DETERMINANTS OF NEONATAL IRON STORES AND COMPARISON OF APPROPRIATE FOR GESTATIONAL AGE (AGA) AND SMALL FOR GESTATIONAL AGE (SGA) IRON STORES

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ABSTRACT

BACKGROUND

Sufficient iron stores is of paramount importance in neonatal period. Controversy exists whether transfer of iron to foetus from the mother is determined by foetal requirements or by maternal iron status. Studies correlating maternal and neonatal iron stores revealed conflicting results.

The aim of the study is to assess the relationship between maternal and neonatal iron indices at birth and to study the impact of Small for Gestational Age (SGA) status on iron status on cord blood samples and at follow up at 4 weeks. This is a prospective study conducted in tertiary care hospital. Neonates are divided into groups based on Small for Gestational Age (SGA) or Appropriate for Gestational Age (AGA) status.

MATERIALS AND METHODS

The maternal venous samples were collected 1 hr. ± 15 min. prior to the delivery. Cord blood sample and venous samples at 6 weeks were collected from the newborn. Samples were estimated for Haemoglobin (Hb), serum ferritin, serum iron and Total Iron-Binding Capacity (TIBC).

RESULTS

Total of 172 mother and newborn pairs are enrolled in the study. Significant correlation was found between maternal Hb and neonatal ferritin (Pearson's correlation coefficient = 0.26, p=0.002). Positive significant correlation was found between maternal iron and neonatal iron (Pearson's correlation coefficient = 0.294, p=0.000). Follow up ferritin levels were significantly low in SGA group (Mean ± SD: 173.9 ± 145.8 in SGA vs. 244.3 ± 159.7 in AGA, p=0.040). There was trend towards significance of ferritin levels at birth among AGA and SGA babies (Mean ± SD: 130 ± 85 in SGA vs. 150 ± 77 in AGA, p=0.08).

CONCLUSION

Neonatal iron stores are affected in case of severe maternal iron deficiency indicated by ferritin levels less than <12 μg/L. Low levels of iron stores at 4 weeks in SGA neonates.

KEYWORDS

Small for Gestational Age, Serum Iron, Serum Ferritin, Total Iron-Binding Capacity, Serum Transferrin.

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BACKGROUND

Iron is the most common micronutrient deficiency in the developing countries like India. Adequate iron stores is critical for rapidly developing foetal and neonatal organ systems. It is a component of various enzymes and required for neurotransmitter synthesis and myelination of central nervous system during the foetal period and postnatal life. Perinatal iron deficiency lead to long lasting neurodevelopmental impairment and early onset of postnatal iron deficiency.[1,2] Conversely, presence of excess free iron has a risk of generating toxic-free radicals, especially in preterm, which have low levels of iron-binding proteins and immature antioxidant systems.[3,4] This highlights the immense need to emphasise on maintaining adequate iron stores in perinatal and neonatal period. Whether maternal dietary iron transfer to foetus is related to maternal iron status is strongly debated. Previous studies on relationship between maternal and neonatal iron status by using multiple parameters showed contrasting results.[5] Understanding relationship between maternal and neonatal iron indices help in formulating protocols to improve maternal and neonatal outcome.

This study was done to evaluate relationship between maternal and neonatal iron stores at birth. Secondary objective is to observe effect of gestational age on iron status in newborn at birth and at 4 weeks.

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MATERIALS AND METHODS

Prospective study conducted in a tertiary care hospital. Institution ethical committee approval and informed consent from parents was obtained. 172 maternal newborn pairs delivered in King George Hospital, Visakhapatnam, were enrolled in the study. It was conducted between May 2016 to May 2017. Babies with major congenital anomalies, sepsis, Rh isoimmunisation and twin deliveries were excluded. Mothers with antepartum haemorrhage, infection and history of blood transfusion in antenatal period were excluded.

Eligible mother infant pairs were followed from the time of enrolment to 28 ± 4 days. The information on baseline parameters and outcomes were recorded in a standard pro forma. The enrolled mother-infant pairs were stratified broadly based on gestational age. New Ballard scoring were taken for the assessment of gestational age.

