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Authors
Guo, Yifan
Zhang, Na
Zhang, Daoqiang
et al.

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Iron homeostasis in pregnancy and spontaneous abortion

Yifan Guo[1,2,3], **Na Zhang**[4], **Daoqiang Zhang**[2,3], **Quanzhong Ren**[1,5], **Tomas Ganz**[6], **Sijin Liu**[1,5], **Elizabeta Nemeth**[6]

[1]State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Science, Chinese Academy of Sciences, Beijing, China

[2]Weifang Medical University, Weifang, China

[3]Weihai Key Laboratory of Autoimmunity, Weihai Central Hospital, Weihai, China

[4]Department of Ultrasound, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China

[5]University of Chinese Academy of Sciences, Beijing, China

[6]Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

Abstract

During pregnancy, iron requirements are increased to support maternal erythropoietic expansion and fetal growth and development. To meet these requirements, dietary iron absorption increases, and available iron stores are mobilized. These adjustments are thought to be in large part mediated by the iron-regulatory hormone hepcidin, which controls the concentrations of ferroportin, the sole exporter of iron into the extracellular fluid and blood plasma. Hepcidin regulation of iron availability during healthy and abnormal pregnancies is not well understood. In our cross-sectional study, we compared hepcidin, iron and hematological parameters between nonpregnant control women, healthy pregnant women in the first and second trimester, and women with spontaneous abortion in the first trimester. We found that in healthy pregnancy, hepcidin increased in the first trimester compared with nonpregnant women, but then decreased during the second trimester. The second trimester hepcidin levels decreased despite stable serum iron concentrations, suggesting active suppression of hepcidin, presumably to enhance iron availability as iron demand increases. In women with spontaneous abortion during the first trimester, hepcidin, serum iron, and ferritin concentrations were all increased compared with the first trimester healthy pregnancy. Although the specific mechanisms remain to be determined, our findings demonstrate that maternal hepcidin is regulated by signals related to the progression of pregnancy, and that pregnancy loss is

Correspondence Elizabeta Nemeth, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA. enemeth@mednet.ucla.edu, OR, Sijin Liu, State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Science, Chinese Academy of Sciences, Beijing 100085, China. sjliu@rcees.ac.cn.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTEREST

EN and TG are stock holders and consultants for Intrinsic Life-Sciences, LLC. The remaining authors declare no competing financial interest.

associated with profound changes in maternal iron metabolism. These observations highlight the existence of fetoplacental signals that modulate maternal iron homeostasis.

1 | INTRODUCTION

Hepcidin, a 25-amino acid peptide hormone synthesized by hepatocytes, plays a central role in systemic iron homeostasis.[1] Hepcidin binds to its receptor ferroportin (FPN also known as SLC40A1), the only known iron exporter, and induces FPN degradation, thereby controlling iron absorption in the duodenum and iron egress from macrophages.[2] Dysregulated hepcidin causes various disorders including anemia and iron overload.[3,4] The regulation of hepcidin has been investigated under, Yifan Guo and Na Zhang contributed equally to this study. numerous pathophysiological conditions, including iron deficiency or overload, changes in erythropoietic activity, and in response to inflammation or infection.[5–7] In contrast, little is known about hepcidin regulation during healthy or abnormal pregnancy.[8,9]

Normal pregnancy is characterized by a greatly increased demand for iron to support placental and fetal growth and expanded maternal erythropoiesis, obligating an approximately 10-fold increase in iron demand from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester.[8,10] In healthy pregnancies, serum hepcidin concentrations were reported to be reduced in the second and third trimesters, presumably to enhance dietary iron absorption and iron release from, macrophages.[11] Little is known about how hepcidin is regulated during the first trimester compared with nonpregnant women and how these patterns are altered in abnormal pregnancies, including spontaneous abortion or fetal demise. Embryo or fetus can become nonviable before maturity.[12,13] To date, a number of distinct mechanisms have been proposed to be responsible for spontaneous abortion, such as hormonal abnormalities, inflammation, and autoimmune disorders.[14–16] However, it is unknown whether abnormal embryonic development or pregnancy loss are associated with dysregulated maternal iron homeostasis.[17]

We examined the changes of maternal hepcidin levels, serum iron, ferritin, and hematological parameters in women with first trimester spontaneous abortion, and first and second trimester normal pregnancies, and compared them to nonpregnant women.

