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Obesity during Pregnancy and Fetal Iron Status: is Hepcidin the link?

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Abstract

Objective—To ascertain the effect of obesity-related inflammation on maternal and fetal iron status. We hypothesized that obese pregnant women would have increased inflammation, hepcidin levels, and that their infants would have impaired iron status compared to lean controls.

Study Design—Fifteen obese (Ob) and fifteen lean (Lc) women were recruited in their second trimester of pregnancy. Markers of iron status, inflammation and hepcidin were measured in maternal and cord blood. Student's t test was used to compare obese and lean groups, and Pearson correlation coefficients were determined between maternal and cord blood values.

Results—Maternal C-reactive protein (CRP) ($p<0.01$) and hepcidin ($p<0.01$) were higher, and cord blood iron ($p<0.01$) was lower in the obese group. Maternal BMI ($p<0.01$) and hepcidin ($p<0.05$) were negatively correlated with cord blood iron status.

Conclusions—Maternal obesity is associated with impaired maternal-fetal iron transfer, potentially through hepcidin upregulation.

Keywords

Maternal obesity; iron deficiency; inflammation

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Conflict of Interest

The authors declare no conflict of interest.

Introduction

Over half of all reproductive age women in industrialized nations are overweight or obese and this burden is growing rapidly in developing nations as well (1-3). Epidemiologic data has shown that infants and children born to obese women are more likely to develop chronic health conditions such as asthma and diabetes, but there have been no studies describing the effect of maternal obesity on infant iron status. Hepcidin, a regulator of iron homeostasis, has been shown to be overexpressed in obesity and to correlate with low iron status in the obese (4-8). Iron reaches the fetus through active transport in the placenta and hepcidin is known to be one regulator of this process (9).

Obesity leads to chronic overexpression of hepcidin as a downstream effect of low-grade chronic inflammation. Specifically obesity leads to increased interleukin (IL)-6 and IL-1 levels which upregulate hepcidin (10-12). Recently, it was reported that hemojuvelin is overexpressed in adipose tissue of obese individuals, and directly upregulates hepcidin through the bone morphogenic protein-hemojuvelin (BMP-HJV) pathway (13). Conversely, hepcidin is kept at a minimum during pregnancy in order to maximize iron transfer to the fetus (14). During the late fetal and early neonatal period, the infant experiences rapid growth, and the nervous system is particularly vulnerable to alterations in the regulation of iron during this time. Impaired fetal iron transport is thought to have lifelong and irreversible effects on neurodevelopment (15-17). In addition, maternal iron deficiency is associated with poor fetal growth and poor weight and height gain during childhood. Thus, identifying factors that affect fetal iron transport is of critical importance.

Subjects and Methods

We conducted a prospective case control study to determine the impact of obesity during pregnancy on maternal and fetal iron status. The study protocol and procedures were approved by Tufts University/Tufts Medical Center IRB and was conducted in accordance with HIPAA regulations. All participants gave written informed consent to participate in this study. All authors had access to collected clinical data.

Study Participants

Thirty women, 15 obese (Ob) and 15 lean controls (Lc), were recruited for this study from the Tufts Medical Center Obstetrics clinic between 24-28 weeks of pregnancy between May, 2010 and December, 2010. Potential subjects were identified from the pre-pregnancy body mass index (BMI) noted on their prenatal records. Subjects were assigned to the control (BMI 20-25 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) group based on their pre-pregnancy BMI. Subjects with pre-gestational diabetes, preeclampsia, autoimmune disease, acute infectious process or the pregnancy complications PPROM (preterm premature rupture of membranes) and chorioamnionitis were excluded from the analysis. All subjects reported taking a standard prenatal vitamin with iron during the current pregnancy. Cord blood was harvested from the neonates of 10 obese women and 11 control women.