The maternal blood samples were collected. Samples were collected 1 hour ± 15 minutes prior to the delivery. Cord blood and venous sample at 4 weeks were collected from the newborn. Measurement of Haemoglobin (Hb), serum ferritin, serum iron and total iron-binding capacity (TIBC) was estimated from the samples. The neonates were followed clinically up to 28 ± 4 days. The serum ferritin was estimated by fully automated bidirectionally interfaced chemiluminescent immunoassay. Serum iron was done by FerroZine method without deproteinization. Serum TIBC was done by spectrophotometric assay. Transferrin saturation % was derived from iron and TIBC values.

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 were analysed by Pearson's correlation coefficient.

RESULTS AND ANALYSIS

190 mother-infant pairs met the eligibility criteria during the study period. Of them, 15 were excluded as their samples were inadequate/haemolysed and could not be processed and 3 were excluded as they had abnormally high ferritin levels (>370 µg/L). 172 mother-infant pairs were enrolled in the study.

	Number of Subjects (n=172)
Gestation (wks.) Mean (SD)	37.3 ± 2.3
Male (%) Female (%)	54 46
Preterm (%) Term (%)	27.3 72.7
Maternal age (in years.) Mean (SD)	22.6 ± 2.6

Table 1. Baseline Characteristics of the Study Group

Males constituted 92 (54%) and females constituted 80 (46%). The mean gestational age of the neonates enrolled is 37.8 ± 1.3 weeks and the mean birth weight is 2680 ± 419 grams. Among the total study population, 125 (72.7%) are term and 47 (27.3%) are preterm. The mean maternal age of study population enrolled is 22.6 ± 2.6 years (Table 1).

	Neonatal Hb	Neonatal Iron	Neonatal TIBC	Neonatal Transferrin	Neonatal Ferritin
Mother Hb					
Pearson co	-0.01	-0.45	0.00	-0.39	0.26
'p' value	0.90	0.00	0.93	0.00	0.00
Mother Iron					
Pearson co	-0.01	0.29	0.01	0.39	0.03
'p' value	0.83	0.00	0.89	0.00	0.62
Mother TIBC					
Pearson co	0.31	0.34	0.11	0.32	-0.27
'p' value	0.00	0.00	0.13	0.00	0.00
Mother Transferrin					
Pearson co	-0.14	0.24	-0.12	0.31	0.15
'p' value	0.11	0.00	0.15	0.00	0.07
Mother Ferritin					
Pearson co	-0.04	-0.12	-0.08	-0.03	0.03
'p' value	0.58	0.10	0.25	0.64	0.64

Table 2. Comparison among Maternal and Neonatal Iron Indices

Analysis of Correlation between Maternal Iron Indices and Neonatal Iron Indices

Correlation was done between various maternal iron indices with neonatal iron indices on cord blood samples. Significant correlation was between maternal Hb and neonatal ferritin (Pearson's correlation coefficient=0.26, p=0.002) Figure 1.

Positive correlation was found between maternal iron and neonatal iron (Pearson's correlation coefficient=0.294, p=0.000) (Figure 2). No significant correlation between maternal ferritin and any of the neonatal iron indices was observed (Table 2).

Pearson co-Pearson correlation coefficient.