2 | MATERIALS AND METHODS

2.1 | Serum samples

All serum samples were remnant specimens from the clinical laboratory, collected from women treated in Beijing Obstetrics and Gynecology Hospital and divided into four groups: nonpregnant control (age-appropriate women without gestation, $n = 20$); pregnant women in the first trimester (pregnancy week <12, ultrasound diagnosis of embryos developing normally, $n = 27$); spontaneous abortion in the first trimester (pregnancy week <12, ultrasound and pathological diagnosis of embryos stopping the development, the samples were collected after the ultrasound confirmation, $n = 36$); pregnant women in the second trimester (pregnancy week between 13 and 28, ultrasound and other diagnoses confirming embryos developing normally, $n = 38$). Patients were excluded if they had anemia, endocrine

abnormalities, uterine malformations, inflammation, cancer, chromosomal abnormalities, thyroid dysfunction, hypertension, diabetes, or other preexisting diagnoses. All samples were obtained with the subject's consent. Information about BMI, pre-pregnancy BMI and parity was not accessible. All blood draws were in the morning, after fasting.

2.2 | Serum biochemical parameters assay

Colorimetric method was used to assay serum iron (Nanjing Jiancheng Bio-engineering Institute, used as previously described[17]). The manufacturer-provided characteristics of the assay were: inter-assay: CV = 6.54%; intra-assay: CV = 3.9%; working range: 1.79–1074.3 μmol/L; the reference range for women: 10.74–30.98 μmol/L.

Serum hepcidin was measured by ELISA (Intrinsic Lifesciences) as previously described.[18] Serum ferritin was measured by ELISA (Cloud-Clone), with assay characteristics as provided by the manufacturer: inter-assay: CV < 12%; intra-assay: CV < 10%; the minimum detectable concentration: less than 4.3 pg/mL. Serum IL-6 was measured by ELISA (R&D Systems). Transferrin saturation was measured by colorimetric method (iron divided by total iron binding capacity [TIBC], Nanjing Jiancheng Bioengineering Institute). The TIBC kits inter-assay CV = 6.32%; intra-assay: CV = 3.8%; working range: 0.05–30 mg/L. The RBCs and hemoglobin concentrations were measured by the clinical laboratory of the hospital, by the Sysmex XN2000 automated hematology analyzer.

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistical version, 22. All of the markers were analyzed using one-way anova. Pearson's correlation analysis was used to assess association between hepcidin and other variables. Comparisons of slopes and intercepts of regression lines was done by analysis of covariance (ANCOVA). $P < .05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Concentrations of serum hepcidin in women with normal and abnormal pregnancy

To gain insights into hepcidin changes in women with normal and abnormal pregnancy, we measured serum hepcidin concentration in a cross-sectional study including nonpregnant control women, pregnant women in the first and second trimester, and pregnant women with spontaneous abortion in the first trimester. The characteristics of our four cohorts are listed in Table 1. As shown in Figure 1A, serum hepcidin concentration was significantly increased by 1.7 times in pregnant women in the first trimester relative to nonpregnant control ($P < .05$). In contrast, serum hepcidin concentration significantly declined in the second trimester, by 3- and 5.9-fold, compared with the nonpregnancy control ($P < .05$) and the first trimester pregnancy ($P < .001$) respectively. The lower concentration of hepcidin would increase the supply of iron to support the increased iron requirements of the mother and her fetus. Hepcidin decrease is not explained by hemodilution of pregnancy, as the magnitude of hepcidin decrease (5.9-fold compared with the first trimester) far exceeds the expected plasma volume expansion (~1.3-fold compared with the first trimester[19]).

The hepcidin concentration in women with spontaneous abortion was further elevated by 1.4-fold compared with the normal first trimester pregnancy ($P < .05$). Hepcidin is subject to regulation by changes in iron stores and plasma concentrations, erythropoietic activity,[20] and inflammation.[21] The effect of inflammation is prominently mediated by IL-6, however, there was no significant difference between IL-6 levels in the first trimester viable pregnancies and the spontaneous abortion group (Supporting Information Figure S1A). Interestingly, there was a mild but significant IL-6 decrease by 30% in the first trimester compared with nonpregnant women ($P < .05$) or compared with the second trimester ($P < .05$). We specifically excluded from this study women with known inflammatory conditions.