Measurements in maternal and cord blood

Maternal blood was collected at 24-28 weeks of gestation, after an 8-14 hour fast, one hour after ingestion of a 50g glucose drink. Blood was collected at this time to minimize venipuncture in subjects. Cord blood was collected after delivery via syringe aspiration from the umbilical vein. Cord blood could not be collected from all subjects. Iron status, specifically serum iron and transferrin saturation (Tsat), were measured with colorimetric endpoint assays (Diagnostic Chemicals Ltd., Oxford, CT, USA). Hematocrit (HCT) was measured using a hematology analyzer (Horiba, Irvine CA). Serum C-reactive protein (CRP) (Abnova, Walnut, CA, USA) and IL-6 (eBioscience, San Diego, CA, USA) were measured with ELISA and hepcidin (Bachem Group, Torrance, CA, USA) was measured with competitive ELISA (c-ELISA). Reduced, oxidized and total glutathione were measured from serum per manufacturer's instruction using the Glutathione Kit (Biovision, Mountainview, CA, USA).

Statistical Analysis

We used Student's t test for Ob vs. Lc group comparisons, and Pearson correlation coefficient analysis to determine correlations between maternal and cord blood parameters. All tests were two sided and judged statistically significant at $p < 0.05$. SAS 9.2 for Windows (SAS Institute, Cary, NC, USA) was used for all analyses. For normally distributed variables, mean ± standard deviations (SD) are reported. A logarithmic transformation was applied to non-normally distributed variables and t tests were done on transformed data. In results, median and interquartile range (IQR) values are reported.

Results

Study population characteristics

The mean pre-pregnancy BMI was 38.6 ± 7.0 kg/m^2 for the Ob group, and 22.8 ± 1.5 kg/m^2 for the Lc group ($p<0.0001$) (Table 1). There were 6 African Americans in the Ob group and none in the Lc group ($p<0.05$). We found no significant differences in iron status, inflammation or hepcidin between obese African American and obese Caucasian women. Average age was not different between the Ob and Lc groups. Importantly, rates of gestational diabetes did not differ between the two groups: one subject in each group developed gestational diabetes and there was no difference in the mean serum glucose level between the two groups based on the glucose tolerance test: 117 ± 33 mg/dl for Ob, and 109 ± 27 mg/dl for Lc. There was no association between maternal BMI and birth weight (data not shown). We found no significant association between maternal BMI and birth weight or Apgar scores (data not shown).

Obese pregnant women have increased oxidative stress, inflammation and higher hepcidin levels

The ratio of serum oxidized to reduced glutathione (oxidized/reduced × 100) was higher in the Ob compared to Lc [Ob: 9.3 ± 1.1 vs. Lc: 7.9 ± 1.2, $p<0.01$], indicating increased oxidative stress in the Ob group. Inflammation, measured as serum CRP, was significantly higher in the Ob compared to Lc [Ob: 14.3 (11.5) mg/L vs. Lc: 5.0 (4.4) mg/L, $p<0.01$]

(Figure 1a). There was no statistically significant difference serum IL-6 between the two groups (Figure 1b). Hepcidin was significantly higher in the Ob vs. Lc group [Ob: 13.5 ± 9.0 ng/ml vs. Lc: 5.1 ± 2.7 ng/ml, $p<0.01$] (Figure 1c). However, serum iron and Tsat were not significantly lower in Ob compared to Lc (Figure 1d-e). HCT was not different between the Lc and Ob group (data not shown).

Infants of obese women have impaired iron stores

We found no statistically significant differences in CRP, IL-6 or hepcidin levels in cord bloods between the Ob and Lc groups (Figure 1f-h). Consistent with Rehu's previous report, cord blood hepcidin was approximately ten times higher than hepcidin levels in the mothers (14). Adjusting for mode of delivery did not affect hepcidin or inflammation differences in cord blood. Serum iron and Tsat were found to be significantly lower in cord blood from Ob compared to Lc [Iron: Ob, 97.3 ± 29.9 μg/dl vs. Lc, 147.7 ± 21.7 μg/dl, $p<0.01$; and Tsat: Ob, 39.6% vs. Lc, 63.5%, $p=0.01$] (Figure 1i-j). On average, HCT was not significantly different between the two groups (data not shown). These results suggest that iron transfer to the fetus is hindered in obese pregnant women.

