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# Iron status of full-term infants in early infancy is not associated with maternal ferritin levels nor infant feeding practice

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## Abstract

Iron deficiency (ID) in early life is associated with morbidities. Most fetal iron required for infant growth is acquired in the third trimester from maternal iron store. However, how prenatal iron level affects ferritin level in early infancy remains controversial. This study aimed to examine the associations between maternal ferritin levels and cord blood serum ferritin (CBSF) and to compare the ferritin levels between different feeding practices in early infancy. Healthy Chinese mothers with uncomplicated pregnancy and their infants were followed up at 3 months post-delivery for questionnaire completion and infant blood collection. Infants who were predominantly breastfed and those who were predominantly formula fed were included in this analysis. Serum ferritin levels were measured in maternal blood samples collected upon delivery, cord blood and infant blood samples at 3 months of age. Ninety-seven mother–baby dyads were included. Maternal ID is common (56 %) while the CBSF levels were significantly higher than maternal ferritin levels. Only three infants (3 %) had ID at 3 months of age. There were no significant correlations between maternal ferritin levels with CBSF ($r$ 0·168, $P = 0·108$) nor with infant ferritin levels at 3 months of age ($r$ 0·023, $P = 0·828$). Infant ferritin levels at 3 months were significantly and independently associated with CBSF ($P = 0·007$) and birth weight ($P < 0·001$) after adjusting for maternal age, parity, maternal education, infant sex and feeding practice. In conclusion, maternal ID was common upon delivery. However, maternal ferritin levels were not significantly associated with CBSF concentrations nor infant ferritin concentrations at 3 months of age.

**Key words:** **Iron status: Ferritin: Iron deficiency: Pregnancy: Cord blood: Infant: Children**

Iron deficiency (ID) is the most common micronutrient deficiency globally[1,2]. Pregnant women and young children are at risk of ID. During pregnancy, there is an increased demand for iron to accommodate the needs of the fetal–placental unit. This increase in physiological demand for iron renders pregnant women vulnerable to ID. In fact, ID is the major cause of anaemia in pregnancy and can increase the perinatal maternal morbidity and mortality[3,4]. Iron is also an essential micronutrient for fetal and infant brain development. ID in early life is associated with worse cognitive, motor, social, emotional as well as neurophysiological development[5,6]. Besides neurodevelopment, iron is also essential for proper immune function affecting both innate and adaptive cell and has implications for childhood atopic diseases[7–10].

Globally, there is an increasing trend of breast-feeding especially in developing countries[11]. Exclusive breast-feeding for 6 months has been recommended by the WHO given the many benefits of breast-feeding[12]. However, exclusive breast-feeding, particularly in the context of maternal ID and late weaning (defined as introducing foods and gradually reducing the amount of milk beyond 6 months of age), may be a risk factor of ID in the infants, which has potential adverse impact on neurocognitive development[13–15]. Therefore, it is important to evaluate the iron status of young infants, the effect of feeding practices on development of ID and the risk factors of ID in early infancy.

Maternal ID is prevalent worldwide varying from 20 to 90 %[16]. Previous investigation performed in the Department of Obstetrics and Gynaecology, Prince of Wales Hospital, concurred a significant prevalence (39 %) of ID (serum ferritin < 15 µg/l) among 100 asymptomatic pregnant women. On the other hand, data about the prevalence of ID in early infancy are limited. Most fetal iron needed for infant growth is acquired in the third trimester from maternal iron store, in preparation for the high growth rate in the first 6 months of life[17,18]. Iron status at birth is therefore critical and impaired iron status may persist into early childhood. However, low maternal prenatal iron levels measured as serum ferritin have not been consistently linked with low cord blood serum ferritin (CBSF) concentrations[19]. A recent meta-analysis reported that maternal biomarkers of iron status correlated poorly

**Abbreviations:** CBSF, cord blood serum ferritin; ID, iron deficiency.

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with those in newborns[19]. However, others found that maternal ID or anaemia, especially the severe type, adversely affected cord blood or infant iron status[20–24]. Further studies are needed to evaluate how prenatal maternal iron status affects newborn's ferritin level at birth. Such data are necessary to guide future recommendations regarding the need of iron supplement in pregnant or lactating women and/or their infants. Hence, this study aimed to examine the associations between maternal prenatal ferritin levels with CBSF and to compare the ferritin levels with different feeding practices in early infancy at 3 months of age.

