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Prenatal maternal stress predicts cord-blood ferritin concentration

Abstract

Aim: To examine the relationship between maternal stress in early pregnancy and cord-blood ferritin concentration.
Methods: The sample consisted of 140 pregnant women who lived in a region that was under rocket attack during a military operation (December 2008 to January 2009). Mothers in the stress group (n=63) were in their first trimester during this period. Mothers in the control group (n=77) became pregnant 4–5 months after the attacks ended. Maternal subjective stress was reported retrospectively. Cord-blood ferritin concentration was compared between stress and control groups, and was the dependent variable in a hierarchical multiple regression analysis.
Results: The mean cord-blood ferritin concentration was lower in the stress group compared to the control group (145.7±62.0 vs. 169.3±85.4 ng/mL, $P<0.05$). The cumulative distribution of cord-blood ferritin showed a shift to the left for the stress group. Hierarchical multiple regression analysis revealed that maternal subjective stress was a predictor for cord-blood ferritin concentration (hierarchical regression: $\beta=-0.18$, $P<0.05$), especially in the stress group (simple slope analysis: $\beta=-0.32$, $P<0.01$).
Conclusion: Maternal stress during the first trimester of pregnancy is associated with lower cord-blood ferritin concentration.

Keywords: Cord-blood; ferritin; fetal; iron deficiency; stress; prenatal.

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Introduction

Iron is an essential component of every living cell and plays an important role in critical cellular functions for all organ systems. Iron is particularly vital for early brain growth and function, as it supports neuronal and glial energy metabolism, neurotransmitter synthesis, and myelination [5, 10, 12, 13, 19, 20, 25, 32]. Studies in young animals show that iron is prioritized to the red cells over all other organs [14]. Anemia is a late manifestation of iron deficiency. Before anemia develops, the storage form of iron becomes depleted especially in the placenta and liver, followed by decreased tissue iron concentration in the heart and brain [22, 23]. Fetal iron deficiency in animal models relates to impaired growth and functioning of multiple organ systems, predisposes the animal to postnatal iron deficiency, and contributes to long-lasting neurodevelopmental impairments [24]. Several human studies indicate that poor perinatal iron status is associated with poor iron status in late infancy [15, 17] and with short- and/or long-term neurobehavioral deficits [2, 3, 27, 31]. These studies suggest that fetal and perinatal iron

deficiency is a risk factor for impaired infant iron status and neurobehavioral outcomes. These findings seem to fit with the framework of developmental origins of health and disease [4].

To control and prevent fetal and perinatal iron deficiency, it is important to map the factors that affect iron homeostasis during the perinatal period. Well-known risk factors are maternal iron deficiency, maternal physical health status (e.g., diabetes), maternal lifestyle habits (e.g., smoking), gestational age (pre-term), birth weight (intrauterine growth restriction), and multiple gestation [24]. Research in monkeys indicates that maternal stress during pregnancy may be another risk factor for early iron deficiency [9]. Monkey mothers were disturbed by intermittent noise during early or late gestation. Their infants, especially those with lower birth weight and larger growth rates, were more likely to develop iron deficiency anemia, compared to infants of non-stressed mothers.

The purpose of the present study was to examine perinatal iron status in newborns whose mothers were or were not exposed to stress early in pregnancy. Perinatal iron status was measured by cord-blood serum ferritin concentration, which has been recognized as an effective biomarker of fetal iron status [28]. Stress early in pregnancy was defined as being in the first trimester of pregnancy and living in southern Israel during a military operation ("Oferet-Yetzuka", December 27, 2008–January 18, 2009), when there were more than 600 rocket attacks in the area. In addition, maternal retrospective subjective stress was evaluated to measure perceived psychological stress. Our hypothesis was that stress during the first trimester of pregnancy due to being in a war zone and higher levels of perceived stress would predict lower cord-blood ferritin concentrations.