3.2 | Concentrations of iron-related parameters during normal and abnormal pregnancy

We measured the concentration of serum iron and compared them between the four groups (Figure 1B). Maternal serum iron concentration remained constant during the first or second trimester of normal pregnancies and was similar to the serum iron concentration in nonpregnant women. Considering that iron consumption by the fetal tissues and maternal erythropoiesis increases in the second trimester, the maintenance of pre-pregnancy serum iron levels during this period is consistent with increased supply of iron into the circulation, likely mediated by decreased hepcidin. In women with spontaneous abortion, the serum iron concentration was significantly increased by 2.2 times compared with the first trimester normal pregnancy ($P < .001$). Transferrin saturation (TSAT), a ratio of serum iron and TIBC concentrations, is a clinical indicator of the difference between iron supply and utilization, and also represents the amount of iron available for erythropoiesis and other vital processes. TIBC was unchanged in healthy pregnancy compared with nonpregnant women but was significantly decreased in women with spontaneous abortion compared with the first trimester with healthy pregnancy (Figure 1C, $P < .05$). For transferrin saturation (Figure 1D), compared with nonpregnant women, TSAT was not significantly changed in the first and second trimester. In contrast, in women after spontaneous abortion, this indicator was significantly elevated by 3.1 times compared with the first trimester ($P < .001$). Ferritin concentration was not significantly changed in the first trimester, but was reduced by 1.7-fold in second trimester ($P < .05$) compared with the nonpregnant women (Figure 1C), reflecting the mobilization of iron stores. Serum ferritin was significantly elevated by 66% in women who suffered spontaneous abortion compared with those with normal pregnancy in the first trimester ($P < .05$).

We next examined hemoglobin and red blood cell (RBC) parameters. As shown in Figure 1F and Supporting Information Figure S1B, in the first trimester of normal pregnancies, hemoglobin and RBC were not significantly changed relative to nonpregnant controls, then decreased in the second trimester compared with the first trimester ($P < .001$), presumably because of the expected expansion of blood volume.[8] RBC concentration in spontaneous abortion women was slightly reduced compared with the healthy first trimester ($P < .05$), with hemoglobin decrease not reaching statistical significance.

In all pregnancy groups (first trimester with healthy and spontaneous abortion groups and second trimester), serum hepcidin correlated positively with serum ferritin (Figure 2, Pearson correlation healthy first trimester $R = 0.46$, $P = .02$, $N = 27$; first trimester fetal

demise $R = 0.76$, $P = 9 \times 10^{-8}$, $N = 36$; second trimester $R = 0.57$, $P = 2 \times 10^{-4}$, $N = 38$). No other significant correlation was noted between hepcidin and iron or inflammatory parameters. Interestingly, as indicated by different intercepts of the regression lines, there was a significant shift in the relationship between hepcidin and ferritin between the nonpregnant controls and the first trimester (Figure 2A, $P = .017$) so that the 1st trimester hepcidin was higher relative to ferritin. An opposite shift in the relationship between hepcidin and ferritin occurred between the first and second trimesters (Figure 2B, $P < .0001$), wherein the 2nd trimester hepcidin was lower relative to ferritin than in the 1st trimester. Spontaneous abortion during the first trimester on average increased both ferritin and hepcidin (Figure 1) but did not significantly alter the relationship between ferritin and hepcidin compared with the healthy 1st trimester, as measured by the slope and intercept of the respective regression lines (Figure 2C).