## Methods

### Study design and population

Healthy Chinese mothers with uncomplicated pregnancy were recruited from a cohort which was established to evaluate gestational age-specific thyroid function during pregnancy[25]. Between July 2014 and January 2016, pregnant women attended antenatal care in their first trimester of pregnancy were recruited by research personnel in the antenatal clinic at the Prince of Wales Hospital, which is a tertiary teaching hospital in Hong Kong. After delivery, mothers were again approached and invited to join this study by our research personnel in the postnatal ward. Written informed consent was obtained for the postnatal follow-up study as well as retrieval of the antenatal blood and cord blood samples for nutritional and related studies. Women who carried a singleton pregnancy without history of thyroid dysfunction, hyperemesis gravidarum, autoimmune disease or any other major medical condition with cord blood samples available were eligible for this study. Exclusion criteria were multiple pregnancy, preterm delivery at less than 37 weeks of gestation, infants with congenital anomalies, syndromal diseases, chronic renal or hepatic diseases, metabolic disease, chronic gastrointestinal diseases and/or malabsorption. This study was approved by the Clinical Research Ethics Committee.

### Data and blood collection

Venous blood samples were collected and stored when the participating mothers were admitted to the Prince of Wales Hospital for delivery. Blood samples were collected into a clotted blood tube and archived. Immediately after delivery, umbilical cord blood was collected by midwives by needle puncture of the umbilical cord vein. All samples were centrifuged and aliquoted for storage at −80°C until analysis.

The recruited mother–child dyads were then invited to attend scheduled research clinic at 3 months postnatal age. Parents were asked to complete a self-administered questionnaire to provide information on potential confounders related to health outcomes of the subjects including sex, birth weight, gestational age, season of birth, number of older siblings at birth, parental educational level, household income, smoking habit during pregnancy, duration of breast-feeding, environmental tobacco exposure, day care attendance, dog or cat exposure, parental history of allergies, asthma, allergic rhinitis and eczema. They were also asked to complete a questionnaire concerning their child's (a) feeding pattern, duration of breast-feeding, amount of milk consumed, (b) nutritional supplementation pattern, (c) maternal dietary habits and nutritional supplementation during pregnancy and lactation and (d) health condition. Trained research staff measured the infant's recumbent length using length board and weight with minimal clothing. During the visit, venous blood sample was collected from the infant subjects into a clotted blood tube. All samples were centrifuged, aliquoted and archived for storage at −80°C until analysis.

For the purpose of this study to evaluate the ferritin levels with different feeding practices in early infancy at 3 months of age, infants who were predominantly breastfed and those who were predominantly formula fed were included in the analysis. Measurement of ferritin levels was not performed in other infants because of the resources limitation. Infants were considered predominantly breastfed if they were having < 200 ml formula milk/d, which would be approximately < 20 % of daily milk consumption and has been used to define breastfed infants in previous studies[26]. On the other hand, infants were considered predominantly formula fed infants if they were having ≥ 600 ml formula milk/d.

### Ferritin measurement

Upon sample collection, serum was separated from whole blood and stored in −80°C before use. Serum ferritin level was measured by commercial sandwich ELISA kit (Demeditec Diagnostics GmbH). Undiluted samples were added to the ELISA, according to the manufacturer's instruction. Intra-assay coefficient variation and inter-assay coefficient variation were 6·13 and 5·8 %, respectively. Optical density at 450 nm was measured by μQuant Microplate Spectrophotometer (Bio-Tek, Winooski). In this study, maternal and infant ID were defined as serum ferritin levels < 30 and < 12 μg/l, respectively[18,27,28]. The higher levels of ferritin to define maternal ID were used because of the higher iron demand during pregnancy[18].