Participants and methods

Participants

The study was approved by the Barzilai Medical Center and the Israeli Ministry of Health Ethics Committees, and informed consent was obtained from each participant. Israeli women were recruited as they checked in to the delivery-room reception area of the Barzilai Medical Center to give birth. The medical center serves the city of Ashkelon and the surrounding region. Recruitment occurred in two phases. In the first phase (29 July to 30 September 2009), we recruited women who had lived in the area exposed to rocket attacks during the first trimester of pregnancy. In the second phase (1 March to 30 May 2010), we recruited women who had lived in the same area and become pregnant 4–5 months after the rocket attacks ended. Based on our knowledge of the state of mind in Israeli society, we assumed that 4–5 months after the attacks ended would be enough time to recover from the attacks' stressful effects. Inclusion criteria were living in the city of Ashkelon or a nearby village throughout pregnancy, age over 18 years, healthy, no drug use or intake of more than one glass of wine or other alcohol per week during pregnancy, no psychosis or mental health problems, an uncomplicated (e.g., no maternal diabetes or hypertension) and singleton pregnancy, a term delivery (≥37 weeks), normal birth weight (2500–4000 g), 5-min Apgar score ≥9, cord-blood ferritin concentration ≤370 ng/mL [28], and no evidence of any major perinatal complications.

One hundred and eighty women were enrolled in the study: 90 in the first phase and 90 in the second phase. In the first phase, 15 women were excluded because they reported that they did not live in the area throughout pregnancy or had left the area for more than a week during the attacks. Of the remaining 165 women, 12 women in the first phase (15.5%) and 13 women in the second phase (14%) were excluded because they did not complete the entire interview conducted after delivery or because of an incomplete blood test. This resulted in a final sample of 140 mothers and their infants. Those enrolled in the first phase were defined as the stress group (n=63), and those enrolled in the second phase were defined as the control group (n=77).

Procedure and measures

Brief screening questions were asked at the reception desk to identify healthy women with no pregnancy complications. Labor continued as usual in the delivery room, and cord-blood was collected after birth. On the first or second day after delivery, mothers participated in a semi-structured interview about background and health during pregnancy and filled out questionnaires about depression and anxiety. Mothers were also asked to evaluate their level of stress during pregnancy by using a visual analog scale. Pregnancy and delivery charts were reviewed for additional information.

Maternal data including age, marital status, education, occupation, alcohol and drug use, prenatal care, pregnancy check-ups, and health were obtained from the semi-structured interview and postpartum maternal interview. A socioeconomic status index [18] was computed yielding a continuous socioeconomic status measure ranging from 8 to 66. Data on infant birth outcomes were gathered from hospital records.

Depression was assessed by the Beck Depression Inventory. The inventory, which contains 21 items, was completed by the mother to assess depressive symptoms during the previous week. Items are rated on a four-point scale and summed to a total score (score range 0–63). Extensive data support the measure's internal consistency and content validity [6, 26]. Reliability analysis of the Beck Depression Inventory (internal consistency) in our sample yielded a Cronbach's α coefficient of 0.84. Anxiety was assessed by the State-Trait Anxiety Inventory. We used the trait anxiety subscale which consists of 20 items, rated on a four-point scale (1="not at all" and 4="very much so"). Maternal anxiety scores were summed to a total score (range 20–80). Detailed information regarding reliability and validity is reported in the test manual [29]. Reliability analysis of the State-Trait Anxiety Inventory (internal consistency) in our sample yielded a Cronbach's α coefficient of 0.88.

Maternal subjective stress during pregnancy was evaluated by using a 100-mm retrospective visual analog scale (1="low stress" to 100="high stress"). Mothers were asked to mark on the scale the

amount of subjective stress they had experienced during pregnancy. The length from the lower value to the mark was measured. This scale is similar to other subjective measures of mood or anxiety [11, 30]. Because the study was designed after the attacks ended and approved shortly before the women in the stress group were due to give birth, measuring maternal stress throughout pregnancy was not possible. Therefore, one global retrospective measurement of maternal subjective stress during pregnancy was selected. In addition, this measurement was chosen because other subjective stress measures were not available in Hebrew.

Maternal iron status was based on the routine pre-partum blood sample collected in the delivery room. Hemoglobin and red blood cell distribution width (RDW) values were taken from the delivery charts. Ferritin is not part of the regular blood test before labor. Because the women were recruited at the delivery-room reception, we thought that asking for an additional blood test at this sensitive time would increase the likelihood of women deciding not to participate. Cord-blood samples were collected, and serum ferritin concentrations were determined at the biochemistry and the hematological laboratories of Barzilai Medical Center.