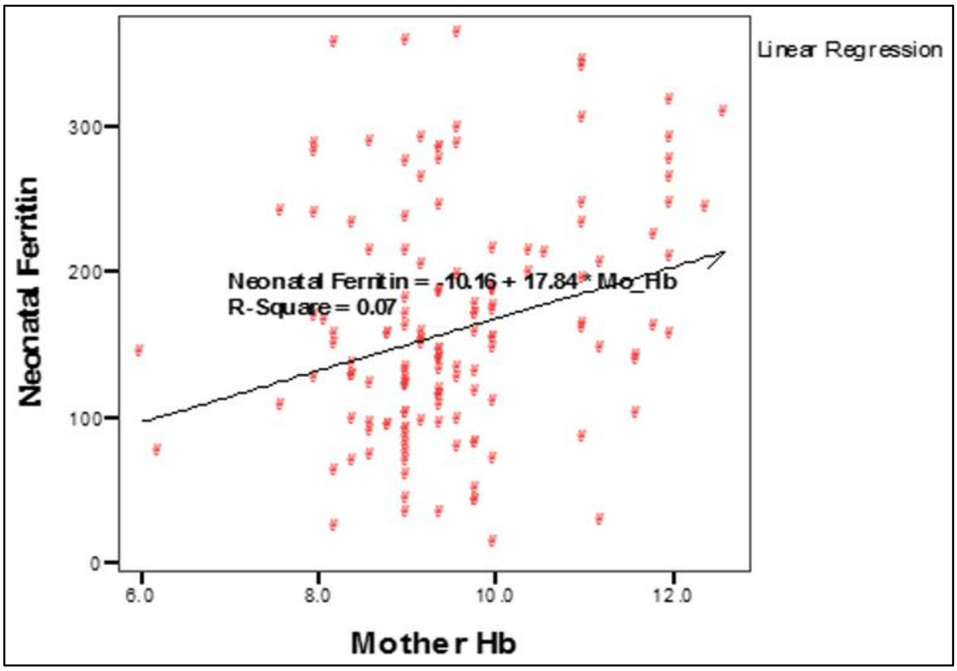

Figure 1

Pearson correlation coefficient=0.26, p=0.002.

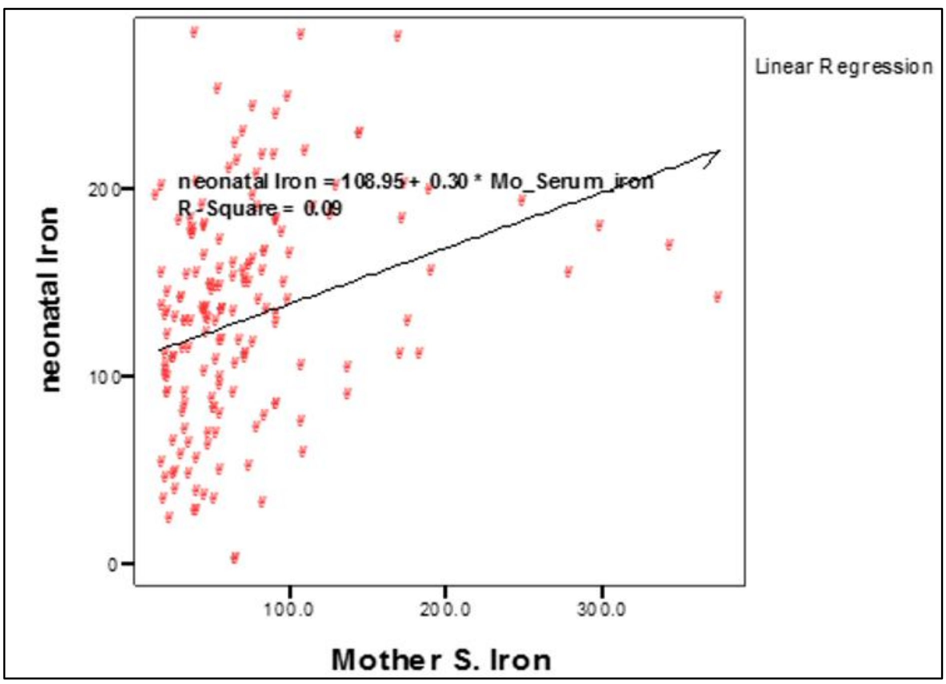

Figure 2

Pearson correlation coefficient=0.294.

Analysis of Correlation between Neonatal Iron Indices at Birth and Followup

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

Comparison of Neonatal Iron Stores between Term and Preterm Neonates

Mean neonatal ferritin levels in preterm and term newborn are 129 ± 81 and 159 ± 79, respectively. Neonatal ferritin levels were significantly low in preterm group as compared to term group (p=0.040) (Figure 3). Mean Hb levels in preterm and term newborn were 14.5 ± 2.1 and 15.0 ± 2.1, respectively. Neonatal Hb concentrations were significantly low in preterm group as compared to term group (p=0.028) Follow up samples at 4 weeks showed significantly lower serum iron concentrations in preterm when compared to term group (Mean ± SD: 35.5 ± 33.7 in preterm vs. 75.5 ± 54.7 in term, p=0.009).

