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Effect of maternal cigarette smoking on newborn iron stores

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Abstract

Background: Maternal smoking has been known to have a negative impact on the well being of the developing fetus. Prenatal smoking has been associated with premature births, low birth weight and with certain birth defects. Small research studies have also found a negative correlation between maternal smoking and neonatal body iron.

Objectives: To study and compare the relationship between maternal and infants' body iron in smokers and non-smokers in a large matched-pair cohort.

Methods: This was a prospective cohort study involving 144 mothers – 72 smokers and 72 non-smokers and their respective infants. Samples were obtained from maternal and infants' cord blood at delivery for Serum transferrin receptor (sTfR) and ferritin levels. Serum TfR and ferritin were measured by RAMCO ELISA and RIA assays. Total Body Iron (TBI) was calculated using the sTfR/ferritin ratio in a previously described formula by Cook et al.

Results: Women who smoked had lower sTfR, higher ferritin and higher body iron compared to nonsmoking women. In contrast to their respective mothers, we found a small, but statistically significant negative correlation between smoking and infants' total body iron. The number of packs per day smoked was also negatively correlated with infants' ferritin and total body iron. Lower birth weight was noted in babies of smokers compared to nonsmokers (mean /- SD=3270 +/-475 vs. 3393 g +/- 475 g, p=0.03).

Conclusion: Women who smoked during pregnancy had higher iron stores but their newborn infants had lower iron stores than those of non-smoking mothers. The more packs per day (PPD) and more days smoked during pregnancy led to lower total body iron of the babies. There may be a negative dose-dependent response between fetal smoke exposure and infant iron stores.

Abbreviations: STfR: Serum transferrin receptor, TBI: Total body iron, ID: Iron deficiency, SD: Standard deviation, PPD: Packs per day

Introduction

An adequate body iron balance is essential to the function of all mammalian cells. Iron deficiency (ID) is the most common micronutrient deficiency in the world affecting 2 billion individuals and 30-50% of pregnant women [1]. The requirement for absorbed iron is increased gradually throughout pregnancy from 1 mg/day in the first trimester to almost 8 mg/day in the third trimester. The absorbed iron is used to expand the woman's red cell mass, fulfill the fetus' iron requirements and compensate for blood loss at delivery. Iron deficiency anemia (IDA) in pregnancy is a significant concern due to the importance of iron for growth and development for the fetus and newborn infant [2].

Current initiatives to reduce the high prevalence of nutritional IDA have highlighted the need for reliable methods to assess iron status. Various iron status markers have been described in the past including serum ferritin, serum transferrin receptor (sTfR), hemoglobin and hepcidin, though most have limitations. Hepcidin, for example is a crucial protein in iron homeostasis [3] but reference values have not been determined in newborns. Maternal hemoglobin, while inexpensive and simple to test, is significantly affected by normal hemodilution of pregnancy making this marker a poor indicator of the pregnant woman's iron status [4,5].

Alternatively, serum ferritin indicates available iron stores in healthy individuals. The serum transferin receptors (sTfRs) are detached receptors from erythrocytes, and their increased number indicates depleted iron stores. Therefore, in our study we assessed maternal and newborn iron stores using the method described by Cook and Skikne [6,7] utilizing the ratio of ferritin to sTfR to calculate total body iron (TBI). Total body iron allows the spectrum of iron status to be compared among individuals.

The aim of this study was to evaluate the TBI in pregnant women

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and their infants. We evaluated the mothers' smoking status and education, and compared this information with their apparently healthy term newborn infants' iron status, birth weight and length.

We hypothesized that maternal smoking has a negative impact on infants' iron status.

Methods

Subjects

Study subjects were a subset of women enrolled in a randomized controlled phase III clinical trial to provide the omega-3 fatty acid, docosahexaenoic acid, during the last half of pregnancy (NCT00266825). Written informed consent was obtained from each pregnant woman that included permission to analyze maternal and cord blood nutrients. The local institutional review board approved the study.

For the present subordinate study, all subjects from the original trial who smoked and delivered a healthy, term infant were pair-matched for age, race and pregnancy history with a subject from the study who did not smoke. A smoker was defined as someone who smoked within 1 year of becoming pregnant whether or not she stopped smoking during pregnancy. Information about maternal background (age, number of previous births and years of education) was obtained at enrollment for the initial trial. The women answered questions about vitamin supplementation and cigarette smoking habits before and during pregnancy at enrollment and at 6 weeks postpartum. Answers were used to calculate pack years of smoking prior to pregnancy and the number of days and number of packs per day (PPD) smoked during pregnancy. Table 1 illustrates the demographic characteristics of the mothers. Information on the infant's birth weight, length, and head circumference was collected from the infant's medical record.

