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ORIGINAL ARTICLE

Longitudinal Analysis of the Interaction Between Obesity and Pregnancy on Iron Homeostasis: Role of Hepcidin

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Background and Aims. When pregnancy occurs in obese women, two opposite mechanisms for iron homeostasis concur: increased need for available iron to support erythropoiesis and decreased iron mobilization from diets and stores due to obesity-related inflammation linked to overexpressed hepcidin. Few studies have examined the role of hepcidin on maternal iron homeostasis in the context of obese pregnancy. The aim of the study was to evaluate the combined effect of maternal obesity and pregnancy on hepcidin and maternal iron status while accounting for inflammation and iron supplementation.

Methods. We conducted a secondary analysis of a cohort of pregnant women recruited from a referral obstetric hospital in Mexico City. Circulating biomarkers of iron status (hepcidin, ferritin [SF], transferrin receptor [sTfR], erythropoietin [EPO]), and inflammation (C-reactive protein [CRP], tumor necrosis factor-[TNF]α, and interleukin-[IL]6) were determined monthly throughout pregnancy. Repeated measures ANOVA and logistic regression models were used for statistics.

Results. Twenty-three obese (Ob) and 25 lean (Lc) women were studied. SF and hepcidin declined, and EPO and sTfR increased throughout pregnancy in both groups. sTfR increased more in Ob than in Lc ($p = 0.024$). The smallest hepcidin decline occurred in iron-supplemented Ob women compared to non-supplemented Lc women ($p = 0.022$). The risk for iron deficiency at the end of pregnancy was higher for Ob than for Lc (OR = 4.45, 95% CI = 2.07–9.58) after adjusting for iron supplementation and hepcidin concentration.

Conclusion. Pre-gestational obesity increases the risk of maternal iron deficiency despite iron supplementation. Overexpressed hepcidin appears to be a potential mechanism.

Key Words: Iron, Iron deficiency, Pregnancy, Obesity, Hepcidin.

Introduction

During pregnancy, iron requirements increase from a net saving in early weeks to a need of >6 mg/d during the third trimester (1). This significant increase is to provide for maternal erythrocyte mass expansion, high fetal oxygen demand for growth and development, deposition of adequate iron stores to support early infant growth, and to compensate for blood loss at delivery (2,3). To this, an increase in iron bioavailability is stimulated by a fall in hepcidin concentration (4).

The 25-amino acid peptide hepcidin is an iron-regulatory hormone that is feedback regulated by iron concentration and requirements for erythropoiesis. When iron bioavailability is required, the expression of hepcidin declines to promote iron absorption and mobilization. If this response is sustained as in pregnancy, a progressive iron depletion

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may occur, which is observed as low serum ferritin and high soluble transferrin receptor (sTfR). In contrast, if serum iron is high, as in iron supplementation, hepcidin increases and interacts with its receptor ferroportin to negatively regulate iron availability through inhibition of dietary absorption and release from macrophages and hepatocytes (5). Independently of iron homeostasis, hepcidin expression is also stimulated by inflammation. This was observed in *in vitro* and *in vivo* studies, which demonstrated that IL-6 and supernatants of polysaccharide-activated macrophages induced hepcidin expression in human hepatocytes and cell lines (6) and that urinary hepcidin rose after the infusion of IL-6 and polysaccharides to human volunteers (7).

Accordingly, obesity is a low-grade chronic inflammatory condition linked to the overexpression of hepcidin and secondarily to iron homeostasis (8). A study conducted in Mexico reported that obese women have higher hepcidin concentration and two-fold higher risk for iron deficiency than non-obese women (9). Likewise, a recent meta-analysis concluded that obese young individuals have lower serum iron and lower transferrin saturation than non-obese individuals as well as an increased risk for iron deficiency (10). However, only few studies have evaluated the influence of obesity on hepcidin and iron status during pregnancy, but their results are inconclusive. For instance, whereas a cross-sectional study reported higher hepcidin and C-reactive protein and lower cord blood iron in obese than in lean pregnant women (11), another comparable study failed to identify differences in serum hepcidin or in iron status in a sample of pregnant adolescent girls (12). Likewise, a study that used a longitudinal design found a higher concentration of hepcidin at early and mid-gestation and higher concentrations of sTfR at late gestation in obese than in lean women (13), but a similar longitudinal study found opposite results because the concentration of sTfR from mid- to late pregnancy increased less in obese than in normal-weight women (14).

