Dietary iron intake, iron status, and gestational diabetes

Cuilin Zhang and Shristi Rawal

Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

ABSTRACT

Pregnant women are particularly vulnerable to iron deficiency and related adverse pregnancy outcomes and, as such, are routinely recommended for iron supplementation. Emerging evidence from both animal and population-based studies, however, has raised potential concerns because significant associations have been observed between greater iron stores and disturbances in glucose metabolism, including increased risk of type 2 diabetes among nonpregnant individuals. Yet, the evidence is uncertain regarding the role of iron in the development of gestational diabetes mellitus (GDM), a common pregnancy complication which has short-term and long-term adverse health ramifications for both women and their children. In this review, we critically and systematically evaluate available data examining the risk of GDM associated with dietary iron, iron supplementation, and iron status as measured by blood concentrations of several indicators. We also discuss major methodologic concerns regarding the available epidemiologic studies on iron and GDM. *Am J Clin Nutr* 2017;106(Suppl):1672S–80S.

Keywords: gestational diabetes mellitus, dietary iron, iron status, pregnancy, iron supplementation

INTRODUCTION

Free iron, with its strong pro-oxidant properties and consequent ability to generate reactive oxygen species, can contribute to increased oxidative stress and cellular damage and, hence, may be potentially hazardous in excess (1). The pancreatic β cells are vulnerable to oxidative stress because their antioxidative defense mechanisms are particularly weak (2). Although adequate iron is critical to normal β cell function and glucose homeostasis, studies based on mouse models of hereditary or dietary iron overload show that excess iron may disrupt glucose homeostasis by several potential mechanisms involving multiple tissues and organs. For example, oxidative stress from excess iron accumulation can lead to β cell damage and apoptosis and, consequently, contribute to decreased insulin secretion (3). High iron stores in the liver may induce insulin resistance by impairing insulin signaling and by attenuating the liver's ability to extract insulin (4, 5). In adipocytes, excess iron can diminish insulin-induced glucose transport, whereas in the muscles it may lead to a switch from glucose to fatty acid oxidation (6, 7).

In humans, iron status is primarily regulated by the intestinal iron absorption of consumed external iron (8, 9), as discussed elsewhere in these proceedings (10). Dietary iron is present in 2 forms: heme iron (animal flesh products) and nonheme iron (plants, some animal products, and supplements). The absorption of nonheme iron is tightly controlled by iron status and the liver-derived peptide hormone hepcidin (11, 12). Heme iron constitutes $\sim$10% of total dietary iron intake in a typical Western diet but accounts for nearly two-thirds of absorbed iron because of its substantially higher absorption (12). Moreover, iron utilization and bioavailability from heme iron sources are considerably higher than those observed for nonheme ferrous sulfate in both pregnant and nonpregnant individuals (12–14). However, neither the precise mechanisms nor the regulation of heme iron absorption is fully understood (12). Of note, iron absorption and homeostasis is also intimately linked to the inflammatory response (15). Hepcidin, the central regulator of iron homeostasis, is upregulated by inflammatory stress response pathways leading to decreased dietary iron absorption and the sequestering of iron in hepatocytes and macrophages (15). Circulating concentrations of iron markers, such as ferritin and transferrin receptors, may also increase in the presence of infection or inflammation, further complicating the accurate estimation of iron status in human populations (16, 17).

Iron deficiency is common among pregnant women, and as such, iron supplementation is often recommended to pregnant women (18). Emerging evidence from both animal and population-based studies, however, has raised potential concerns because significant associations have been observed between greater iron status and disturbances in glucose metabolism, including increased risk of type 2 diabetes among nonpregnant individuals (1, 19, 20). A meta-analysis of 12 studies from 2012 (20) concluded that high iron stores [as assessed by elevated serum ferritin (SF) concentrations] were significantly associated with an elevated risk of type 2 diabetes among nonpregnant individuals, with the evidence consistent among prospective studies (pooled RR: 1.66; 95% CI: 1.15, 2.39). Of note, all of

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Address correspondence to CZ (e-mail: zhangcu@mail.nih.gov).