4 | DISCUSSION

Iron is essential for placental and fetal development[9] and severe iron deficiency can cause adverse pregnancy outcomes such as increased risk of preterm labor,[22] fetal loss, and even perinatal death.[23] In addition to the iron needed for the growth of the placenta and of the fetus, iron is also necessary to support the expansion of the maternal red cell compartment. The average pregnancy requires about 1 g of iron, an amount which exceeds the iron stores of nearly all women. During the first trimester, the iron requirement is relatively minor: by the end of the first trimester, the combined fetal-placental mass is less than 100 g and maternal weight gain or expansion of the erythron has not yet taken place. Most spontaneous abortions occur during the first trimester. During the second trimester, both maternal and fetoplacental weight gain greatly accelerate and iron demand increases to meet the requirements of these growing tissues. The additional iron is generated from increased maternal iron absorption from the diet and from the mobilization of iron from maternal stores, both controlled by the iron-regulatory hormone hepcidin. We assessed maternal hepcidin, iron and hematological parameters in a cohort of Chinese women with or without pregnancy. We showed that in the first trimester, maternal hepcidin is surprisingly increased compared with nonpregnant women. This occurred despite the lack of change in iron parameters and even lower IL-6 concentrations in this cohort. In the second trimester of normal pregnancy, we found a profound decrease in maternal hepcidin, similarly to the reports in European and African women,[11,24,25] presumably to maintain a higher iron supply to support fetal growth and maternal erythropoietic expansion. However, unlike in the European cohort (and not assessed in the African cohort), serum iron and transferrin saturation was maintained in our second trimester group, arguing against pregnancy-related hypoferremia as the primary driver of hepcidin suppression. Although hepcidin still correlated with ferritin in all pregnancy cohorts, the correlation was significantly shifted in the first trimester compared with nonpregnant women with higher intercepts indicating increased hepcidin in the 1st trimester relative to ferritin. In contrast, in the second compared with the first trimester, the correlation was significantly shifted in the opposite direction with lower intercepts indicating decreased hepcidin in the 2nd trimester relative to ferritin. Thus, both the increase of hepcidin in the 1st trimester compared with nonpregnant women, and the decrease of hepcidin concentration in the 2nd compared with the 1st trimester appears

independent of iron status or inflammation. Our results suggest that hepcidin is regulated by signals related to the progression of pregnancy, but the underlying mechanisms remain to be determined.

Spontaneous abortion is a clinically common manifestation of abnormal pregnancy. To confirm spontaneous abortion, we generally rely on ultrasound and test of human chorionic gonadotropin (HCG) in serum or urine. It is completely unknown whether abnormal pregnancy causes a perturbation in iron homeostasis or conversely whether abnormal iron changes could contribute to abnormal pregnancy. In our study, we found that maternal iron concentrations, transferrin saturation, and serum ferritin in the first trimester spontaneous abortion group were significantly increased compared with the healthy first trimester pregnancy. As the transport of maternal iron across the placenta to fetus is unidirectional,[9] it is possible that spontaneous abortion may lead to accumulation of iron in maternal plasma because maternal iron was no longer transported to the fetus through the placenta. As a result, hepcidin concentrations may have been increased by the homeostatic regulatory systems in response to the increased iron concentrations in maternal plasma. No inflammation was noted, as measured by IL-6 levels, and RBCs mildly decreased in the spontaneous abortion group compared with the healthy first trimester pregnancies. Profound hormonal changes resulting from the spontaneous abortion may also contribute to the disordered iron homeostasis in the mother.

The cross-sectional design of the study and moderate numbers of patients in each group were dictated by our focus on relatively large effect size as well as by low availability of samples from patients with spontaneous abortions and our limited resources. These could be considered limitations of the study.