Statistical analysis

Data were analyzed using SPSS 18.0 (SPSS, Chicago, IL, USA). Background characteristics were compared between groups (stress vs. control) using *t*-tests for continuous variables and χ^2 analyses for categorical variables. One-tailed test was used for cord-blood ferritin concentration because the hypothesis was unidirectional. The relations between cord-blood ferritin concentration, background characteristics, maternal iron status, and maternal subjective stress were evaluated. Pearson correlations were used for continuous variables, and *t*-test analyses for categorical variables. Descriptive statistics were used to consider group differences in the cumulative distribution of cord-blood ferritin. In addition, cord-blood ferritin percentiles for infants in the control and stress groups in the present study were compared to those of low-risk term and pre-term infants in a normative study [28].

Cord-blood ferritin concentration was used as the dependent variable in a hierarchical multiple regression analysis with three steps. Step 1 included maternal and infant background variables. These variables were used as controls because of their established relationship with cord-blood ferritin concentration [24] or when they statistically related to cord-blood ferritin concentration or group (stress vs. control) in our sample. Step 2 included two stress variables: group variable as a categorical variable (stress vs. control) and maternal subjective stress as a continuous variable. Step 3 included the interactions between group (stress vs. control) and maternal subjective stress and between group and background variables that showed significant and meaningful differences between the groups. The variables were mean centered prior to the construction of the interaction terms in order to minimize any problems of multicollinearity [1].

Results

Mothers in the stress group averaged 2 years younger than mothers in the control group, and a higher proportion of them had been smoking. The mean hemoglobin concentration was slightly lower for mothers in the stress group than for those in the control group. There were no significant group differences in infant background characteristics (Table 1).

Cord-blood ferritin concentrations in the stress group (145.7±62.0 ng/mL) were significantly lower than in the control group (169.3±85.4 ng/mL) ($t_{(138)}$=1.83, P<0.05, one-tailed). In addition, ferritin concentrations were higher in females than in males (mean 171.9±76.6 and 143.8±74.0 ng/mL, respectively; $t_{(138)}$=–2.2, P<0.05), mainly due to

	Stress group (n=63)	Control group (n=77)	P-value
Mother and family variables			
Mother age (years)	28.5 (4.6)	30.5 (5.7)	0.026
Mother married (yes), % (n)	98.4 (62)	97.4 (75)	ns
Number of children	2.6 (1.6)	2.2 (1.4)	ns
Smoking (yes), % (n)	17.5 (11)	6.5 (5)	0.039
Socioeconomic status	37.2 (11.1)	34.3 (11.2)	ns
Beck Depression Inventory	4.8 (4.8)	5.0 (5.2)	ns
Maternal anxiety (trait)	30.7 (8.7)	31.5 (7.9)	ns
Hemoglobin (g/dL)	11.87 (1.2)	12.26 (0.9)	0.029
RDW (%)	14.5 (2.0)	14.7 (2.7)	ns
Infant variables			
Gender (male), % (n)	42.9 (27)	50.6 (39)	ns
Gestational age (weeks)	39.8 (1.0)	39.8 (1.0)	ns
Birth weight (g)	3327 (327.5)	3278 (344.5)	ns
Infant height (cm)	51.0 (2.2)	50.4 (2.6)	ns
Head circumference (cm)	34.4 (1.2)	34.2 (1.1)	ns
Weight-for-gestational age (z)	0.00 (0.8)	0.12 (0.8)	ns

Table 1 Background characteristics and iron measures in the stress and control groups.
Values are shown as mean (SD) unless otherwise indicated. RDW=distribution width, ns=Not significant.

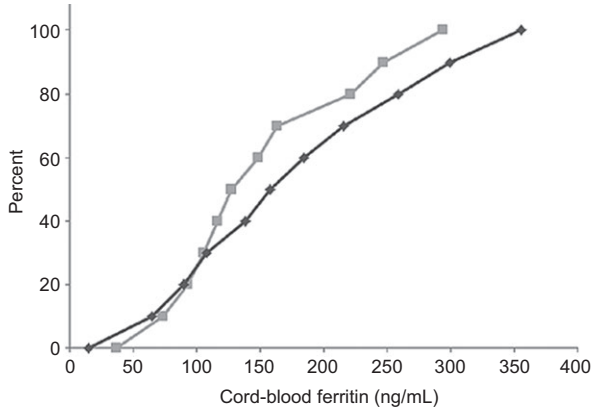

Figure 1 The figure shows the shift to the left of the cumulative distribution of cord-blood ferritin concentration in the stress group (gray line) compared to the control group (black line).

differences in the control group. Ferritin concentrations were significantly correlated with gestational age (r=0.20; P<0.05). There were no other statistically significant correlations between cord-blood ferritin concentration and any of the background characteristics, including socioeconomic status, maternal depression, and anxiety.