Abbreviations used: CRP, C-reactive protein; GDM, gestational diabetes mellitus; SF, serum ferritin; sTfR, soluble transferrin receptor.

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TABLE 1
Summary of published studies examining the risk of GDM associated with dietary or supplemental iron intake during or before pregnancy[1]

Study, year	Comparison groups	Crude effect size RR/OR (95% CI)	Adjusted effect size RR/OR (95% CI)	Covariates
Dietary heme iron intake				
Bowers et al. (27), 2011	Highest vs. lowest quintile (median 1.60 vs. 0.66 mg/d)	2.13 (1.70, 2.67)	1.55 (1.13, 2.13)	Age, parity, BMI, physical activity, glycemic load, polyunsaturated fat intake, cereal fiber, smoking, alcohol, total calories, saturated fat, dietary cholesterol, and family history of diabetes
Qiu et al. (28), 2011	Highest vs. lowest quartile (median 1.43 vs. 0.30 mg/d)	2.12 (1.31, 3.43)	2.15 (1.09, 4.27)	Age, daily energy intake, race/ethnicity, parity, physical activity, prepregnancy BMI, dietary fiber, vitamin C, saturated fat, cholesterol, and red and processed meat intake
Darling et al. (29), 2016	Highest vs. lowest quintile (mean 50 vs. 0.28 mg/d)	2.53 (1.70, 3.78)	1.55 (0.98, 2.46)	Total calories, nonheme iron intake, iron supplements use, BMI, and dietary cholesterol
Dietary nonheme iron intake				
Bowers et al. (27), 2011	Highest vs. lowest quintile (median 45.33 vs. 7.58 mg/d)	0.79 (0.65, 0.96)	0.97 (0.78, 1.20)	Age, parity, BMI, physical activity, glycemic load, polyunsaturated fat intake, cereal fiber, smoking, alcohol, total calories, and family history of diabetes
Qiu et al. (28), 2011	Highest vs. lowest quartile (median 19.60 vs. 7.16 mg/d)	0.54 (0.29, 0.99)	0.61 (0.31, 1.18)	Age, daily energy intake, race/ethnicity, parity, physical activity, prepregnancy BMI, dietary fiber, vitamin C, saturated fat, cholesterol, and red and processed meat intake
Darling et al. (29), 2016	Highest vs. lowest quintile (mean 13.39 vs. 9.85 mg/d)	0.53 (0.34, 0.83)	0.48 (0.28, 0.81)	Total calories, heme iron intake, iron supplements use, age, glycemic index, and dietary fiber
Supplemental iron				
Palma et al. (32), 2008	Iron supplementation users vs. nonusers	Not provided	Not provided (null association)	Not applicable
Bo et al. (33), 2009	Iron supplementation users vs. nonusers	3.03 (2.18, 4.20)	3.36 (1.50, 7.53)	Age, family history of diabetes, prepregnancy BMI, education, smoking, parity, duration of iron supplementation, and employment
Darling et al. (29), 2016	Iron supplementation users vs. nonusers	Not provided	0.78 (0.60, 1.02)	Total calories, dietary iron intake, and BMI
Bowers et al. (27), 2011	Highest vs. lowest quintile (median 60 vs. 0 mg/d)	0.99 (0.81, 1.20)	1.04 (0.84, 1.28)	Age, parity, BMI, physical activity, glycemic load, polyunsaturated fat intake, cereal fiber, smoking, alcohol, total calories, and family history of diabetes
Chan et al. (34), 2009	Supplementation with 300 mg ferrous sulfate tablet vs. placebo	1.04 (0.70, 1.53)	Not applicable	Not applicable
Ouladsahebmadarek et al. (35), 2011	Supplementation with 30 mg elemental iron vs. placebo	Not provided	Not provided (null association)	Not applicable
Kinnunen et al. (36), 2016	Selective iron supplementation vs. routine iron supplementation	Not provided	Not provided (null association)	Not applicable
Dietary total iron				
Bowers et al. (27), 2011	Highest vs. lowest quintile (median 18.90 vs. 10.30 mg/d)	0.83 (0.68, 1.02)	1.12 (0.87, 1.45)	Age, parity, BMI, physical activity, glycemic load, polyunsaturated fat intake, cereal fiber, smoking, alcohol, total calories, and family history of diabetes