### Statistical analysis

Sample size for this study was constrained by the original cohort size and the limited resources for biochemical measurements. By two-sample *t* test, an unequal sample size of 42 in a group and 55 in another was able to detect an effect size of 0·58 with 80 % power and 5 % type 1 error. This sample size of 97 was able to detect a prevalence of ID at 50 % with a tolerable error of 10% with a precision of 95 % CI[29]. Primary outcome measure was the serum ferritin levels in maternal blood samples upon delivery, umbilical CBSF and infant blood samples at 3 months of age. Baseline characteristics were described using frequencies for categorical variables and means and standard deviations for continuous variables. Chi-square test was used for comparison of categorical data, and *t* test and Mann–Whitney *U* test were used for normally distributed data and skewed data, respectively. Correlations between maternal ferritin, CBSF levels and infant ferritin levels were assessed by Pearson correlation. Linear regression was used to examine the associations between maternal blood ferritin with CBSF and postnatal infant ferritin levels, and between CBSF and infant ferritin levels at 3 months old, with adjustment for potential confounding factors. A two-tailed *P* value of less than 0·05 was considered statistically

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significant for all analyses. All statistical analysis was performed by the SPSS statistic package (IBM® SPSS® Statistics, version 23.0, SPSS Hong Kong Ltd.).

## Results

Between July 2014 and January 2016, 524 women were included in the original cohort[25]. Among this original cohort, 329 were eligible to join this study, 144 (44 %) agreed to join the study and attended the follow-up at 3 months post-delivery. Ninety-seven mother–baby dyads were included in this study. When compared with the non-respondents, the included mother–baby dyads did not demonstrate significant differences in maternal or infant characteristics (Table 1). Among the ninety-seven included mother–baby dyads, fifty-five infants were predominantly formula fed, while forty-two were predominantly breastfed. The characteristics of the mothers and infants are presented in Table 2. There were no statistically significant differences in the mother or baby characteristics between the two feeding practices. None of the infants was on additional nutritional supplements.

Maternal ID is common (56 %). Only three infants in this cohort had ID at 3 months of age (3 %). None of those who were predominantly formula fed was iron deficient.

The CBSF levels were significantly higher than the maternal ferritin levels (148·9 ± 53·4 μg/l *v.* 36·4 ± 35·9 μg/l). There were no significant correlations between maternal ferritin levels with CBSF ($r$ 0·168, $P = 0·108$) nor with infant ferritin levels at 3 months old ($r$ 0·023, $P = 0·828$) (Table 3). By multivariable linear regression, the maternal ferritin levels were not significantly associated with CBSF levels after adjusting for maternal age, parity, maternal education, infant sex and birth weight ($P = 0·068$; B = 0·29, 95 % CI −0·02, 0·59) (Table 4). Maternal ferritin levels were not significantly associated with infant ferritin concentrations at 3 months old either with adjustment for maternal age, parity, maternal education, infant sex and birth weight ($P = 0·396$; B = 0·12, 95 % CI −0·15, 0·39) (Table 4). The associations remained not significant after further adjustment to CBSF concentrations ($P = 0·74$; B = 0·05, 95 % CI −0·22, 0·31).

There was significant correlation between CBSF and infant ferritin levels at 3 months of age ($r$ 0·37, $P < 0·001$) (Table 3). By multivariable linear regression, infant ferritin levels at 3 months old were significantly and independently associated with CBSF ($P = 0·007$; B = 0·25, 95 % CI 0·07, 0·43) and birth weight ($P < 0·001$; B = 0·05, 95 % CI 0·03, 0·08), after adjusting for maternal age, parity, maternal education, maternal ferritin levels, infant sex and feeding practice (Table 5).

