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Review

Is oxidative stress induced by iron status associated with gestational diabetes mellitus?

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ABSTRACT

Gestational diabetes mellitus (GDM) is a common pregnancy complication in high risk populations, and is associated with increased perinatal and long term outcomes for both mothers and newborns. Both its prevention and early management can be reinforced by identifying risks factors, particularly those factors influencing glucose metabolism. On the other hand, several epidemiological studies have shown an increased oxidative stress (OS) in pregnant women with GDM. Elevated OS was also reported in pregnant women supplemented with iron, which can generate OS and may also influence insulin resistance. This review summarizes the current state of knowledge, highlighting the potential relationship between OS induced by iron status and the development of GDM.

Contents

Introduction

Gestational diabetes mellitus is defined as carbohydrate intolerance resulting in hyperglycemia of variable severity that occurs or is first recognized during pregnancy. GDM is characterized by pancreatic β-cell function that is insufficient to meet body insulin needs, probably due to autoimmune diseases, genetic abnormalities or insulin resistance [1]. The prevalence of GDM may range from 1% to 14% of all pregnancies, depending on the studied population and diagnostic criteria [2]; The criteria recently proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) would diagnose ~18% of all women as having GDM [3]. GDM is associated with increased perinatal risks for newborns including macrosomia, shoulder dystocia, birth injuries, hypoglycemia and long term health outcomes including childhood obesity, impairment of glucose tolerance and intellectual achievement. Maternal risks include preeclampsia, cesarean delivery, and increased risk of developing type 2 diabetes late in life [4]. Recently, recommendations to lower the diagnostic thresholds for GDM, to optimize the detection of women who may be at risk have been proposed by international experts [3].

Insulin resistance or relative insulin deficiency both before and during pregnancy have been proposed to be risk factors for GDM [5]. Underlying mechanisms potentially involved inflammation and OS processes. Association between iron and GDM has also been examined and biological intertwining of iron status and insulin resistance has been proposed [6–9]. Large prospective cohort studies reported that high iron dietary intake and serum ferritin levels (a biomarker of body iron stores) were positively associated with

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diabetes risk [6,9–11] and inflammation [12]. Elevated iron status may increase the risk of type 2 diabetes by increasing OS according to the pro-oxidant property of free iron and the relationships between OS and insulin resistance [13]. While a recent theory on the redox paradox regulation of insulin suggests that a low level of free radical might be necessary to improve insulin sensitivity, a high level inducing an OS is tightly associated with hyperglycemia. Iron may also induce insulin resistance by reducing the insulin extraction capacity of the liver, leading to a decrease in glucose uptake by adipocytes and muscles. An enhancement of free fatty acid oxidation may cause iron deposition in pancreatic β-cells resulting in impaired insulin secretion [8]. Finally, the association between high iron levels and a high incidence of type 2 diabetes may partly be explained by the filling of both transferrin metal-binding sites by iron [14], leading to a deficiency of chromium, an essential element that increases insulin sensitivity [15]. Interestingly, induction of near iron deficiency by reducing the iron intake or ferritin levels in carbohydrate-intolerant subjects has been shown to improve insulin sensitivity [16,17]. Within the framework of this biological possible causal implication between iron and GDM onset, we aim to summarize the current state of knowledge of body iron status involved in the development of GDM, with a focus on the potential role of OS induced by iron in the generation and progression of this disease. According to the hypothesis that a high iron status and OS constitute the main factors leading to the development of insulin resistance, and considering on the other hand that iron deficiency prevalence increases during pregnancy as iron requirements are increased due to the iron needs of the growing fetus, this literature review firstly aim to answer the question: should iron supplementation be given to non-anemic pregnant women and if so which dose of iron might be proposed to avoid the risk of inducing GDM?

