Relationship between maternal iron and cord blood iron status: A prospective study

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ABSTRACT

Background: Iron sufficiency is of paramount importance in the neonatal period. Controversy exists whether the transfer of iron to the fetus from the mother is determined by fetal demands or by maternal iron stores. Numerous studies correlating maternal and neonatal iron stores revealed conflicting results. **Aims:** To study the relationship between maternal and neonatal iron indices at birth and to observe the impact of gestational age on iron stores in neonates. **Methods and Materials:** This prospective study was conducted in neonatal care unit of the tertiary hospital. Total 195 mother and newborn pairs are enrolled in the study. Neonates were divided into groups based on gestational age. The maternal venous samples were collected 1 h ± 15 min before the delivery. Cord blood sample and venous samples were drawn from a peripheral vein in neonates who came for follow-up at 4 weeks. Samples were analyzed for hemoglobin (Hb), serum ferritin, serum iron, and total iron-binding capacity. **Results:** Significant positive correlation was found between maternal Hb and neonatal ferritin (Pearson's correlation coefficient =0.26, p=0.002) and maternal iron and neonatal iron (Pearson's correlation coefficient =0.294, p=0.000). Ferritin concentration of cord blood samples in neonates born to mothers with ferritin levels <12 µg/L showed significant correlation. Mean ferritin in preterm neonates (128.9±80.7 µg/dl) was significantly lower than in term neonates (156.9±78.6 µg/dl) (p=0.040). Mean Hb in preterm neonates (14.5±2.1 g/dl) was significantly lower than in term neonates (15.0±2.1 g/dl) (p=0.028). 4-week samples showed significantly lower serum iron concentrations in preterm when compared to term group. Serum ferritin levels at birth showed positive correlation at 4 weeks. (Pearson's correlation coefficient =0.211, p=0.028). **Conclusions:** Neonatal iron stores are affected in case of severe maternal iron deficiency indicated by ferritin levels <12 µg/L. Gestational age has a significant impact on neonatal iron stores. Neonates with a deficient iron store at birth likely to have low iron stores at 4 weeks.

Key words: *Cord iron indices, Gestational age, Maternal ferritin*

Iron is the most common micronutrient deficiency in the developing countries like India. Adequate iron stores are critical for rapidly developing fetal and neonatal organ systems. It is a component of various enzymes and required for neurotransmitter synthesis and myelination of central nervous system during the fetal period and postnatal life. Perinatal iron deficiency leads to long-lasting neurodevelopmental impairment and early onset of postnatal iron deficiency [1,2]. Conversely, the presence of excess free iron has a risk of generating toxic free radicals, especially in preterms which have low levels of iron-binding proteins and immature antioxidant systems [3,4]. This highlights the immense need to maintain adequate iron stores in the perinatal and neonatal period.

Whether a maternal dietary iron transfer to the fetus is related to maternal iron status is still debated. Previous studies on the relationship between maternal and neonatal iron status using multiple parameters showed contrasting results [5]. Understanding relationships between maternal and neonatal iron indices help in formulating the protocols to improve the maternal and neonatal outcome. Therefore, this study was planned to evaluate the relationship between maternal and neonatal iron stores at birth and to observe the effect of gestational age on iron status in newborns at birth and 4 weeks.

MATERIALS AND METHODS

This prospective study was conducted in a tertiary care institution of Andhra Pradesh from November 2014 to August 2016. Approval from the Institutional Ethical Committee and informed consent from parents was obtained. The maternal-newborn pairs delivered during the study were enrolled in the study. Babies with major congenital anomalies, sepsis, and pathological jaundice requiring treatment and twin deliveries were excluded. Mothers with antepartum hemorrhage, infection, and history of blood transfusion in antenatal period were also excluded. Eligible mother-infant pairs were followed from the time of enrollment to 28±4 days. The information on baseline parameters and outcomes was recorded in a standard pro forma. The enrolled mother-infant pairs were stratified broadly based on gestational age. New Ballard scoring was done for the assessment of gestational age.

The maternal blood samples were collected 1 h ± 15 min before the delivery. After the delivery of the baby, 5 ml of blood collected from the cord by sectioning the cord between two clamps placed 4-5 inches apart. The venous sample was drawn from a peripheral vein in neonates who came for follow-up at 4 weeks. Measurement of hemoglobin (Hb), serum ferritin, serum iron, and total iron-binding capacity (TIBC) was done from these samples. The neonates were followed clinically up to 28±4 days in the neonatal clinic after discharge. The serum ferritin was estimated by fully automated bidirectional interfaced chemiluminescent immunoassay. Serum iron was done by ferrozine method without deproteinization. Serum TIBC was done by spectrophotometric assay. Baseline variables were described using descriptive statistics. Effect of maternal iron indices on neonatal iron indices and the effect of neonatal iron indices at birth on the follow-up iron indices was analyzed by Pearson's correlation coefficient.