(Continued)

TABLE 1 (*Continued*)

Study, year	Comparison groups	Crude effect size RR/OR (95% CI)	Adjusted effect size RR/OR (95% CI)	Covariates
Behboudi-Gandevani et al. (31), 2013	Deficient iron intakes (<50% RDA recommendation) vs. sufficient iron intake	Not provided	0.70 (0.40, 1.13)	Age, BMI, education, parity, passive smoking, history of GDM, family history of diabetes, deficient zinc intake, and serum zinc, iron and hemoglobin concentrations
Total iron intake (including supplements)				
Bowers et al. (27), 2011	Highest vs. lowest quintile (median 49.80 vs. 10.70 mg/d)	0.78 (0.64, 0.96)	0.90 (0.72, 1.12)	Age, parity, BMI, physical activity, glycemic load, polyunsaturated fat intake, cereal fiber, smoking, alcohol, total calories, and family history of diabetes
Helin et al. (30), 2012	Highest 20% vs. lowest 80% (≥110 vs. <14.2 mg/d)	1.31 (0.70, 2.44)	1.66 (0.84, 3.30)	Age, BMI, family history of diabetes, prior GDM or macrosomia, total energy intake, gestational weight gain, and dietary fiber and SFAs

[1] GDM, gestational diabetes mellitus; RDA, Recommended Dietary Allowance.

these studies accounted for major potential confounders including BMI (in kg/m^2). Of the 12 studies, 4 studies (21–24) observed a significant positive association between ferritin concentrations and type 2 diabetes even after the adjustment for inflammatory status measured by C-reactive protein (CRP), adipokines, or cytokines. Accounting for inflammatory status is important because SF is elevated by inflammation. In animal models of type 2 diabetes, lowering iron concentrations through dietary iron restriction, iron chelation, or phlebotomy has been shown to improve β cell function (1). Yet, the evidence is unclear regarding the role of iron in the development of gestational diabetes mellitus (GDM), a common pregnancy complication that has short-term and long-term adverse health ramifications for both women and their children (25, 26). In this review, we critically evaluate available data on the association of GDM with different sources of dietary iron from food (i.e., heme compared with nonheme iron) and iron supplements, as well as iron status measured by the blood concentration of several indicators.

IRON INTAKE AND GDM

Dietary iron intake and the risk of GDM

The association of dietary iron intake from food with GDM risk has been examined in several studies (27–31), with the majority (27–29) being conducted among US populations (**Table 1**).

Among the 3 prospective studies, the 2 earliest studies (27, 28) found that only dietary heme iron intake was significantly associated with an increased risk of GDM. In the large prospective study conducted in the Nurses' Health Study cohort (n = 13,475), long-term consumption of dietary heme iron, but not total or nonheme iron intake, was significantly associated with the risk of GDM (27). The association with dietary heme iron was significant after adjusting for several risk factors of GDM including BMI, as well as dietary factors such as total calories, glycemic load, polyunsaturated fat intake, cereal fiber, saturated fat, and dietary cholesterol (27). The second study (28), which examined dietary iron intake in a cohort in Seattle, Washington (n = 3158), reported that women in the highest quartile of heme iron intake during the preconceptional and/or early pregnancy period had more than a 2-fold risk of GDM compared with those who were in the lowest quartile, even after adjusting for BMI and other major established GDM risk factors, as well as dietary intakes of saturated fat, cholesterol, and red and processed meat. In a recent meta-analysis (37) of these 2 prospective studies (27, 28), the adjusted RR for the risk of GDM associated with the highest compared with the lowest amount of dietary heme iron intake was 1.53 (95% CI: 1.17, 2.00). In contrast, a small prospective study from Iran (31) reported no significant differences in nutritional intakes of iron during early pregnancy by subsequent GDM status in midpregnancy. Notably, heme and nonheme iron intakes were not examined separately in this study. Inference from the study was also hindered because of the small number of GDM cases (n = 72) and failure to control for other dietary risk factors of GDM that could confound the association (e.g., dietary fat, cholesterol, fiber). Interestingly, data from a recent retrospective study (29) showed a lower risk of GDM associated with higher nonheme iron intakes before pregnancy. Because diets high in vegetables, fruits, legumes, and nuts are

