

Review Article

Maternal Serum Iron and Zinc Levels and Gestational Diabetes

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Abstract

Gestational diabetes, a metabolic disturbance in pregnancy has many predisposing factors such as maternal age, history of gestational diabetes, familial history of diabetes, and obesity. There have been many studies performed all over the world to recognize more risk factors for gestational diabetes in order to better control it. Micronutrients such as iron and zinc status in the body are good examples in this regard. The studies have shown that despite the increased need for iron during pregnancy, if there is an iron overload in body, it may predispose the mother to gestational diabetes; but there has been no significant relationship observed between body zinc status and gestational diabetes occurrence. Thus, medical practitioners should consider checking the iron status of pregnant women before giving iron supplements to them.

Keywords: Gestational Diabetes Mellitus; Iron; Zinc; Pregnancy

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Introduction

Gestational diabetes mellitus (GDM) is becoming a great challenge in pregnancy for medical practitioners all over the world because of the ever-increasing incidence of obesity and sedentary lifestyles, which are the main predisposing factors for diabetes and gestational diabetes too. Apart from taking the necessary measures for controlling the established predisposing factors for GDM, there is a great need to identify any potential factors affecting this metabolic disturbance in pregnancy. There have been many investigations performed in recent years to find these potential risk factors and define their effects on GDM, some of which have been micronutrients and minerals including iron and zinc body stores.

There is no definite risk factor for GDM, but many factors have been proposed, such as age, familial history of diabetes, and history of GDM. About iron and its role in inducing GDM, there have been many studies performed, but still it is a

controversial issue, despite the increasing number of investigations confirming the role of high body iron stores and also serum levels in inducing GDM [1].

In this review, the metabolic changes of maternal iron and zinc in pregnancy and their role in the occurrence of GDM are discussed.

Metabolic changes in pregnancy

There are many systemic and metabolic changes in pregnancy that result in outstanding alterations in oxygen and energy consumption not only in fetoplacental unit but also in other organs. Placenta can influence body homeostasis, from the beginning of its formation, and when quite matures, it approximately uses 1% of basal metabolic energy. There is only one thin layer of chorionic cells between maternal and fetal vasculature system in human placenta to facilitate gas, nutrient and metabolic products' exchange [2]. There are positive correlations between maternal serum and cord blood levels of

micronutrients including iron and zinc showing that most micronutrients pass rather freely from placental barrier and maternal reservoirs are the main micronutrient providers for the fetus [3].

Iron and pregnancy

Iron is a micronutrient needed for many essential functions of the body; operating in multiple enzymatic functions, constituting a major part of hemoglobin, and thus playing a great role in body tissues' oxygenation. During pregnancy, the fetus gets all its needed iron from maternal sources even when the mother has poor iron reserve thus causing or exacerbating maternal anemia [4]. There is an increased need for iron during pregnancy especially during the second and third trimesters when the fetus needs much more iron for growth and development. Iron absorption in mother is decreased in the first trimester of pregnancy, but increases continuously by pregnancy progression into second and third trimesters. The daily requirements for iron during the first, second and third trimesters of pregnancy are approximately 0.8, 4-5, and >6 mg respectively, so most women need iron supplementation after the first trimester of pregnancy [5]. Homeostatic balance of iron in pregnancy is maintained through increased iron absorption, tissue oxygenation, and heart output [6].

In many countries especially in the developing ones where most women in reproductive ages are iron deficient, or suffer from iron deficiency anemia,

it is a common practice to provide iron supplementation for all pregnant women after the 16th week of pregnancy. But this practice has its own downfalls; recent studies have shown that increased iron in the body or iron overload may cause some complications such as intra uterine growth retardation (IUGR), preterm labor, preeclampsia, and gestational diabetes [7].