RESULTS

One hundred and ninety-five mother-infant pairs met the eligibility criteria during the study. Of them, seventeen were excluded as their samples were inadequate/hemolyzed and could not be processed and six were excluded as they had abnormally high ferritin levels (>370 µg/L). One hundred and seventy-two mother-infant pairs were included for the final analysis. Males constituted 54.7% (94) and females constituted 45.3% (78) of the cases. The mean gestational age of the neonates enrolled was 37.3±2.3 weeks, and the mean birth weight was 2780±419 g. Among the study population, 125 (72.7%) were term and 47 (27.3%) were preterm. The median (interquartile range) of measured iron indices of mother and cord blood is shown in Table 1. The correlation was analyzed between various maternal iron indices with neonatal iron indices using Pearson's correlation coefficient (Table 2).

A significant correlation was observed between maternal Hb and neonatal ferritin (Pearson's coefficient =0.26, p=0.002). A positive correlation was found between maternal iron and neonatal iron (Pearson's coefficient =0.294, p=0.000). No significant correlation between maternal ferritin and any of the neonatal iron indices was observed (Table 2). The iron indices of babies born to mothers with ferritin level <12 µg/L were compared with those with ferritin level >12 µg/L. A significantly low ferritin concentrations were observed in the neonates born to mothers with ferritin levels <12 µg/L (p=0.02) as shown in Table 3.

The mean neonatal ferritin levels were significantly low in preterm group (128.9±80 µg/dl) as compared to term group (156.9±78.6 µg/dl) (p=0.040). As expected, mean neonatal Hb concentrations were also significantly low in preterm group (14.5±2.1 g/dl) as compared to term group (15.0±2.1 g/dl), p=0.028). Follow-up samples at 4 weeks showed significantly lower serum iron concentrations in preterms (35.5±33.7 µg/dl) than in term neonates (75.5±54.7 µg/dl) (p=0.009). Neonatal Hb

Table 1: Baseline characteristics of the study group

Number of participants	No of individuals (n=172)
Gestation (weeks)	
Mean±SD	37.3±2.3
Median (IQR)	38 (36.39)
Neonates (%)	
Male	54.7
Female	45.3
Preterm (%)	27.3
Term (%)	72.7
Maternal indices	
Median (IQR)	
Hb	9.4 (9,10)
Iron	85 (57,124.5)
Ferritin	28 (25,58)
TIBC	504 (450,582.5)
Neonatal indices at birth	
Median (IQR)	
Hb	15.6 (14,16.8)
Iron	162 (118.5,208)
Ferritin	95 (40,166)
TIBC	314 (263,381)

Hb: Hemoglobin, TIBC: Total iron-binding capacity, IQR: Interquartile range, SD: Standard deviation

and serum iron values on cord blood samples were found to have a significant correlation with corresponding values at 4 weeks of age. Significant correlation of serum ferritin levels at birth with following levels at 4 weeks was also observed (Pearson's coefficient =0.211, p=0.028).

DISCUSSION

Iron deficiency is a common nutritional deficiency in pregnancy. It has a significant influence on the maternal and neonatal outcome [6]. Maternal iron transported by serum transferrin binds to transferrin receptor on the maternal side of syncytiotrophoblast. Iron that is taken up is transferred to the receptor on the fetal side of placenta [7]. Increased fetal requirements and maternal iron insufficiency leads to increased expression of TfR receptors resulting in increased availability of iron at the maternal surface for increased placental uptake [8]. It is uncertain whether the amount of iron transferred across the placenta is proportional to iron available in the mother or the whether the fetus receives the iron preferentially as per its requirements. Many studies are done to find a correlation between maternal and neonatal iron status, but the results are conflicting [9]. Some studies reported that transfer of iron to fetus occur independent of maternal iron levels, leading to severe deficiency in mother [10,11]. In severe maternal iron deficiency, even upregulation of receptors fail to provide sufficient iron transfer to fetus, leading to low reserves of fetal iron stores [12,13].