Maternal BMI correlates with cord blood outcomes

There was a moderate and statistically significant correlation between maternal BMI and maternal CRP ($r=0.5$, $p=0.006$) and maternal BMI and maternal hepcidin ($r=0.4$, $p=0.04$). Correlation coefficient analysis also showed that maternal BMI was strongly negatively correlated with iron status in cord blood, both for serum iron ($r= -0.8$, $p=0.002$) and Tsat ($r= -0.7$, $p=0.009$) (Figure 2a and c). In addition, there was a significant moderate negative correlation between maternal hepcidin and cord blood serum iron ($r=-0.6$, $p=0.02$) and cord blood Tsat ($r=-0.6$, $p=0.02$) (Figure 2b and d). This suggests that BMI contributes to higher hepcidin levels and inflammation in mothers, and is a strong contributor to impaired maternal-fetal iron transport and fetal iron stores.

Discussion

This is the first study to report the effect of obesity in pregnancy on hepcidin levels and maternal-fetal iron transfer. In our population, obesity was associated with lower income and African American race. These factors have been shown to be associated with obesity in the US overall. Surprisingly, we did not have more subjects with gestational diabetes or asthma in our Ob group. The number of neonates that were delivered by Cesarean section did not differ between the Ob and Lc groups. It is interesting that there was no significant association between maternal weight and birth weight in the Ob group which has been reported in large epidemiologic studies. This could be due to the size of our cohort or due to the slightly higher number of preterm infants born to obese subjects, which decreased the mean birth weight in that group.

There is extensive evidence showing obese individuals to have significantly higher hepcidin and greater risk of iron deficiency than lean individuals, but this is the first study showing this phenomenon in obese pregnant women. We have shown that inflammation and hepcidin

are higher in obese than in lean pregnant women. More importantly, we demonstrate that this is associated with lower iron status in their neonates.

Neonatal iron deficiency has been best studied in the context of undernutrition. In our study, neonates born to obese women have iron profiles which closely resemble those of infants born to iron deficient women (18), although their mothers were not iron deficient. This further supports the idea that obesity-related inflammation may be contributing to impaired maternal-fetal iron transport. Under non-inflammatory conditions a pregnant population with low iron status would have low levels of hepcidin in order to maximize iron absorption and availability (14), thereby enhancing iron transfer to the fetus. However, obese pregnancy is characterized by inflammation, which upregulates hepcidin and decreases circulating iron transfer to the fetus. Although the mechanism leading to low iron status in neonates may be different in obese pregnancy compared to maternal undernutrition, the impact of a relative deficiency in this critical nutrient on fetal and infant neurodevelopment bears close monitoring.

IL-6 upregulates hepcidin expression through the Jak/STAT pathway. It has been recently shown that hepcidin is also upregulated through the BMP pathway by hemojuvelin production in adipose tissue of obese individuals. Although we did not observe a statistically significant difference in serum IL-6 between the Lc and Ob group, further studies should evaluate the contribution of these pathways to low fetal iron status and diminished iron transfer in placenta.

Obese women and their infants are at risk for chronic inflammation and oxidative stress (19). Our Ob cohort had increased inflammation and oxidative stress compared to the Lc cohort. Our data suggest that this chronic inflammation and oxidative stress may upregulate hepcidin, thereby impairing iron transport to the fetus. However, iron supplementation in obese pregnant women and their infants is a complex question since providing free iron, a potent oxidant, may further exacerbate the already present oxidative stress.

Strengths of this study are that we have been able to follow women through pregnancy and delivery, allowing accurate pairing of maternal and fetal data. Given the prospective data collection we were able to exclude confounding conditions, such as acute infections. We used BMI as an indicator of obesity, but body composition, percentage body fat and information on dietary intake of iron absorption enhancers and inhibitors would have provided additional valuable information. The sample size is small, but despite this we have shown a strong relationship between maternal obesity and offspring iron status. A Tsat< 20% has been used to define iron deficiency (18). In our control subjects, 57% of the women had Tsat<20% and in our obese subjects, 75% of the women had Tsat<20%; however, these differences were not statistically significant. Subgroup analysis comparing iron deficient and iron replete obese and lean mothers and infants was not possible due to the small sample size of the subgroups, and therefore such analysis is needed in future studies.

In conclusion, we have shown, for the first time, that maternal obesity is associated with impaired iron transfer to the fetus. We speculate that this is due to the effects of a chronic pro-inflammatory environment and increased levels of hepcidin.