TABLE 2
Prospective studies reporting the association between the indicators of iron status and the risk of GDM[1]

Study, year	Comparison groups	Crude OR (95% CI)	Adjusted OR (95% CI)	Covariates
SF				
Tarim et al. (42), 2004	SF top 50th vs. bottom 50th percentile (≥19.7 vs. <19.7 μg/L)	Not provided (positive association)	Not provided (null association)	Not applicable
Chen et al. (43), 2006	Highest 20% vs. lowest 80% (>131.38 vs. ≤131.38 pmol/L)	2.05 (1.10, 3.86)	1.84 (0.95, 3.58)	Age, ethnicity, parity, family history of diabetes, gestational age at blood collection, cigarette smoking, and prepregnancy BMI
Zein et al. (57), 2015	Highest vs. lowest quartile (≥38.5 vs. <13.0 μg/L)	2.49 (0.53, 10.84)	1.62 (0.20, 12.95)	Age, BMI, and CRP concentrations
Khambalia et al. (48), 2016	Unit change in SF (μg/L)	1.60 (1.28, 1.99)	1.41 (1.11, 1.78)	Age, country of birth, parity, weight, smoking, hypertensive disorders in pregnancy, and CRP concentrations
Khambalia et al. (49), 2016	Iron deficient vs. not based on SF concentration (<12 vs. ≥12 μg/L)	0.41 (0.23, 0.75)	0.43 (0.23, 0.78)	Age, gestational age, weight, parity, smoking, insurance type, socioeconomic status, and CRP concentration
Bowers et al. (54), 2016[2]	Highest vs. lowest quintile (median 141.0 vs. 25.0 μg/L)	2.33 (1.41, 3.84)	2.22 (1.23, 4.01)	Age, family history of diabetes, physical activity, prepregnancy BMI, CRP concentration, and oxidized LDL
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 10–14 wk of gestation (≥174.0 vs. ≤77.05 pmol/L)	2.11 (1.06, 4.20)	2.43 (1.12, 5.28)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 15–26 wk of gestation (≥119.4 vs. ≤49.6 pmol/L)	3.06 (1.27, 7.34)	3.95 (1.38, 11.30)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Soluble transferrin receptor				
Khambalia et al. (48), 2016	Unit change in sTfR (nmol/L)	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)	Age, country of birth, parity, weight, smoking, hypertensive disorders in pregnancy, and CRP concentration
Khambalia et al. (49), 2016	Iron deficient vs. not based on sTfR concentrations (≥21 vs. <21 nmol/L)	1.25 (0.82, 1.92)	Not provided	Not applicable
Bowers et al. (54), 2016[2]	Highest vs. lowest quintile (median 2.26 vs. 0.79 mg/L)	2.10 (1.10, 1.18)	1.48 (0.82, 2.70)	Age, family history of diabetes, physical activity, prepregnancy BMI, parity, CRP concentration, and oxidized LDL
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 10–14 wk of gestation (≥33.9 nmol/L vs. ≤22.3 nmol/L)	1.23 (0.62, 2.46)	1.00 (0.45, 2.20)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 15–26 wk of gestation (≥35.0 vs. ≤24.2 nmol/L)	1.23 (0.56, 2.67)	1.17 (0.49, 2.82)	Age, gestational age, parity education, family history of diabetes, and prepregnancy BMI and CRP concentration
Serum Iron				
Behboudi-Gandevani et al. (31), 2013	Unit change in serum iron (μg/dL)	Not provided	1.01 (1.00, 1.01)	Age, BMI, education, parity, passive smoking, history of GDM, family history of diabetes, deficient zinc/iron intake, and serum zinc and hemoglobin concentrations
Hemoglobin				
Lao et al. (61), 2002	Highest 25% vs. lowest 75% (>13.0 vs. ≤13.0 g/dL)	1.87 (1.18, 2.96)	1.73 (1.08, 2.78)	Age, BMI, and parity
Tarim et al. (42), 2004	Hemoglobin in top 50th vs. bottom 50th percentile (≥12.2 vs. <12.2 g/dL)	Not provided (positive association)	Not provided (null association)	Not applicable
Chen et al. (43), 2006	Highest 20% vs. lowest 80% (>130 vs. ≤130 g/L)	Not provided	0.81 (0.36, .81)	Age, ethnicity, parity, family history of diabetes, gestational age at blood collection, cigarette smoking, and prepregnancy BMI