Zinc and pregnancy

Zinc as an important micronutrient is necessary for many functions in the body, including immunological functions, division of cells, and protein synthesis. Zinc plays an essential role in growth and development of fetus during pregnancy, and if the mother because of consuming little animal source foods- the main source of providing zinc in nutrition- or much phytate source foods- inhibiting zinc absorption suffers zinc deficiency ,there will be adverse outcomes such as preterm birth, low birth weight, and increased overall infant mortality. In a study performed in Tehran on 1033 pregnant women, it was observed that women with preeclampsia had significantly lower zinc levels in their early stages of pregnancy in comparison to normal women [8]. In the studies evaluating the effect of zinc supplementation on pregnancy outcomes, the improved outcomes were included preterm birth. Since zinc enhances maternal immune functions ,it ,reduces the incidence or the severity of maternal infections which in turn lead to reducing infection-induced preterm births [9].

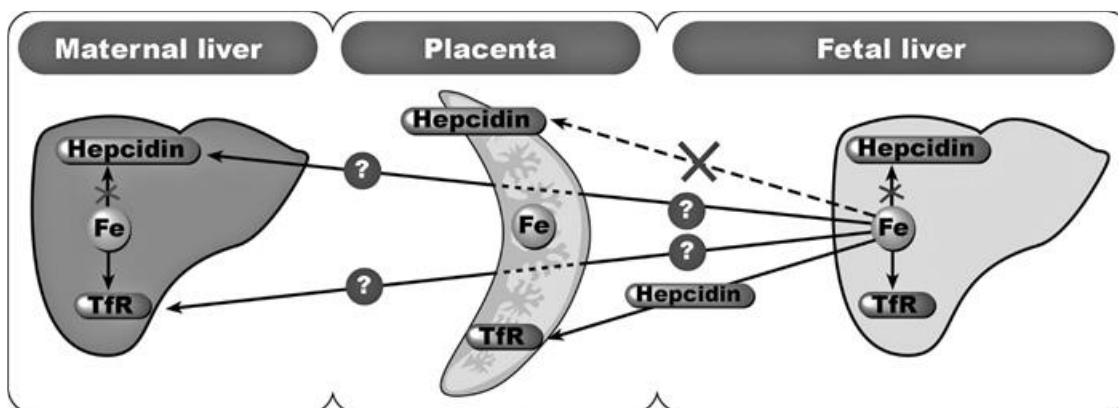


Figure 1. adapted from [4]. A summary of the proposed model for fetal regulation of iron metabolism during pregnancy. The model shows the pathways identified in these experiments and suggests how the different organs and systems interact.

Zinc deficiency can have other harmful effects in pregnancy, such as prolonged labour, intrauterine growth retardation (IUGR), teratogenesis, abortion, and still birth. Several studies have found a positive correlation between maternal serum zinc levels and birth weight, and also found that zinc supplementation may reduce some complications of pregnancy such as gestational hypertension, delivery problems, IUGR, preterm labour and small for gestational age (SGA) infants [10]. On the other hand a study in Iran showed that among the trace elements iron, zinc, copper, magnesium, and calcium; only maternal serum levels of calcium were inversely related to low birth weight occurrence [11].

There are some physiologic changes in zinc metabolism during pregnancy which result in 15-35% decreased plasma zinc and increased zinc content of erythrocytes- probably both due to increased plasma volume in pregnancy [12]. There is an excess need for zinc in pregnancy because of both pregnancy and fetal demand for healthy growth and development [13].

It is estimated that because of the weight gain in pregnancy, and thus the increased need for preserving zinc concentration in the newly developed tissues, the need for zinc increases about 5-7 percentage of total zinc concentration in the body; approximately 100 mg more zinc are needed during pregnancy, which is mainly used and stored in the fetus and uterine muscles. It is postulated that apart from the need to increase zinc intake during pregnancy, there are some compensatory mechanisms in the body to meet this excess need for zinc in pregnancy, such as some alterations in intestinal zinc absorption to increase the amount of absorbed zinc and contribute to the balance of the homeostatic status of zinc. The other possible mechanisms to meet this excess need are: reduced zinc secretion in gastrointestinal and urinary tracts, and decreased zinc release from maternal tissues. There is no evidence for reduced fecal zinc content in pregnancy; on the other hand, it is established that urinary zinc content is increased during pregnancy, possibly because of the increased glomerular filtration rate. For maternal tissues releasing zinc; studies have shown the same bone mineral contents, before and after pregnancy (30% of body zinc is