Many gaps still remain in our understanding of how maternal and fetal hepcidin are regulated in normal and pathological pregnancy and how they contribute to pregnancy outcomes. Studies in diverse populations of the changes in iron parameters and circulating hepcidin in normal and abnormal pregnancies are the first step toward improved understanding of the underlying mechanisms. As we demonstrated, placental-fetal iron utilization impacts maternal iron metabolism, and mechanistic studies of this relationship are not only of fundamental interest but could provide useful markers of placental and fetal health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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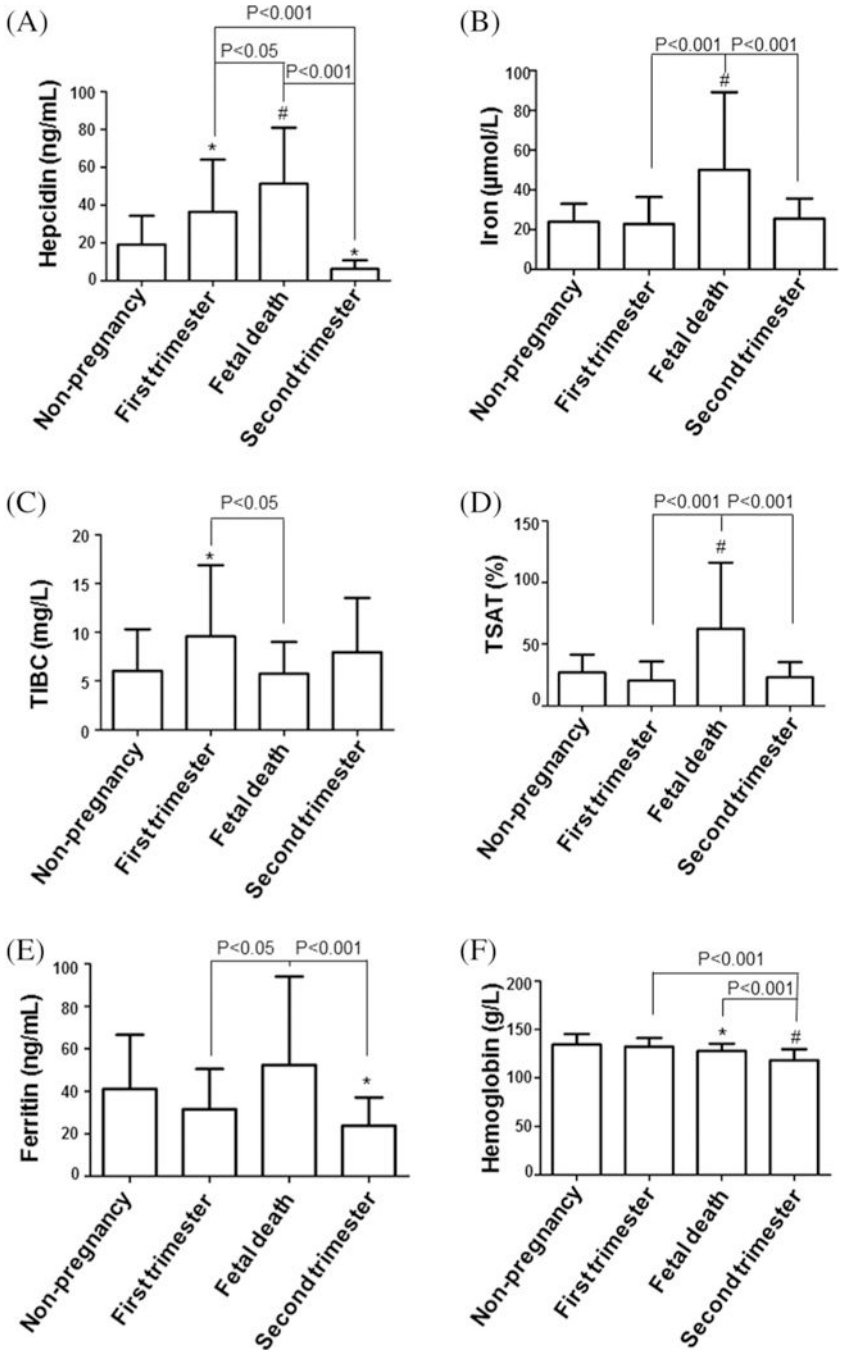

FIGURE 1.

Concentration of serum hepcidin and iron-related markers in physiological and pathological pregnancy. The concentration of hepcidin (**A**), iron (**B**), TIBC (**C**), transferrin saturation (**D**), ferritin (**E**),and hemoglobin (**F**) were measured in nonpregnant control women, pregnant women in the first or second trimester, and women with spontaneous abortion in the first trimester. **P*<.05; #*P*<.001, compared with nonpregnant controls, or as indicated. Data are presented as mean ± SD