(Continued)

TABLE 2 (*Continued*)

Study, year	Comparison groups	Crude OR (95% CI)	Adjusted OR (95% CI)	Covariates
Tan et al. (62), 2011	High vs. low hemoglobin (≥11.5 vs. <11.5 g/dL)	1.30 (1.1, 1.4)	1.50 (1.0, 2.1)	Age, ethnicity, height, weight, family history of diabetes, gestational age, red blood cell count, and glycosuria at initial visit
Zein et al. (57), 2015	Hemoglobin in top 50th vs. bottom 50th percentile (≥125 vs. <125 g/L)	Not provided (null association)	Not provided	Not applicable
sTfR:SF ratio				
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 10–14 wk of gestation (≥77.84 vs. ≤27.65)	0.47 (0.22, 1.00)	0.33 (0.14, 0.80)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 15–26 wk of gestation (≥130.88 vs. ≤40.40)	0.25 (0.10, 0.64)	0.15 (0.05, 0.48)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Hepcidin				
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 10–14 wk of gestation (≥18.71 vs. ≤6.97 ng/mL)	1.32 (0.66, 2.67)	1.11 (0.51, 2.44)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration
Rawal et al. (55), 2017[2]	Highest vs. lowest quartile at 15–26 wk of gestation (≥7.92 vs. ≤4.00 ng/mL)	2.40 (1.08, 5.35)	2.61 (1.07, 6.36)	Age, gestational age, parity, education, family history of diabetes, and prepregnancy BMI and CRP concentration

[1] CRP, C-reactive protein; GDM, gestational diabetes mellitus; SF, serum ferritin; sTfR, soluble transferrin receptor.
[2] Measurements taken in plasma not serum.

rich in nonheme iron, nonheme iron intake could reflect a healthy dietary pattern that is protective of GDM (38, 39). Although dietary fiber intake was adjusted in this study (29), the investigators did not account for an overall dietary pattern or a healthy lifestyle, either of which is likely to relate to the suggestive protective effect of nonheme iron. Inference of findings from the study was further limited by its retrospective design. Overall, emerging yet limited data to date suggest that dietary heme iron is positively and significantly associated with GDM risk, whereas findings with nonheme iron are inconclusive in general.