**Table 1.** Comparison of characteristics between respondents and non-respondents
(Mean values and standard deviations; numbers and percentages)

| | Respondents (*n* 97) | | Non-respondents (*n* 329) | | |
|---|---|---|---|---|---|
| Characteristics | *n* | % | *n* | % | *P* |
| Maternal age, years | | | | | 0·53 |
| Mean | 31·4 | | 31·7 | | |
| SD | 3·7 | | 3·9 | | |
| Primigravida | 65 | 67·0 | 209 | 63·5 | 0·53 |
| Gestation of birth, weeks | | | | | 0·06 |
| Mean | 39·2 | | 39·4 | | |
| SD | 1·2 | | 1·1 | | |
| Sex | | | | | |
| Boys | 49 | 50·5 | 178 | 54·1 | 0·53 |
| Girls | 48 | 49·5 | 151 | 45·9 | |
| Birth weight, g | | | | | 0·11 |
| Mean | 3136 | | 3207 | | |
| SD | 348 | | 386 | | |

## Discussion

Our study demonstrated that maternal ID was common upon the time of delivery. However, maternal ferritin levels were not significantly associated with newborn's CBSF concentrations nor infant ferritin concentrations at 3 months of age. ID at early infancy was uncommon in our cohort. The serum ferritin levels in early postnatal period at 3 months of age were not significantly different between predominantly breastfed and predominantly formula fed infants.

Our study echoed the findings from some previous studies that no correlation was found between the maternal iron status in late pregnancy and newborn's iron status[19]. However, some studies suggest the otherwise[20–24]. The conflicting results might be explained by the different methodology adopted to assess iron status and different definitions to define ID. In addition, some studies demonstrate that the cord blood ferritin levels do not decrease until the ferritin value of the mother is markedly low[24]. A study done in rural southeastern China with large sample size and consideration of the effects of inflammation have found that maternal and neonatal iron status are related only if maternal iron status is compromised[30]. The findings have supported the active transplacental transport of iron. The exact mechanism how iron is transported across placental membranes, which iron transporter proteins are involved in different placental cells and how the process is regulated, remains not fully understood. It is known that nutrient transport across the placenta is carried out by the syncytiotrophoblast, which is the primary barrier between the maternal and fetal circulation. Iron is delivered to the placenta through the maternal circulation, where iron is complexed with transferrin, ferritin or heme. Transferrin-bound iron is believed to be the predominant iron source transported by the placenta. It binds to the placental transferrin receptor 1 which is highly expressed in human placenta facing the maternal circulation and is a critical transporter mediating placental iron uptake while ferroportin facing the fetal circulation mediating the iron export out of the syncytiotrophoblast into fetal circulation[31]. Iron homoeostasis has been shown to have altered in pregnancy to allow maximal availability of iron for the fetus with low maternal hepcidin, which is a key regulator of iron homoeostasis[32]. With maternal ID, critical transporters (transferrin receptor 1 and ferroportin) are strongly regulated and mediated through iron regulator protein 1. In case of severe maternal ID, *in vitro* study demonstrated that the placental adaption, through regulation of transferrin receptor 1 and ferroportin, would prioritise placental iron in the face of fetal ID to maintain placental mitochondrial respiration and function[33]. Therefore, more studies are needed to

**Table 2.** Comparisons of maternal and infant characteristics between groups with different feeding practices (Mean values and standard deviations; numbers and percentages)