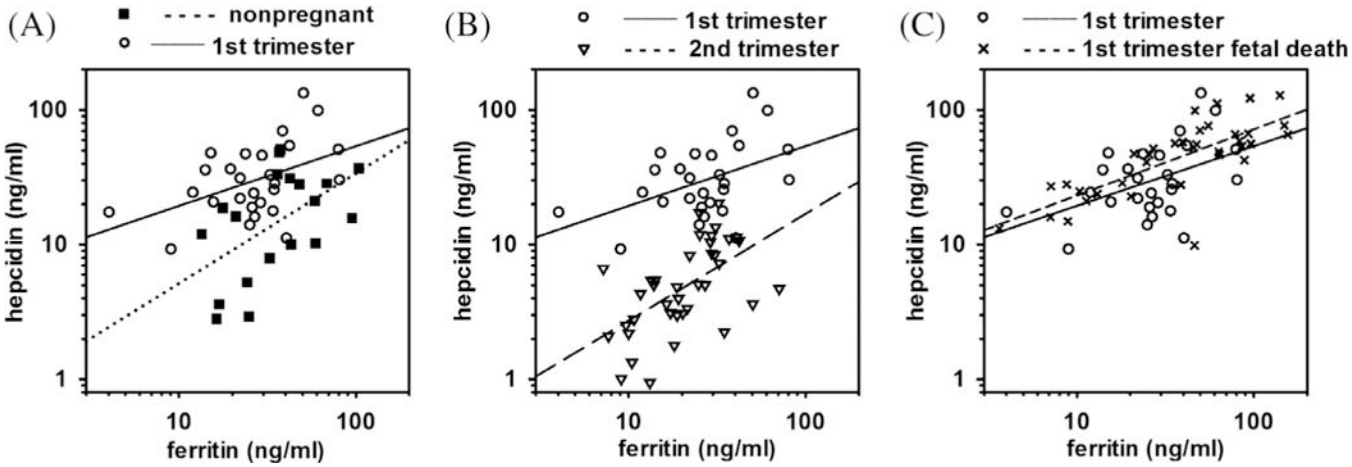

FIGURE 2.

The relationship between hepcidin and ferritin in physiological and pathological pregnancy. Scatter plots (log–log scale) and regression lines of hepcidin vs ferritin in: (**A**) nonpregnant women (solid squares and dotted line) compare to the healthy first trimester (open circles and solid line); (**B**) healthy first trimester (open circles and solid line) compared with healthy second trimester (triangles and dashed line); and (**C**) healthy first trimester (open circles and solid line) compared with first trimester fetal demise (crosses and dashed line). Regression equations: Nonpregnant women: Log(hepcidin) = 0.82 * log(ferritin) – 0.11 (dashed); healthy 1st trimester: Log(hepcidin) = 0.44* log(ferritin) + 0.84 (solid); healthy 2nd trimester: Log(hepcidin) = 0.79 * log(ferritin) – 0.36; 1st trimester spontaneous abortion: Log(hepcidin) = 0.49 * log(ferritin) + 0.87. Comparisons of slopes and intercepts of regression lines within each panel by analysis of covariance (ANCOVA) shows that the intercepts in panel **A** and **B** are significantly different at $P = .017$ and $P < .0001$, respectively

TABLE 1

Characteristics of the study subjects

Parameter	Nonpregnant women	Pregnant women in 1st trimester	Spontaneous abortion in 1st trimester	Pregnant women in 2nd trimester
Number	20	27	36	38
Age	33.5 ± 4.7	31.6 ± 3.2	31.8 ± 4.8	32.5 ± 4.8
Gestational age	–	7.2 ± 1.0	9.0 ± 1.4	24.9 ± 1.3
Iron supplements	–	–	–	8/38
Anemic	–	–	–	–
Hepcidin (ng/mL)	19.1 ± 15.2	36.4 ± 27.6 *	51.3 ± 29.5 #a	6.2 ± 4.6 *bd
Ferritin (ng/mL)	41.1 ± 25.5	31.6 ± 18.9	52.4 ± 41.5 a	23.7 ± 13.3 *d
Iron (μmol/L)	23.9 ± 9.1	22.7 ± 13.6	50.1 ± 39.0 #b	25.4 ± 10.2 d
Transferrin saturation (%)	27.0 ± 14.5	20.3 ± 15.5	62.5 ± 53.5 #b	22.9 ± 12.4 d
TIBC (mg/L)	6.0 ± 4.3	9.6 ± 7.3 *	5.7 ± 3.3 a	8.0 ± 5.6
IL-6 (pg/mL)	7.0 ± 2.3	5.4 ± 2.0 *	5.9 ± 1.9	7.0 ± 1.8 ac
Hemoglobin (g/L)	134.4 ± 10.8	132.2 ± 9.0	125.9 ± 10.7 *	118.2 ± 11.3 #bd
RBC (10^{12}/L)	4.5 ± 0.5	4.5 ± 0.5	4.2 ± 0.5 *a	3.8 ± 0.3 #bd

Data are presented as a number, or mean ± SD, with

*, $P < .05$

#, $P < .001$, compared with nonpregnant controls

a, $P < .05$

b, $P < .001$, compared with pregnant women in 1st trimester

c, $P < .05$

d, $P < .001$, compared with spontaneous abortion in 1st trimester.

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