Intakes of iron supplements and the risk of GDM

Besides food, iron-containing dietary supplements are another common source of iron intake among pregnant women. The majority of iron supplements contain nonheme iron in the form of ferrous and ferric iron salts, such as ferrous sulfate, ferric sulfate, and ferrous fumarate (18, 40). The effects of iron supplementation on the risk of GDM have been examined in 2 large randomized control trials (34, 36) (Table 1). In the trial conducted in Hong Kong (34), either an iron supplement (300 mg ferrous sulfate tablet containing 60 mg elemental Fe) or a placebo tablet was prescribed to women with hemoglobin concentrations within the usual range [i.e., those who had either low (<8 g/dL) or high (>14 g/dL) hemoglobin concentrations at a baseline of <16 wk of gestation were excluded]. No effect of iron supplementation was observed on the risk of GDM (RR: 1.04; 95% CI: 0.70, 1.53), yet inference from these findings was limited by low compliance (54.4%) and the exclusion of women with an elevated iron status at baseline. In a more recent trial in Finland (36), no significant difference was observed in the combined incidence of metabolic outcomes (e.g., glycosuria or GDM) or related adverse pregnancy outcomes (large-for-gestational-age) between women who were advised to take routine iron supplementation (100 mg elemental Fe) and women who were not advised to take iron supplements unless they were anemic. However, the effect of iron supplementation specifically on GDM was not reported in this trial (36). In addition, in a study based on a secondary analysis of a randomized controlled trial (35) that examined the impact of iron supplementation on multiple pregnancy outcomes, no significant differences in the GDM incidence were observed between the iron supplementation and the placebo groups (Table 1). However, the study had only a few GDM cases (n = 5) and, hence, may not have been adequately powered to detect a significant effect. Taken together, data from existing clinical trials on iron supplement do not provide conclusive findings on their impact on the GDM occurrence because of their inherent limitations in study design.

Findings from observational studies (27, 29, 32) on iron supplementation and GDM are also generally inconclusive (Table 1). In a large study including 500 GDM cases (33), iron supplementation lasting ≥2 wk during pregnancy was related to a >3-fold increased risk of GDM (RR: 3.36; 95% CI: 1.50, 7.53). However, inference from this study was limited in that iron supplementation was assessed in midpregnancy at the same time as GDM diagnosis. Furthermore, iron intake from diet other than the supplement was not assessed and accounted for in this study (33).

Indicators of body iron status and GDM risk

SF concentration and GDM risk

A number of indicators have been used to characterize maternal iron status during pregnancy. SF concentration, an indicator of iron stores, has been most often examined in relation to the risk of GDM. A significant and positive association between SF concentration and GDM has been observed in several (41–55), although not in all, previous studies (56–59). The majority of these studies were cross-sectional in design, with SF concentration measured either during or close to the time of GDM diagnosis (41, 44, 45, 47, 50–53, 56). It should be noted, however, that SF is also an acute-phase reactant that may increase as a result of the subclinical inflammation associated with GDM (60). Prospective studies that measure SF concentration well before GDM diagnosis are, hence, critical to preclude the possibility of reverse causation. Only a few prospective studies (42, 43, 48, 49, 54, 55, 57) to date have investigated associations of SF concentration with the subsequent risk of GDM (**Table 2**). Overall, findings from prospective studies consistently support that high SF concentrations in pregnancy are associated with an elevated risk of GDM. Of note, a recent prospective study (55), which measured SF concentrations by using blood samples collected longitudinally through pregnancy, demonstrated that SF concentrations in both the first and second trimesters were significantly and positively associated with a subsequent risk of GDM, even after accounting for inflammation measured via CRP levels. Findings from 2 recent meta-analyses (37, 48) also demonstrated a significant and positive association between SF concentrations and the risk of GDM. For instance, in one of the meta-analyses (37) that included 4 prospective studies (42, 43, 46, 57), women with the highest SF concentrations had a >3-fold greater risk of GDM compared with those with the lowest concentrations (pooled RR: 3.22; 95% CI: 1.73, 6.00).

Soluble transferrin receptor and GDM risk

The concentration of soluble transferrin receptor (sTfR), an indicator of tissue iron deficiency, is not influenced materially by the acute-phase response and, hence, may serve as a useful indicator of iron status in the presence of inflammation (60, 63, 64). In particular, examining both SF and sTfR concentrations and assessing iron status as a ratio of sTfR to SF (sTfR:SF ratio) may capture the full spectrum of iron homeostasis in terms of cellular iron need as well as the availability of iron stores (60, 63, 65). The association of sTfR concentrations with subsequent GDM risk was examined in 4 prospective studies (48, 49, 54, 55). sTfR concentrations were not significantly associated with GDM risk in these studies (Table 2). We are aware of only one study (55) that has examined the sTfR:SF ratio in association with GDM risk. In this prospective and longitudinal study among women in a multiracial US cohort (55), the risk of GDM was not significantly associated with sTfR concentrations but was significantly and inversely associated with the sTfR:SF ratio in both the first and second trimesters, even after the adjustment of BMI, CRP concentrations, and other major risk factors of GDM (Table 2).