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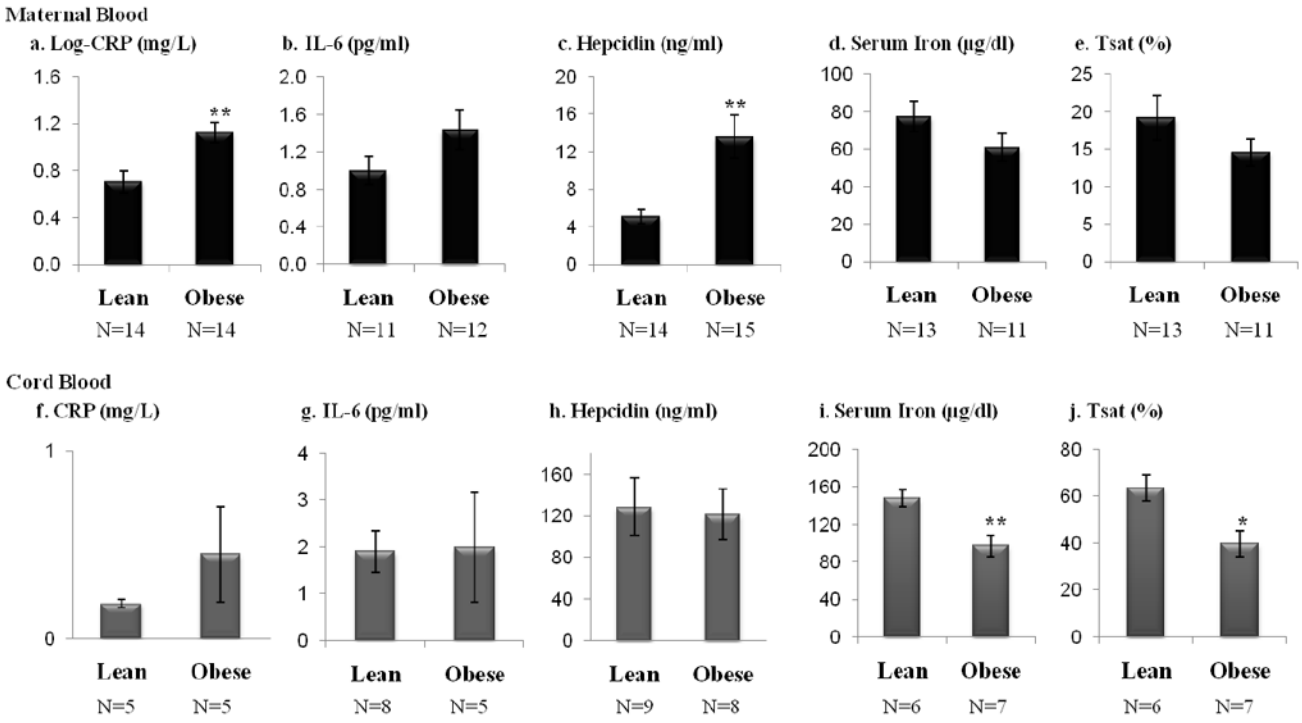

Figure 1. Hepcidin, inflammation and iron status in maternal and cord blood

Maternal and cord blood CRP, IL-6, hepcidin, serum iron and Tsat were measured as described in methods and Student's t test was used to determine differences between Ob and Lc groups (*p=0.01, **p<0.01). Mean ± SE are shown.