The cumulative distribution of cord-blood ferritin in the two groups showed a shift to the left for the stress group, indicating lower ferritin concentrations than for the control group (Figure 1). Cord-blood ferritin percentiles in the control group were similar to and somewhat higher than those of term infants in the normative sample. However, in the stress group, cord-blood ferritin percentiles were similar to those of term infants in the normative sample up to the 25th percentile, but somewhat lower than and more similar to those of the pre-term infants at the 50th percentile and above (Table 2).

In Step 1 of the hierarchical multiple regression analysis, four maternal variables (hemoglobin, RDW, age, and smoking) and two infant variables (gender and weight-for-gestational age z-score) were entered as controls. These control variables explained 17% of the variance of cord-blood ferritin concentration ($F_{(6,133)}$=4.44, P<0.01). Maternal hemoglobin and RDW (negative relationship), maternal age (negative relationship), and infant gender (female) were significant predictors of cord-blood ferritin concentration (Table 3). In Step 2, the two stress variables increased the explained variance of cord-blood ferritin concentration by 4% (F change$_{(2,131)}$=3.41, P<0.05). Maternal subjective stress and not group (stress vs. control) was a significant predictor of lower cord-blood ferritin concentration (Table 3).

In Step 3, three interaction terms were constructed and entered into the regression: group×maternal subjective stress, group×maternal hemoglobin, and group×maternal smoking (the interaction term group×maternal age was not constructed because the age differences between the groups had no clear meaning). Step 3 statistically increased the explained variance of cord-blood ferritin concentration by 6% (F change$_{(3,128)}$=3.17, P<0.05, see Table 3). Simple slope analyses revealed that maternal subjective stress was a significant predictor in the stress group (β=−0.32, P<0.01) but not in the control group (β=−0.03), maternal hemoglobin was a significant predictor in the control group (β=0.36, P<0.01) but not in the stress group (β=0.11), and maternal smoking tended to be a significant predictor in the stress group (β=−0.17, P<0.10) but not in the control group (β=0.13).

Discussion

Our results showed differences in cord-blood ferritin distribution in the stress group compared to the control group. The left shift of cord-blood ferritin in the stress group indicates lower cord-blood ferritin levels. In addition, maternal subjective stress predicted cord-blood ferritin concentrations, especially in the stress group. These findings complement the findings of Coe et al. [9] of prenatal stress-related iron-deficiency anemia in the monkey

	Cord-blood ferritin concentrations (ng/mL)				
Percentile	**5th**	**25th**	**50th**	**75th**	**95th**
Present study					
Control group (n=77)	43	99	158	238	318
Stress group (n=63)	69	100	128	182	260
Normative sample					
Low-risk term infants (≥37 weeks) (n=308)	40	84	134	200	309
Low-risk pre-term infants (<37 weeks) (n=149)	35	80	115	170	267

Table 2 Cord-blood ferritin concentration percentiles for infants in the control and stress groups in the present study and low-risk term and pre-term infants in a normative sample [28].

Predictor variables	Step 1	Step 2	Step 3
Maternal variables			
Hemoglobin	0.18*	0.21*	0.22*
RDW	−0.17*	−0.15	0.17*
Age	−0.23**	−0.20*	−0.21*
Smoking	−0.05	−0.06	−0.06
Infant variables			
Gender	0.24**	0.26**	0.28**
Weight-for-gestational age, z-score	0.15	0.17*	0.18*
Stress variables			
Group (stress vs. control)		−0.09	−0.09
Maternal subjective stress		−0.18*	−0.03
Interactions with group (stress vs. control)			
Group×maternal subjective stress			−0.21
Group×maternal hemoglobin			−0.18
Group×maternal smoking			−0.25
R^2	0.17**	0.21**	0.27**

Table 3 Predicting cord-blood ferritin concentration: hierarchical regression analysis.[a]

[a]Standardized coefficient β values are presented (n=140). *P<0.05, **P<0.01. RDW=distribution width, ns=Not significant.

infant. The relationship between maternal stress early in pregnancy and fetal iron status points to another deficit associated with prenatal stress, even in the absence of other effects such as delayed growth, prematurity, immune-system impairment, and other health problems. Our findings fit well with the concept of fetal origins of health and disease, which suggests that many processes governing physiological regulation are encoded during the fetal stage [8].