Hepcidin and GDM risk

Hepcidin, a hepatic hormone that plays a key role in iron homoeostasis, has been gaining interest as a novel indicator for iron status. Emerging evidence supports the idea that hepcidin is the master regulator of iron homeostasis, regulating iron absorption from dietary sources in the gut, recycled iron from macrophages, and iron stores in the liver (66). Despite this, only 2 published studies (47, 55) to date have examined the association between hepcidin concentrations and GDM risk, both of which observed positive associations (Table 2). For instance, in a cross-sectional study including 30 GDM cases (47), hepcidin concentrations at the time of GDM screening were significantly elevated in women with GDM compared with women with normal glucose tolerance. Most recently, in a relatively large prospective longitudinal study including 107 GDM cases (55) from women of multiple races/ethnicities in the United States, hepcidin concentrations during 16–24 wk of gestation were significantly and positively associated with the subsequent risk of GDM. Because the hepcidin concentration could be influenced by inflammation (11), this longitudinal study additionally adjusted for CRP concentrations in their analyses and observed that the significant and positive association between hepcidin and GDM persisted.

Other indicators of iron status and GDM risk

Studies on other indicators of iron status, such as transferrin concentration, hemoglobin, or serum iron concentration, have not been well-studied in the context of GDM risk, particularly in a prospective setting. Overall, findings provide some suggestive evidence of a potential link between higher iron load or stores and greater risk of GDM although the findings were not consistent across all studies (Table 2). For instance, hemoglobin concentrations in pregnancy were positively associated with the risk of GDM in some (42, 45, 61, 62, 67) although not all studies (41, 43, 47, 50, 56, 57, 59). Studies examining serum iron concentration in relation to GDM risk have also been conflicting with mixed reports of positive (31, 41, 45, 47), negative (68), or no association (59, 69, 70) with GDM status. However, the majority of these studies were of small sample size, and inferences from these studies were further limited by insufficient control for potential confounders, such as prepregnancy BMI. Despite these limitations, a meta-analysis (48) pooling data from 7 studies (31, 41, 45, 47, 59, 70, 71) including 337 GDM cases showed that women with GDM had higher concentrations of serum iron than those without (pooled mean difference: 200 μg/L; 95% CI: 147, 253). Future prospective studies of large sample sizes and with a comprehensive adjustment of potential confounders are warranted to further investigate the roles of these iron indicators in the development of GDM.

DISCUSSION

Well-designed prospective studies examining dietary iron, iron supplements, or indicators of iron status with respect to subsequent GDM risk are just emerging and as of yet limited. Accumulating data suggest that dietary iron, in particular heme-iron intake during or before pregnancy, is significantly and positively associated with GDM even after the adjustment for major dietary factors and other major well-documented risk factors of GDM. Yet the possibility of unmeasured residual confounding cannot be ruled out as data on heme iron were mostly based on observational studies. For example, nitrites and other preservatives in processed meat, as well as advanced glycation end products formed during the high-temperature

cooking of animal-derived foods, have been shown to contribute to insulin resistance (72–74). Findings on dietary nonheme iron intakes and iron supplement are inconclusive in general.

Molecular mechanisms underlying the observed associations of GDM with heme iron remain to be elucidated. Iron utilization and bioavailability from the heme iron source was substantially higher than that observed for ferrous sulfate (nonheme iron) in both the pregnant and nonpregnant individuals (12–14). Furthermore, data from animal studies showed considerable differences in tissue deposition of the absorbed heme and nonheme iron tracers, suggesting that some heme may be exported into the circulation in a form different from that of nonheme iron (9). Data also support that there may be differential use of iron from heme and nonheme sources during pregnancy (65). As such, given the same amount of heme and nonheme iron consumption, it is plausible that the effect size and magnitude of their associations with GDM may differ.