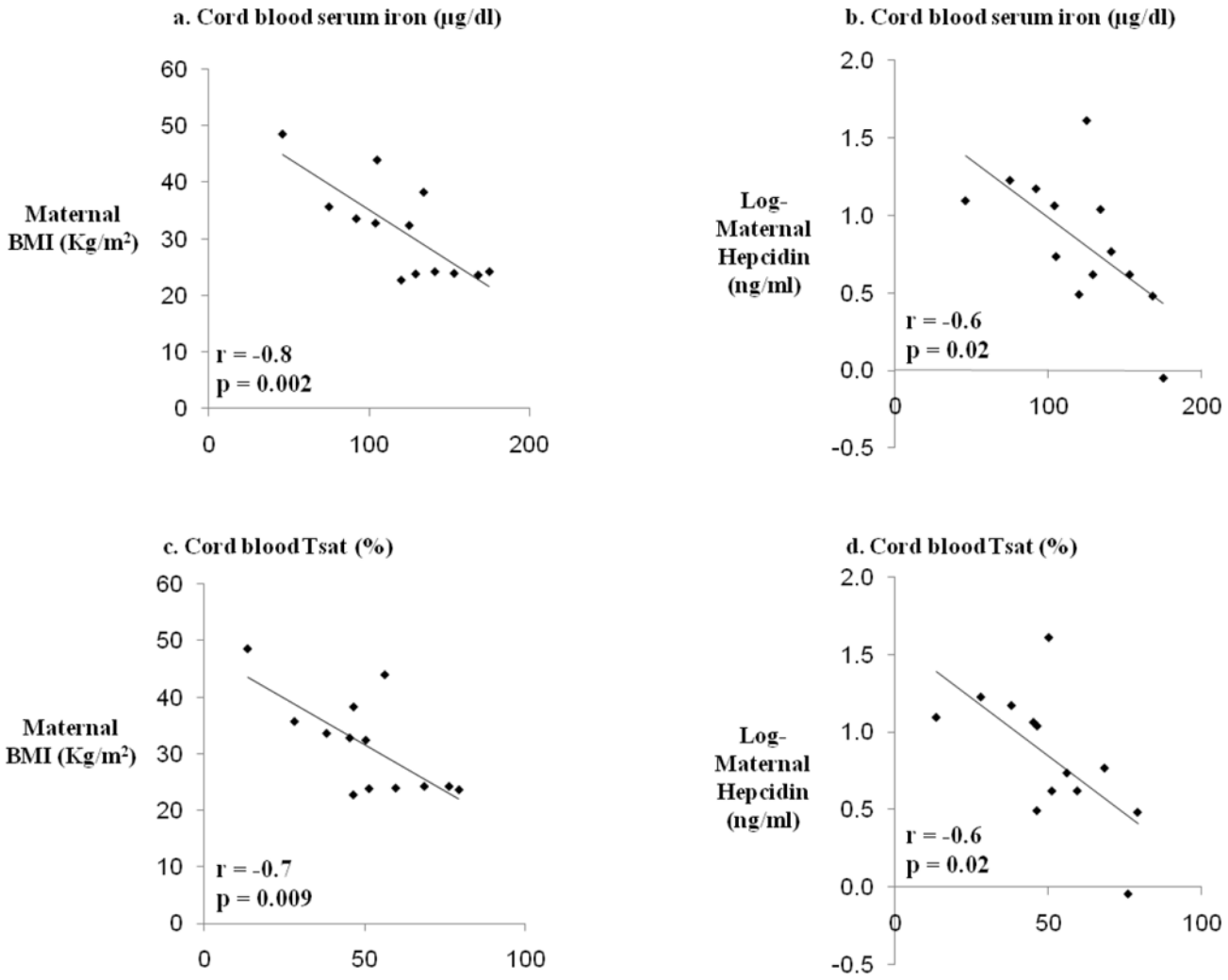

Figure 2. Correlations between maternal BMI and maternal hepcidin with cord blood iron status

Pearson correlation coefficient analysis was used to determine correlations between maternal BMI and cord blood iron status, and between maternal hepcidin and cord blood iron status. Correlation coefficients (r) and p values are shown. Cord blood data was not available from all subjects due to technical limitations.

Table 1

Maternal population characteristics

Participants were recruited as described in the methods section, and the following self reported data was obtained at the recruitment visit. Mean ± SD are shown.

	Obese (n=15)	Lean (n=15)
BMI (kg/m^2)*	38.6 ± 7.0	22.8 ± 1.5
Age (years)	30.0 ± 3.9	32.1 ± 5.8
Education (N with college degree)	7	11
Race (N)**		
Caucasian	6	9
African American	6	0
Hispanic	2	5
Asian	1	1
Mode of delivery (N)		
Vaginal Delivery	8	11
Cesarean	7	4

* Significantly different by Student's t test; $p<0.0001$

** Significantly different by Student's t test; $p<0.05$