A large proportion of iron which fetus receives comes directly from iron absorbed from the maternal gut rather than the maternal stores. A study by O'Brien et al. concluded that transfer of dietary

Table 2: Comparison among maternal and neonatal iron indices

Maternal parameters	Neonatal Hb	Neonatal iron	Neonatal TIBC	Neonatal transferrin	Neonatal ferritin
Hb					
Pearson co	−0.01	−0.45	0.00	−0.39	0.26
p	0.90	0.00	0.93	0.00	0.00
Iron					
Pearson co	−0.01	0.29	0.01	0.39	0.03
p	0.83	0.00	0.89	0.00	0.62
TIBC					
Pearson co	0.31	0.34	0.11	0.32	−0.27
p	0.00	0.00	0.13	0.00	0.00
Transferrin					
Pearson co	−0.14	0.24	−0.12	0.31	0.15
p	0.11	0.00	0.15	0.00	0.07
Ferritin					
Pearson co	−0.04	−0.12	−0.08	−0.03	0.03
p	0.58	0.10	0.25	0.64	0.64

Pearson co: Pearson correlation coefficient. TIBC: Total iron-binding capacity, Hb: Hemoglobin

Table 3: Comparison of effect of low maternal stores on neonatal indices

Cord blood indicies	Maternal ferritin <12 µg/dl	Maternal ferritin >12 µg/dl	"p"
Neonatal Hb (g/dl)	16.3±1.9	15.1±2.1	0.03
Neonatal iron (µg/dl)	143.1±57.5	128.6±57.4	0.24
Neonatal TIBC (µg/dl)	278.9±79.8	248.8±76.9	0.07
Neonatal transferrin (%)	48.6±19.5	53.8±24.6	0.37
Neonatal ferritin (µg/L)	115.2±65	155.1±81	0.02

TIBC: Total iron-binding capacity, Hb: Hemoglobin

iron to the fetus is related to maternal iron status [5]. Physiological changes such as increased plasma volume and erythropoiesis during pregnancy have profound impact on biochemical parameters used for assessing iron stores. Multiple parameters including Hb, serum iron, red cell distribution width, mean corpuscular volume, TIBC, percentage of transferrin saturation, and serum ferritin were used by several investigators. Serum ferritin found to be the single best parameter to assess iron status in pregnant mothers; although it can elevate by inflammation [14]. It's still unclear about the optimal parameter for the assessment of iron status in the neonatal period. Serum ferritin is the major storage form and correlate with body iron stores, and the cutoff values for neonates recently established [15].

In the current study population, there was a significant positive correlation between maternal Hb and neonatal ferritin concentrations at birth. Singla et al., in their study found a linear correlation between maternal Hb with cord Hb and iron levels [16]. No correlation was observed between maternal and neonatal ferritin concentrations at birth. Rios et al., Kelly et al., and Puolakka et al. did not find any correlation between maternal and umbilical cord ferritin levels [17-19]. The threshold of maternal ferritin concentration below which fetal iron accretion is affected was estimated as <12 µg/L [20]. At this level, even with upregulation of receptors not much iron will bind to transferrin receptors on the maternal side of placenta resulting in less transfer of iron to the fetus. In our study, significant lower ferritin concentrations were observed in the babies with maternal ferritin levels <12 µg/L than those born to mothers with ferritin level >12 µg/L. Similar observations were made by Jaime-Perez et al. [20].

Transfer of iron to the fetus begins in the first trimester of pregnancy, but maximum transport occurs after 30 weeks of gestation. Fetal transfer of iron will be interrupted due to premature delivery [7]. In this study, iron stores in preterm neonates were significantly less as compared to the term neonates on cord blood samples. Similar observations were also made by Mukhopadhyay et al., Jansson et al., and Messer et al. [21-23]. Serum ferritin levels reflecting iron stores progressively increase with gestational age, with mean levels of 63 µg/l at 23 weeks and 171 µg/l at 41 weeks, respectively [15]. The optimal timing for administration of prophylactic enteral iron supplementation in preterm and very low birth weight infants is unclear [24]. The American Academy of Pediatrics recommends 2 mg/kg/day of supplemental iron on milk feeding from 1 month of age and extending through 12 months of age [25]. In the present study, preterm neonates also showed significant lower Hb levels at 4 weeks compared to term neonates. Neonates with low iron stores at birth tend to have significantly lower iron stores at 4-week postnatal age.

A major limitation of this study was that it has not taken into account influence of other maternal factors such as pregnancy-induced hypertension and gestational diabetes on neonatal stores. Second, preterm neonates are not categorized into small for gestational age (SGA) and appropriate for gestational age groups as there was small number of SGA preterm neonates in the study.

CONCLUSION

There is no correlation between maternal iron stores and neonatal iron stores unless there is severe maternal depletion indicated by maternal serum ferritin levels <12 µg/L. Iron stores in preterm neonates are significantly less in the face of severe depleted maternal stores. Severe maternal hypoferritinemia and gestational age significantly influence the iron status of neonates at birth and those neonates born with low iron stores at birth are likely to have low iron stores at 4 weeks. Therefore, early supplementation of iron at 4 weeks of age particularly in preterm neonates and in those neonates whose maternal serum ferritin levels are <12 µg/L may be useful.

