<37 weeks) [10], which has extensively been associated with increased neonatal mortality and a wide array of neonatal morbidities [20].

DISCUSSION

Hereditary hemochromatosis, inherited in an autosomal recessive fashion, is one of the most common genetic disorders amongst Caucasians, affecting 1 in every 300-500 individuals [1]. When the physiologic, dilutional iron deficiency of pregnancy and its associated adverse neonatal outcomes are taken into account, it can be understood why mutations for HH may have been selected for from an evolutionary standpoint. With mutations for HH being so prevalent, it calls into question the universal use of iron supplements in pregnancy as well as the lack of recommendations for routine iron studies at initial prenatal visits [6,21].

The WHO bases its evidence on a Cochrane review that reports that women who take daily iron supplements throughout pregnancy are less likely to have low birth weight infants compared to controls and have a reduced risk of maternal anemia and iron deficiency at term by 70% and 50%, respectively [6,22]. However, the WHO states this intervention seems to be most effective amongst populations with

high prevalence of iron deficiency anemia. It does not speculate on the effects of iron supplementation in iron-sufficient populations and could not therein show a clear benefit of supplementation on maternal and infant clinical outcomes [6,22]. The United States Preventative Task Force (USPSTF) contradicts the WHO and states that there is insufficient evidence to advocate for universal iron supplementation in pregnancy as the benefits do not outweigh the risks for women with sufficient iron stores [21]. A trial conducted by Ziaei et al., found that iron supplementation throughout pregnancy in women with elevated hemoglobin levels was associated with increased rates of low birth weight and hypertensive disorders of pregnancy compared to controls [23]. Iron supplementation has also been shown to increase symptoms of morning sickness and nausea in the first trimester and carries the risk of damaging the stomach lining, leading to severe constipation or diarrhea [24].

Iron supplementation could be a larger risk than intended for women with sufficient iron stores or predispositions to iron overload (e.g., HH, disorders requiring frequent transfusions). Given the prevalence of HH and risk for iron over-supplementation in iron-sufficient individuals, it could be argued that iron supplementation in pregnancy should be recommended on a case-by-case basis per iron studies throughout the course of pregnancy.

CONCLUSION

Iron overload in pregnancy carries similar risks as iron deficiency for the mother and fetus. Maternal adverse outcomes of iron overload include hypertensive disorders of pregnancy and gestational diabetes mellitus. Neonatal adverse outcomes from maternal iron overload are under-studied; however, studies suggest associations with neurocognitive deficits, preterm birth, and later development of T1DM. The recent findings of risks affiliated with iron overload in pregnancy raises doubts surrounding the universal use of iron supplementation in prenatal care. More studies are needed to determine whether iron supplementation in iron sufficient pregnant women should be routinely recommended. Future guidelines on prenatal care could benefit from research into the effects of specific *HFE* gene mutations. There is adequate evidence to support the association between elevated hepcidin levels and preeclampsia in the third trimester, future exploration of hepcidin as an early biomarker for preeclampsia could be revealing.

DISCLOSURES AND CONFLICT OF INTEREST

All authors have no relevant conflicts of interest to declare.

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