| Characteristics | All, *n* 97 | | Predominantly breastfed infants, *n* 42 | | Predominantly formula fed infants, *n* 55 | | *P* |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Maternal | | | | | | | |
| Maternal age, years | | | | | | | 0·469 |
| Mean | 31·4 | | 30·6 | | 31·2 | | |
| SD | 3·7 | | 3·9 | | 3·7 | | |
| Primigravida | 65 | 67 | 30 | 71 | 35 | 64 | 0·515 |
| Education | | | | | | | |
| Secondary | 56 | 57·7 | 24 | 57 | 32 | 58 | 0·755 |
| Tertiary or above | 41 | 42·3 | 18 | 43 | 23 | 42 | |
| Serum ferritin concentration, μg/l | | | | | | | 0·609 |
| Mean | 36·4 | | 34·1 | | 38·0 | | |
| SD | 35·9 | | 27·4 | | 41·1 | | |
| Iron deficiency | 54 | 56 | 22 | 52 | 32 | 58 | 0·864 |
| Infant | | | | | | | |
| Sex | | | | | | | |
| Boys | 49 | 50·5 | 22 | 52 | 27 | 49 | 0·838 |
| Girls | 48 | 49·5 | 20 | 48 | 28 | 51 | |
| Gestation of birth, weeks | | | | | | | 0·088 |
| Mean | 39·2 | | 39·0 | | 39·4 | | |
| SD | 1·2 | | 1·3 | | 1·1 | | |
| Birth weight, g | | | | | | | 0·289 |
| Mean | 3136·1 | | 3093·0 | | 3169·0 | | |
| SD | 348·1 | | 399·9 | | 302·5 | | |
| Body weight at 3 months, kg | | | | | | | 0·061 |
| Mean | 6·5 | | 6·4 | | 6·6 | | |
| SD | 0·7 | | 0·7 | | 0·7 | | |
| Body length at 3 months, cm | | | | | | | 0·061 |
| Mean | 62·8 | | 62·3 | | 63·2 | | |
| SD | 2·4 | | 2·3 | | 2·5 | | |
| Ferritin concentrations, μg/l | | | | | | | |
| Cord blood serum | | | | | | | 0·535 |
| Mean | 148·9 | | 145·0 | | 151·9 | | |
| SD | 53·4 | | 44·8 | | 59·3 | | |
| At 3 months old | | | | | | | 0·190 |
| Mean | 94·0 | | 86·5 | | 99·8 | | |
| SD | 49·7 | | 47·3 | | 51·1 | | |
| Iron deficiency at 3 months, *n* (%) | 3 | 3 | 3 | 7 | 0 | 0 | 0·078 |

**Table 3.** Pearson correlations among maternal ferritin, cord blood serum ferritin and infant ferritin concentrations

| Measurements | Maternal ferritin | *P* | Cord blood serum ferritin | *P* |
|---|---|---|---|---|
| Infant ferritin at 3 months old | *r* 0·023 | *P* = 0·828 | *r* 0·370 | *P* < 0·001 |
| Cord blood serum ferritin | *r* 0·168 | *P* = 0·108 | – | |

assess whether more optimal maternal iron can improve the infant iron status. Although maternal iron status was not found to be correlated with infant iron status in our study, it is important to note that maternal ID and anaemia are associated with adverse pregnancy outcomes such as preterm delivery and low birth weight, and prenatal iron use could improve birth weight in a dose–response fashion[34,35]. Moreover, fetal ID might occur in severe maternal ID[24,30,33]. Therefore, the optimisation of maternal iron status remains important to improve pregnancy outcomes.

From our study, we have found that CBSF was an independent determinant of the ferritin levels at 3 months of age, which was not surprising. Moreover, at 3 months of age, there were no significant differences in ferritin levels with different feeding practices despite the fortification of the infant formulae. Majority of the iron demand for early postnatal period in the first 6 months of life is acquired transplacentally in the third trimester from maternal iron store[17,18]. Iron status at birth is therefore critical for the first few months of life especially if the dietary iron intake is limited. From our study, apparently the risk of ID in early postnatal period was rather low as long as the fetal iron store was adequate.