The comparison between cord-blood ferritin concentration in our study to those of term and pre-term infants in the normative sample published by Siddappa et al. [28] showed relatively lower levels of cord-blood ferritin in the higher percentiles in the stress group which were similar to those of pre-term infants. The 5th percentile of cord-blood ferritin concentration, especially in the stress group, is relatively high compared to the normative sample. Nevertheless, it is relatively lower than the 5th percentile of cord-blood ferritin concentration found in previous studies to be related to poorer short- and long-term neurobehavioral outcomes [2, 3, 31]. This study focused on fetal iron status and did not include any data on neurobehavioral outcomes. Future studies that examine neurobehavioral effects early in life are needed in iron deficiency research.

The biological mechanisms, by which stress during pregnancy impact maternal-placental-fetal iron regulation, are not well known [7]. There are three primary biological paths by which maternal stress might affect prenatal iron status: (1) perinatal factors (birth weight and gestational age), (2) placental dysfunction, and (3) maternal iron status [21]. Chen et al. [7] reported that psychological stress decreases iron absorption and impairs the expression of iron transporters in the small intestine of adult rats. As our study focused on maternal stress early in pregnancy in low-risk, full-term babies within the normal birth-weight range and there appeared to be little effect on maternal iron status in the stress group at the end of gestation, it is reasonable to suspect placental-dysfunction processes. Maternal environmental influences such as stress, hypoxemia (due to smoking or hypertension), protein deprivation, caloric deficiency or excess, infections, and other factors can result in profound alterations in placental gene-expression patterns and their consequences for growth, differentiation, and metabolism [16]. Future research is required to identify the specific path by which maternal stress early in pregnancy influences fetal iron status.

Some limitations, such as small sample size, convenience sampling, and lack of data on maternal iron status prior to exposure to stress, resulted from the need to design the study rapidly in order to enroll women who were in early pregnancy during the 1-month period of rocket attacks. As in any small study, it is crucial to replicate the findings in larger samples. Another limitation relates to the measurement of maternal stress. The perception of stress may be as important as exposure to a stressor and can reflect factors other than the stressor of interest. Therefore, we added the maternal subjective retrospective stress visual analog scale as a simple, non-invasive, and rapid measure of stress. In the future, other psychosocial risk factors of maternal stress as well as physiological measures, such as cortisol levels in saliva, blood, or hair samples, could be included. Assessing perceived stresses and physiological stress responses prospectively could be a strong design.

We, like others, used cord-blood serum ferritin as a biomarker for fetal iron status. Because several conditions could increase serum ferritin levels [28], we excluded infants with high cord-blood ferritin. Even so, we found a wide range of cord-blood ferritin concentrations in our study. This may indicate that some newborns are at risk for developing severe iron deficiency and iron-deficiency anemia in infancy. Our findings suggest that infants whose mothers were stressed during pregnancy are a previously unrecognized risk group for iron deficiency. It may be advisable to consider an additional hematological examination before the standard well-baby visit at 9–12 months of age, especially in high-risk populations, so that iron deficiency anemia can be detected early and treated before it becomes chronic and severe.

Conclusion

Our findings indicate that prenatal maternal stress early in pregnancy predicts lower cord-blood ferritin concentration. Although several maternal and fetal variables have already been recognized as potential risk factors for perinatal iron deficiency [24], our study is the first to suggest that maternal stress in early gestation might be another risk factor. Further study is needed to test the hypothesis that these effects are specific to maternal stress in early pregnancy. Another issue warranting further research is to explore the relations between fetal iron metabolism and other maternal stressors, such as life events, sleep disorders, and obesity. Future studies will have to address the effects of timing, degree, and nature of prenatal maternal stress on fetal and perinatal iron status.

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