stored in the bones). Thus the only compensatory mechanism to meet excess pregnancy zinc demand, is possibly the increased intestinal absorption of zinc during pregnancy.

If any condition obscures transfer of zinc to fetus, such as high doses of iron supplementation, cigarette smoking, or alcohol consumption; both mother and fetus may be prone to zinc deficiency consequences [10].

A study on adolescent pregnancies in Brazil showed that there were no differences between adolescent and adult pregnant women in their zinc biochemical reactions to pregnancy. It was also observed that the pregnant adolescents had lower plasma zinc concentrations than non-pregnant adolescents [12].

Iron and gestational diabetes

The first evidence for the role of iron overload in inducing diabetes was found when scientists observed that hemochromatosis patients were more at risk for acquiring type 2 diabetes. Then it was observed that frequent blood donations and decreasing iron stores of the body reduced insulin resistance. A likely hypothesis for the mechanism of iron-induced diabetes is the link between iron overload in liver, hepatic dysfunction, and insulin resistance [14]. Thus iron overload may play a role in increasing insulin resistance, and as there is a physiologic predisposition to insulin resistance in pregnancy due to hormonal changes and homeostatic alterations, it is logical to speculate that iron overload has a potential effect on gestational diabetes.

In a systematic review and meta-analysis published in 2015, there was a significant positive correlation found between serum ferritin and heme iron levels and risk of GDM, but no relationship found between serum transferrin and GDM. Of the predisposing factors investigated in that study, maternal age was the most important risk factor for GDM. It should be considered that if serum ferritin levels are high, it may be due to either high body iron stores, or some inflammation because of ferritin's being an acute phase reactant [1].

Oxidative stress and iron

In early pregnancy, there is a hypoxic environment in placenta, but with increasing placental

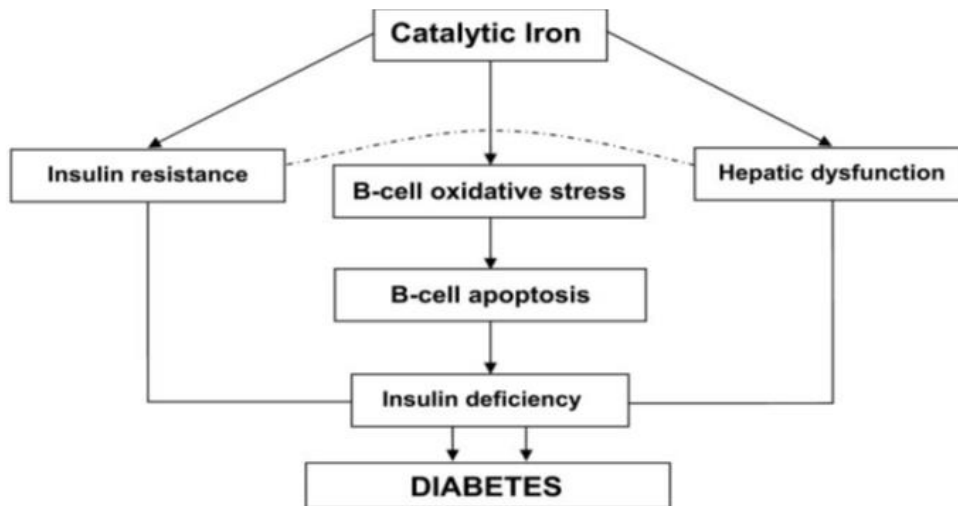


Figure 2. adapted from [14]. Pathogenic pathways for iron in induction of diabetes.

maturity and vascularization, it becomes oxygen rich with a great number of mitochondria, which result in production of reactive oxygen species (ROS). ROS enhance free iron production from iron-sulfur clusters.