There were several limitations to address in our study. First, the iron status was estimated with serum ferritin concentrations. However, they were not adjusted for inflammation, which could

**Table 4.** Multivariable linear regression analysis for the associations between maternal ferritin and cord blood serum ferritin or infant ferritin concentrations ($\beta$-coefficients and 95 % confidence intervals)

| | Cord blood serum ferritin | | | Infant ferritin at 3 months old | | |
|---|---|---|---|---|---|---|
| Independent variables | $\beta$ | 95 % CI | *P* | $\beta$ | 95 % CI | *P* |
| Maternal ferritin concentrations | 0·29 | −0·02, 0·59 | 0·068 | 0·12 | −0·15, 0·39 | 0·396 |
| Maternal age | −0·20 | −3·12, 2·72 | 0·893 | 0·19 | −2·37, 2·74 | 0·885 |
| Maternal education | −6·79 | −16·1, 2·56 | 0·152 | −5·53 | −13·63, 2·58 | 0·179 |
| Parity | 5·83 | −18·1, 29·7 | 0·629 | −1·81 | −22·72, 19·09 | 0·864 |
| Infant male sex | −8·95 | −31·0, 13·1 | 0·423 | −17·6 | −36·86, 1·58 | 0·072 |
| Birth weight | 0·03 | −0·002, 0·06 | 0·069 | 0·06 | 0·04 – 0·09 | <0·001 |

**Table 5.** Multivariable linear regression analysis for the associations between cord blood serum ferritin and infant ferritin concentrations ($\beta$-coefficients and 95 % confidence intervals)

| | Infant ferritin at 3 months old | | |
|---|---|---|---|
| Independent variables | $\beta$ | 95 % CI | *P* |
| Cord blood serum ferritin | 0·25 | 0·07, 0·43 | 0·007 |
| Maternal ferritin concentrations | 0·02 | −0·10, 0·14 | 0·787 |
| Maternal age | 0·17 | −2·32, 2·66 | 0·891 |
| Maternal education | −3·90 | −11·99, 4·18 | 0·179 |
| Parity | −3·91 | −24·26, 16·45 | 0·704 |
| Infant male sex | −14·90 | −33·85, 4·04 | 0·121 |
| Birth weight | 0·05 | 0·03, 0·08 | <0·001 |
| Breast-feeding | −7·27 | −26·66, 12·12 | 0·458 |

affect the assessment of both maternal, cord blood and infant ferritin levels[34]. Second, the complete blood counts were not available from the mother nor the infants that the anaemic status could not be assessed. The definition of ID from the WHO was adopted in this study; however, there is limited evidence regarding the definitions in relation to clinical outcomes[35]. Future studies to elucidate clinically relevant iron adequacy are needed to define the appropriate cut-offs. The comparisons of characteristics between subjects included and the non-respondents did not demonstrate significant differences in both maternal and infant characteristics, suggesting self-selection was unlikely. However, as the sample size was small, although there were no statistically significant differences in the ferritin levels between infants having different feeding practices, the results might be limited by the small sample number. Moreover, the definitions of feeding practice were arbitrary. Studies with larger sample size and longer follow-up period are needed to compare exclusive breast-feeding, partial breast-feeding and formula feeding infants and assess how various feeding practices affect the iron status of the infants and clinical outcomes. The types of formulae being used were not specifically recorded in this study and there might be variations in the iron content among different formulae. However, the requirements on nutritional composition of infant formulae have been regulated locally that they are fortified with iron to a general standard[36]. Finally, the time of cord clamping was not assessed while delayed cord clamping would improve infant iron status. Despite the limitations, this study has provided valuable information that would aid in the planning of future studies to evaluate iron status of pregnant women and their children as well as the long-term implications of the iron status in utero and early life.

## *Conclusion*

Maternal ID was common upon the time of delivery. However, maternal ferritin levels were not significantly associated with newborn's CBSF concentrations nor infant ferritin concentrations at 3 months of age. ID was uncommon in our cohort at 3 months of age despite the prevalence of maternal ID. The ferritin status did not differ significantly between infants who were predominantly breastfed and those who were predominantly formula fed. More studies with large sample size and longer follow-up period are needed to assess whether more optimal maternal iron can improve the infant iron status and related health outcomes.

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