Total body iron measurements

We analyzed ferritin and sTfR concentration in maternal peripheral blood and infant cord blood at the time of delivery. The ferritin concentration was measured by RAMCO RIA assay according to the manufacturer's instructions. We used the RAMCO ELISA assay to measure sTfR. The total body iron was calculated using the formula described by Cook *et al.* [6]:

Body iron (mg/kg)=-[log (sTfR*/ferritin)-2.8229]/0.1207.

Positive body iron indicates availability of iron and negative body iron indicates tissue iron deficit.

Table 1. Maternal demographic characteristics.

	Smokers (n=72)	Non-Smokers (n=72)
Race/Ethnicity		
Caucasian	39 (54.2%)	39 (54.2%)
African American	28 (38.9%)	28 (38.9%)
Hispanic	5 (6.9%)	5 (6.9%)
Education (years)	12.5	14.2
Age at delivery (years)	25.4	25.4
Gestational days smoked		
Average	130	NA
Min	0	NA
Max	287	NA
Average cigarettes/day	6.5	NA

Table 2. Iron status markers of smoker and non smoker pregnant women.

	sTfR (mg/L)	Ferritin (µ/L)	sTfR/Ferritin	Body iron (mg/kg)
Non-Smokers	**6.24** SD 3.67	**30.3** SD 26.5	**470** SD 647	**3.8** SD 4.27
Smokers	**5.02** SD 2.64	**36.2** SD 27.6	**361** SD 649	**4.9** SD 4.09

Table 3. Correlation between amount of smoking and smokers' infants iron parameters and body measurements at delivery.

	PPD smoked during pregnancy	Number of days smoked during pregnancy
Cord STfR	NS	r 0.175 p 0.039
Cord Ferritin	r -0.172 p 0.044	r -0.199 **p 0.020**
Total Body Iron	r -0.168 p 0.048	r -0.215 **p 0.011**
Birth Weight	r -0.221 p 0.008	r -0.230 **p 0.006**
Birth Length	r -0.201 p 0.016	r -0.166 p 0.047

Statistical analysis

All statistical tests performed were non parametric, including Spearman's correlations and the exact Chi^2 and Mann- Whitney U tests (SPSS v 17, Chicago, Ill). Tests were two tailed. Differences were considered statistically significant if $p<0.05$.

Results

Infant and maternal total body iron and smoking status

Table 2 shows that women who smoked had lower sTfR, higher ferritin and higher body iron compared to nonsmoking women.

In contrast to their respective mothers, we found a small but statistically significant negative correlation between smoking and infants' total body iron. The number of packs per day (PPD) smoked was negatively correlated with the infants' ferritin and total body iron. The number of days smoked during pregnancy was also negatively correlated with the infants' ferritin and total body iron and positively correlated with infant's sTfR. These data are shown on Table 3.

Infants' measurements at birth and smoking status

Birth weight was lower in babies of smokers compared to nonsmokers (mean/- SD=3270 +/-475 vs. 3393g +/- 475g, p=0.03). Mean head circumference measurements in babies of smokers were 34.1 cm (SD 1.4 cm) and in babies of non-smokers they were 33.9cm (SD 1.6cm). This difference was not statistically significant. Mean body length measurements in infants of mothers who smoked were 49.8cm (SD 2.5cm) and in infants of nonsmoking mothers 50.1cm (SD 2.6cm). This difference was also not statistically significant.

Correlation studies revealed that birth weight in infants of smokers was negatively correlated with PPD smoked and number of days smoked. Birth length in the same infants was also negatively correlated with PPD smoked and number of days smoked. Table 3 describes these data.

Maternal education and smoking status

Our results showed that maternal iron status increased significantly

Table 4. Correlations between maternal education and iron parameters in smokers and nonsmokers.

	Smokers		Non-Smokers	
	Spearman r_s	**p values**	**Spearman r_s**	**p values**
PPD smoked during pregnancy	- 0.244	0.003	NA	NA
No of days smoked during pregnancy	-0.323	<0.001	NA	NA
Hemoglobin at enrollment g/dL	0.214	0.071	0.315	0.007
Maternal ferritin at delivery µg/L	0.262	0.026	0.423	<0.001
Maternal TBI at delivery mg/kg	0.153	0.199	0.321	0.006
Maternal sTfR/Ferritin	-.0192	0.021	-0.321	0.006

with increasing maternal education [r_s 0.192, p=0.021] in smokers and non smokers. Maternal education was inversely associated with smoking [r_s (-) 0.244, P=0.003] and the number of days smoked among smokers [r_s (-) 0.323, p<0.001] during pregnancy. Table 4 illustrates these findings.