REFERENCES

1. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006;64:S34-43.
2. Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron-deficiency anemia. Child Dev. 1998;69(1):24-36.
3. Jansson LT. Iron, oxygen stress, and preterm infant. Iron Metabolism in Infants. Boca Raton: CRC Press; 1990. p. 73-85.
4. Inder TE, Clemett RS, Austin NC, Graham P, Darlow BA. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. J Pediatr. 1997;131(4):541-4.
5. O'Brien KO, Zavaleta N, Abrams SA, Caulfield LE. Maternal iron status influences iron transfer to the fetus during the third trimester of pregnancy. Am J Clin Nutr. 2003;77(4):924-30.
6. Scholl TO. Iron status during pregnancy: Setting the stage for mother and infant. Am J Clin Nutr. 2005;81(5):1218S-22S.
7. Allen LH. Anemia and iron deficiency: Effects on pregnancy outcome. Am J Clin Nutr. 2000;71 5 Suppl:1280S-4S.
8. Liao QK, Kong PA, Gao J, Li FY, Qian ZM. Expression of ferritin receptor in placental microvilli membrane in pregnant women with different iron status at mid-term gestation. Eur J Clin Nutr. 2001;55(8):651-6.
9. Agrawal V, Jain V, Sahu P. Cord blood iron status in maternal iron deficiency anaemia. Natl J Integr Res Med. 2016;7(3):21-4.
10. Emery D, Barry D. Comparison of Maori and non-Maori maternal and fetal iron parameters. N Z Med J. 2004;117(1195):U909.
11. Erdem A, Erdem M, Arslan M, Yazici G, Eskandari R, Himmetoglu O. The effect of maternal anemia and iron deficiency on fetal erythropoiesis: Comparison between serum erythropoietin, hemoglobin and ferritin levels in mothers and newborns. J Matern Fetal Neonatal Med. 2002;11(5):329-32.
12. Paiva Ade A, Rondó PH, Pagliusi RA, Latorre Mdo R, Cardoso MA, Gondim SS. Relationship between the iron status of pregnant women and their newborns. Rev Saude Publica. 2007;41(3):321-7.
13. Siddique H, Ayyub M, Nadeem M. Correlation of iron status between pregnant women and their corresponding new borns. J Rawal Med Coll. 2013;17(1):84-7.
14. Scholl TO, Reilly T. Anemia, iron and pregnancy outcome. J Nutr. 2000;130 2S Suppl:443S-7S.
15. Siddappa AM, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: A review of the literature and standards for ferritin concentrations. Neonatology. 2007;92(2):73-82.
16. Singla PN, Tyagi M, Kumar A, Dash D, Shankar R. Fetal growth in maternal anaemia. J Trop Pediatr. 1997;43(2):89-92.
17. Rios E, Lipschitz DA, Cook JD, Smith NJ. Relationship of maternal and infant iron stores as assessed by determination of plasma ferritin. Pediatrics. 1975;55(5):694-9.
18. Kelly AM, MacDonald DJ, McDougall AN. Observations on maternal and fetal ferritin concentrations at term. Br J Obstet Gynaecol. 1978;85(5):338-43.
19. Puolakka J, Jänne O, Vihko R. Evaluation by serum ferritin assay of the influence of maternal iron stores on the iron status of newborns and infants. Acta Obstet Gynecol Scand Suppl. 1980;95:53-6.
20. Jaime-Perez JC, Herrera-Garza JL, Gomez-Almaguer D. Sub-optimal fetal iron acquisition under a maternal environment. Arch Med Res. 2005;36(5):598-602.
21. Mukhopadhyay K, Yadav RK, Kishore SS, Garewal G, Jain V, Narang A. Iron status at birth and at 4 weeks in term small-for-gestation infants in comparison with appropriate-for-gestation infants. J Matern Fetal Neonatal Med. 2011;24(7):886-90.
22. Jansson L, Holmberg L, Ekman R. Variation of serum ferritin in low birth weight infants with maternal ferritin, birth weight and gestational age. Acta Haematol. 1979;62(5-6):273-7.
23. Messer RD, Russo AM, McWhirter WR, Sprangemeyer D, Halliday JW. Serum ferritin in term and preterm infants. Aust Paediatr J. 1980;16(3):185-8.
24. Anabrees J. Early enteral prophylactic iron supplementation may be preferred in preterm very low birth weight infants. J Clin Neonatol. 2014;3(1):14-5.
25. Baker RD, Greer FR. Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics. 2010;126(5):1040-50.

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