The current study was undertaken to evaluate the net effect of combined obesity and pregnancy on hepcidin and iron status, using data previously obtained from a longitudinal study of pregnant women (15). Our main hypothesis was that pre-pregnancy obesity yields to an increased hepcidin concentration, which secondarily affects iron status. To test this hypothesis, we assessed serial biomarkers of iron status throughout pregnancy in obese and lean women. Maternal age, gestational age, parity, inflammation and iron supplementation were assessed as confounders.

Methods

Study Population and Design

This is a secondary analysis of data from a cohort of pregnant women who were closely followed to identify early predictors of preeclampsia (15). The study protocol was approved by the Ethics Committee of the Mexican Institute of Social Security (IMSS) (CNIC-2007-785-050).

For the original study, women were selected before week 20 of gestation from an obstetric hospital of the IMSS in Mexico City. Eligible women were normotensive, carrying a singleton pregnancy, and free of chronic hypertension, type 2 diabetes, and smoking. Those who agreed to participate signed an informed consent form and attended the hospital on a monthly basis during pregnancy and on day 6 ± 2 postpartum for clinical evaluation and blood sampling. Self-reported pre-pregnancy weight and height obtained at the first appointment were used to calculate body mass index (BMI).

For the original study, 256 pregnant women were followed. For the present analysis, we excluded data from women who developed preeclampsia or other pregnancy-related complications as well as data from women with pre-pregnancy BMI between 25 and 30 kg/m^2. Women selected as controls were those who had age, parity and gestational age at inclusion comparable to obese women who complied with the study criteria.

Measurements

Blood samples were collected from a peripheral vein after 10 h fasting in vacuum-sealed tubes with EDTA and kept at 4°C until centrifuged at 3000 × g for 15 min within the first half hour after collection. Biochemical determinations were conducted in the Research Unit in Medical Nutrition of the IMSS. The source of the samples was blinded to the technician. Samples were run in duplicate.

Plasma hepcidin (MyBioSource, MBS700759, San Diego, CA), erythropoietin (EPO, DEP00), soluble transferrin receptor (sTfR, DTFR1), interleukin (IL-6, D6050), and tumor necrosis factor (TNF-α, DTA00C) (R&D Systems, Minneapolis, MN) were analyzed by competitive enzyme-linked immunosorbent assay (ELISA). C-reactive protein (CRP, 10286287) and serum ferritin (SF, LKFE1) concentrations were measured by chemiluminescence using commercial kits (Immulite1000 Systems). Coefficients of variation were between 2.5 and 5.5% for hepcidin, EPO, IL-6, CRP and SF; 11% for sTfR; and 10.1% for TNF-α. The sensitivity limits were hepcidin, 6.25 ng/mL; EPO, 0.6 mU/mL; sTfR, 0.42 mg/L; IL-6, 0.70 pg/mL; TNF-α, 0.05 pg/mL; CRP, 0.1 mg/L; and SF, 15 μg/mL.

Statistical Analysis

The Minitab statistical package (v.17, State College, PA) was used for analysis; $p \leq 0.05$ was considered for statistical significance. Because most of the data did not follow a normal distribution, raw data at baseline are analyzed as median (minimum, maximum) for description and compared between obese (Ob: BMI ≥30 kg/m^2) and lean women (Lc: BMI >18.5, <25 kg/m^2) with