There are also numerous macrophages in placenta producing free radicals including reactive chlorine species (RCIS), which create more free iron themselves.

There is a theory that inflammatory cytokines (interleukin 1-β) may have a role in increasing free iron release from mitochondria or ferritin in pregnancy, and also enhancing ferritin synthesis [2].

All these evidence suggest that there is an increasing free iron load in pregnancy.

There are five oxidation states of iron (Fe²⁺-Fe⁶⁺), with the most common ones being Fe²⁺ and Fe³⁺ [15]. Oxygen can produce ROS in body, as iron has a great potency to change valence, when it gets a contact with oxygen, a potent free radical- hydroxyl- is generated from oxygen through Fenton Reaction[7]: Fe²⁺+H₂O₂→Fe³⁺+ OH⁻+ OH⁻[15]

Free radicals such as hydroxyl can harm cells, or various body organs and tissues, and may be important factors in aging, or development of cancer. Oxidative stress also plays a substantial role in the pathogenesis of type 2 diabetes. If there is excess iron in body even in moderate measures, it can impair the synthesis and secretion of insulin.

Moreover, ferritin in high levels has been shown to increase the risk of gestational diabetes [7].

Iron and zinc interaction

There have been many studies suggesting that high concentrations of iron may have unfavourable effects on intestinal absorption of zinc [16].

In a systematic review on iron and zinc supplementation and their status in body, it was found that zinc alone did not have a poor effect on iron status, but when iron and zinc were given together; iron status did not improve as well as when iron alone was given. The researchers did not find any evidence for the adverse effects of iron supplementation on zinc status, and in general they found no strong evidence on beneficial effects of iron and zinc supplementation together, despite the fact that each of them alone caused better status of the supplemented element [17].

On the other hand, a clinical trial performed in Peru on prenatal supplementation in third trimester of pregnancy showed that iron supplementation alone adversely affects zinc absorption percentage, maternal plasma and also cord zinc concentrations, thus it was recommended that zinc be included in prenatal complements[18]. Also in another study in Iran, on 538 pregnant women in their first trimester of pregnancy, it was observed that iron supplementation had negative correlations with serum zinc levels [19].

Taken together, it may be concluded that iron

overload in body can impair zinc absorption and cause some disturbances in homeostatic balance of zinc. As pregnant women because of prenatal supplementations are prone to iron overload, this imbalance in zinc status or overt zinc deficiency should be considered in prenatal care.

Zinc and gestational diabetes

There are limited studies about the relationship between maternal zinc and gestational diabetes; some of them are mentioned below:

A clinical trial on pregnant women with insulin resistance in Iran, showed that an 8 week zinc supplementation had no significant effects on improving insulin resistance, despite the increase in the serum levels of zinc in comparison to the placebo group[20].

In a prospective cohort study on 1033 pregnant women about nutritional intake and serum level of iron and zinc in early pregnancy and occurrence of gestational diabetes, there was no significant relationship between maternal zinc status and GDM, but a positive correlation was found between serum levels of iron and GDM [21].

Conclusion

GDM is a world- wide metabolic challenge in pregnancy with adverse effects on both mothers' and infants' health, that needs extensive care. Researchers are constantly studying to find relevant risk factors for this common pregnancy complication, in order to control them and thus reduce GDM incidence. Iron and zinc are among the studied factors; up to now, the studies have found limited evidence for zinc to affect GDM, but there are many studies suggesting that body iron has positive relations with GDM occurrence. Thus, it should be noted that health policies should not recommend iron supplementation in all pregnant women without first checking for their iron status, and unnecessary iron supplementation should be avoided.

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Conflicts of Interest

There was no conflict of interest in any part of this review.

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