Iron supplementation during pregnancy

Iron requirements are greater in pregnancy than in the nonpregnant state [18] and iron deficiency anemia (IDA) is still prevalent among pregnant women throughout the world [19]. IDA occurring early in pregnancy is associated with low birth weight, prematurity and increased risk for maternal and fetal perinatal mortality [20,21]. Gestational and early postnatal IDA in humans results in concurrent and persistent learning and memory deficits in later childhood and adulthood [22]. Iron supplements are necessary in order to prevent IDA and its consequences for the mother and the newborn. According to criteria of World and Health Organization (WHO), IDA during pregnancy is defined as anemia (hemoglobin (Hb) lower than 110 g/L during the first and third trimester or lower than 105 g/L during the second trimester) accompanied by depleted iron stores [23], which may be indicated by a serum ferritin concentration of less than 12 μg/L [24]. A systemic review and meta-analysis concluded that iron supplementation during pregnancy may be used as a preventive strategy to improve maternal hematological status and birth weight [25]. However, a review of controlled trials failed to demonstrate that daily iron supplementation of iron replete women improves clinical outcome of either the mother or newborn [26]. Iron supplements and increased iron stores have been linked to maternal complications and increased OS during pregnancy. Consequently, while, iron supplementation may improve pregnancy outcomes when mother is anemic, the prophylactic supplementation may increase risk when mother does not have IDA or having high iron stores [27,28]. There is no consensus concerning iron prophylaxis to pregnant women and each country has its specific recommendation concerning this issue. For Canadian guidelines [29], ideally prophylactic iron dose should be the lowest possible between 16 and 20 mg/day which is sufficient to prevent IDA and to minimize potential negative effects on mineral absorption and adverse gastrointestinal symptoms. In Danish non-anemic women, a supplement of 40 mg ferrous iron per day onward 18 weeks of gestation was demonstrated as being effective in preventing IDA, while a dose of 20 mg iron per day appeared to be insufficient [30]. In this study, however, the beneficial effect played only on ferritin levels since the authors found no significant differences between the four iron supplemented groups (20, 40, 60 and 80 mg/day) at delivery regarding Hb, serum soluble transferrin receptors and on newborn outcomes (birth weight, birth length, Apgar score, or cord blood pH). Apparently, there was no benefit of giving higher doses of 60 or 80 mg of iron [31]. In order to ensure adequate iron supply, Milman suggested [32] that individual iron prophylaxis according to serum ferritin concentrations in early pregnancy is most appropriate for developed countries, and iron supplements are not recommended with ferritin level above 70 μg/L, while oral iron supplements of 30–40 mg and 60–80 mg daily are indicated with ferritin values between 30–70 μg/L and <30 μg/L respectively. However in these latest studies the beneficial effect to prevent IDA was determined on mothers' hematological parameters without beneficial outcomes on newborn. A previous study [33], has also conclude to a beneficial effect of iron supplementation to prevent IDA considering only increased hematologic parameters at delivery of the iron supplemented mothers while the control group were remained on the normal range for pregnancy hematological criteria according to WHO [23]. While risks for negative consequences, as premature delivery and low birthweight, increase when women's Hb levels, are below 95–105 g/L at any time in pregnancy or above 130–135 g/L after mid-pregnancy [24]. The below value for Hb was not reached in both studies [32,33] whereas the highest values have been reached with iron supplementation. In a large prospective study on 2654 pregnant women the authors [34] concluded to a beneficial effect of an intravenous iron polymaltose followed by an oral intake of 80 mg/day iron element rather than only taking oral iron tablets to correct anemia. Yet, in this study too, the beneficial effect was established only on ferritin levels and serum Hb concentrations considering the difference of increase between the treatments. However, no beneficial effects of iron supplement on placental cord Hb and the birthweights of the babies in the two arms were observed while, on the contrary, a significant negative association between serum iron and iron saturation and maternal weight is observed. The level of glycemia was not mentioned but iron could have decreased glucose tolerance leading to an increase in weight.

These observations lead to prefer selective iron supplementation over a systematic one [26]. A normal Hb level for pregnancy or a ferritin level at 70 μg/L seems a good indicator to predict a normal pregnancy avoiding the deleterious effect of a too low or too high iron store.

Iron supplementation and oxidative stress in pregnancy

Although iron is an essential mineral, it is also an element of conflicting effects: it can be either beneficial or detrimental to the cell, depending on whether it serves as a micronutrient or as a catalyst of free radical reactions. Through the Fenton reaction iron can generate reactive oxygen or nitrogen species leading to OS, leading to cellular damage by acting on proteins, lipids and DNA. Both localized and generalized iron excess are situations where free radical damage has been observed which can lead to functional disturbances and foster genetic alterations [35]. Mediated OS may thus contribute to β-cell dysfunction and insulin resistance even in the absence of significant iron overload [7,8]. Interesting studies have shown that iron supplementation associated with vitamin C increased oxidative stress whereas vitamin E [36] or polyphenol decreased the oxidative stress induced by iron supplementation [37].