Discussion

There are multiple factors that negatively influence fetal newborn iron stores. In developed countries, the main factors are poorly controlled gestational diabetes mellitus, intrauterine growth restriction (IUGR) due to maternal hypertension and maternal smoking [8]. Other factors include multiple gestation, preterm birth, and both acute and chronic fetal hemorrhage. Iron deficiency during the fetal and neonatal period can result in poor function of multiple organ systems, some of which might not recover despite subsequent correction of iron homeostasis [9].

To our knowledge this is the first report that compares total body iron of infants born to smokers to that of infants born to non-smokers. By measuring the TBI, we observed that maternal smoking led to lower neonatal body iron. We also found that both cigarettes smoked per day (PPD) and the number of days women smoked during pregnancy was associated with lower TBI in the infant at birth. Lower ferritin levels have been reported previously in infants of smokers compared to nonsmokers as evidence of lower neonatal iron status [10,11]. Some researchers have reported lower ferritin and higher sTFR levels in infants born to mothers who smoke and interpreted those as markers of increased erythropoiesis, but not necessarily lower body iron [5]. In contrast, Schiza *et al*. attributed the higher sTFR values and low ferritin values in their patient population of late preterm infants, to iron deficiency, rather than increased erythropoietic activity [12]. We found both lower plasma ferritin and higher sTfR, and based on the calculations for total body iron with the formula described by Cook *et al.* [6], these are indicative of lower neonatal iron status. We also found a positive relationship between newborn sTfR (i.e. as an indicator of iron deficiency) and the number of days smoked during pregnancy.

An alternative explanation of decreased newborn iron status is that placental iron transfer is impaired with maternal smoking. Higher TBI and ferritin and lower sTfR in women who smoke compared to those who did not, is consistent with reduced iron transport across the placenta. Although higher ferritin concentrations could result from chronic generalized inflammation due to smoking, inflammation seems a less likely explanation for higher maternal iron status. This is because we find lower sTfR with smoking. Lower sTfR is considered evidence of better cellular iron status, and sTfR is not influenced by inflammation. Thus we believe higher TBI in women who smoked likely reflects a significantly higher iron status compared to nonsmokers that is most likely due to reduced placental iron transport. Measurement of hemoglobin concentration, hematocrit levels and serum ferritin levels were used in previous research to determine iron stores in smoking mothers. Based on these parameters, researchers concluded that pregnant smokers have low iron stores, however, they did not directly compare iron status of smokers to nonsmokers [13-15] and many studies of pregnant women indicate lower iron status, especially when the indicator used to assess iron status is not corrected for the increase in maternal blood volume during pregnancy.

Maternal smoking affects placental blood flow and vascular resistance [16]. Indices of uterine vascular resistance were observed to increase with more tobacco exposure. A possible consequence is the decrease of blood nutrients and oxygen transported to the fetus leading to growth retardation and hypoxia. Also, hypoxia increases erythropoiesis in the fetus [17,18], and this could be an alternative explanation for decreased iron stores in infants of women who smoked compared to those who did not as they are using all the available iron for red cell production without iron storing.

Many previous studies describe the effect of maternal smoking during pregnancy on infant weight. The majority of these studies show birth weight and length, as well as head circumference are lower in infants delivered to mothers who smoke compared to infants from mothers who do not smoke [19,20]. We confirmed the findings of a smaller study conducted by Machado *et al.* [16] that smoking during pregnancy leads to a decrease in birth weight and length, smoking also affected infant's weight and length measurements at birth in a dose-dependent effect.

We found that maternal education correlated significantly with maternal body iron but did not correlate with the infant's total body iron at birth. Higher education correlated also with less smoking during pregnancy.

A limitation of the study is that we did not measure maternal iron intake and cannot say that intake was similar in smokers and nonsmokers. Another limitation is that we do not know if the fetus was exposed to second hand smoke from other persons who associated with the mother during pregnancy.

In conclusion, our study involves the largest sample to date regarding maternal smoking and total body iron status in term newborn infants. The majority of previous studies used cord hemoglobin level and ferritin level as indicators of the maternal and newborn's iron status. In our study sTfR, ferritin and their ratio were utilized to calculate TBI in pregnancy and at birth as a more accurate assessment of iron status. We found that infants born to mothers who smoke had low body iron while their mothers had higher body iron. We found

inverse relationships between the amount of cigarette smoking and newborn total body iron and growth.

The results of our study should promote awareness among primary care physicians, obstetricians and pediatricians about the harmful effects of maternal smoking during pregnancy and particularly its negative, dose–dependent impact on infants' iron status. This information may be used as a reference when promoting smoking secession in pregnant women and will provide rationale for closer monitoring of iron status of infants of smokers. Ultimately, those measures will lead to optimization of infant's iron stores and decrease the negative impact of iron deficiency on growth, development and cognitive function during childhood.

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