Maternal response to dietary or supplemental iron, as well as their impact on glucose metabolism may be contingent on differences in women's underlying iron status and metabolism. For instance, in a study conducted in a primary health care setting in Finland, an increased total iron intake (including supplemental iron) during pregnancy was associated with a greater GDM risk, but the association was only significant among women who were not anemic at the beginning of the pregnancy (30). Furthermore, in a recent large prospective study among women with a history of GDM who were generally replete in iron, a higher long-term intake of iron supplements after GDM-complicated pregnancy was significantly associated with an increased risk of subsequent type 2 diabetes (75). In the general population, however, iron supplements were not significantly related to type 2 diabetes risk (76). Future studies that use a more systematic and comprehensive approach in characterizing underlying iron status as well changes in iron status in response to dietary and supplementary iron intake are needed to elucidate the role of iron in the development of GDM. In addition, because the majority of studies in this regard were conducted among Caucasian populations, future studies in more racially or ethnically diverse populations are warranted.

Compared with reported iron intakes from diet, serum or plasma measures are more likely to better reflect iron status and may provide important insights into the role of iron in the pathogenesis of GDM. Accumulating data from recent well-designed prospective studies, in combination with findings from meta-analyses, have demonstrated a significant and positive association between SF concentrations in pregnancy and GDM risk, even after accounting for major risk factors of GDM, as well as inflammatory status measured by plasma CRP concentrations. Moreover, emerging prospective and longitudinal data support that higher hepcidin concentrations are associated with an increased GDM risk, independent of inflammatory status. Although hepcidin has been gaining attention as the master regulator of iron homeostasis, the question of which indicators are the most optimal for measuring iron status remains subject to debate. sTfR was previously considered more useful for measuring iron status in the presence of inflammation, yet emerging evidence suggests that its concentrations also increase with infection or high α(1)-acid glycoprotein or CRP concentrations (16, 17, 49). Additional work is, therefore, needed to identify the most appropriate indicators to assess iron status and homeostasis, as well as to characterize high iron status during pregnancy.

Given the close link between iron status and inflammation, it is remarkable how few studies have accounted for inflammation in examining the association between iron status and GDM. Moreover, in the limited number of studies (48, 49, 54, 55, 57) that assessed inflammatory status concurrently with iron status, CRP was the only inflammatory marker measured. Emerging evidence, however, suggests that CRP alone is insufficient to fully characterize inflammation, particularly in the context of assessing nutritional status (77). The use of both CRP and α(1)-acid glycoprotein measures has been suggested to be more accurate at estimating the inflammatory profile and interpreting SF concentrations (77, 78). Hepcidin is known to be regulated by inflammatory cytokines such as IL-1, IL-6, and IL-22 (79), and as such, these markers may be of interest in future studies. Important data gaps need to be addressed to reach a consensus regarding what and how to best use inflammatory markers in analyzing and interpreting iron status indicators.

Collectively, accumulating evidence to date suggests a potential link between greater iron stores or status during pregnancy and an elevated risk of GDM. This is particularly relevant given the short- and long-term adverse health outcomes associated with GDM among pregnant women and their offspring. However, currently it remains inconclusive whether routine iron supplementation among iron-replete pregnant women poses any risk of GDM. Substantive data gaps need to be addressed to clarify the association between iron status and risk of GDM and inform the relative risk and benefit assessment of iron supplementation to iron-replete pregnant women. Recently, in their updated recommendations, the US Preventive Services Task Force (USPSTF) concluded that the evidence is insufficient to recommend for or against routine iron supplementation for nonanemic pregnant women (80). The USPSTF review included only one study (34) examining GDM as a potential adverse outcome, further highlighting the paucity of data in this regard. Well-designed, systematic studies utilizing comprehensive measures of iron status, inflammation, and oxidative stress, as well as dietary and supplementary iron intake before and during pregnancy, are needed to elucidate and establish the link between iron status and GDM. Additional studies should also investigate the utility of individually tailored use of iron supplements, as well as the optimal timing and dose of iron supplementation needed to optimize pregnancy outcomes among women.

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