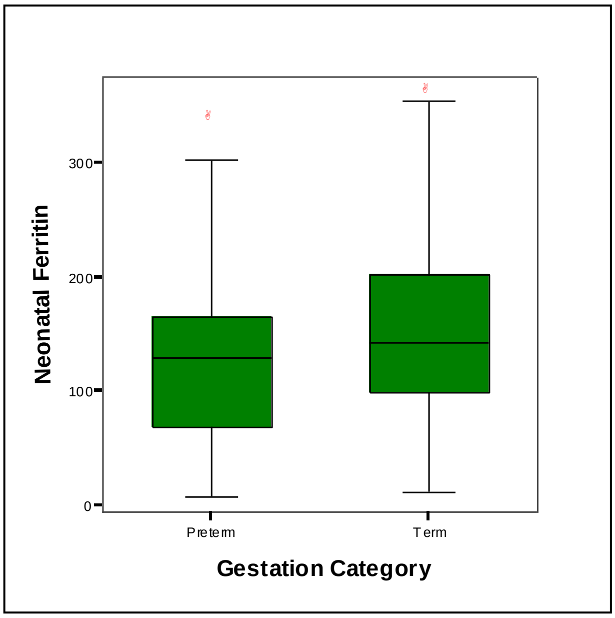

Figure 3. Box Whisker Plot Depicting the Neonatal Ferritin Concentrations in Preterm and Term Groups

Mean ± SD in preterms	-	128.9 ± 80.7
Mean ± SD in terms	-	156.9 ± 78.6
'p' value	-	0.04

	SGA (n=48)	AGA (n=124)	p value
Cord S. ferritin (µg/L)	130.1 ± 85	157.5 ± 77	0.08
Proportion of infants with ferritin ≤35 µg/L (%)	14	4	
Cord S. iron (µg/dL)	111.6 ± 67	124 ± 53	0.21
Cord TIBC (µg/dL)	246 ± 97	242.2 ± 69	0.77
Cord Hb (gm/dL)	14.5 ± 2	15.2 ± 2	0.39
Follow up ferritin (µg/L)	163.9 ± 145	239.3 ± 159	0.04
Follow up Hb (gm/dL)	11.3 ± 1	12 ± 1	0.41

Table 3. Comparison of Neonatal Iron Stores in SGA and AGA Neonates

The iron status at birth and follow up iron indices were compared between AGA and SGA babies. The correlations were analysed using Pearson's correlation coefficient (Table 3). There was trend towards significance of ferritin levels at birth among AGA and SGA babies (Mean ± SD: 130.1 ± 77.3 in SGA vs. 157.5 ± 85.4 in AGA, p=0.08). No other iron index was significantly different in SGA when compared with AGA group. But, follow up ferritin levels were significantly low in SGA group (Mean ± SD: 163.9 ± 145.8 in SGA vs. 235.3 ± 159.7 in AGA, p=0.040). Follow up transferrin saturation levels were less significantly in SGA neonates when compared with AGA neonates.

	Maternal Ferritin <12 µg/dL	Maternal Ferritin >12 µg/dL	'P' Value
Neonatal Hb (gm/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
Follow up Hb (gm/dL)	12.4 ± 1.4	12.0 ± 1.8	0.49
Follow up serum iron (µg/dL)	62.4 ± 51.5	72.3 ± 54.7	0.48
Follow up TIBC (µg/dL)	162.5 ± 64.8	177.1 ± 69	0.41
Follow up transferrin (%)	124.2 ± 84.6	122.2 ± 93.4	0.93
Follow up ferritin (µg/L)	173.4 ± 125.7	233.9 ± 162.3	0.17

Table 4. Comparison of Effect of Low Maternal Stores on Neonatal Indices

Comparison of iron indices of babies born to mothers with ferritin level <12 µg/L and >12 µg/L, significant low ferritin concentrations were observed in the neonates born to mothers with ferritin levels <12 µg/L (p=0.02) (Table 4).

DISCUSSION

Iron deficiency is common nutritional deficiency in pregnancy. It has significant influence on maternal and neonatal outcome.[6] Transfer of maternal iron to foetus occur via placenta against concentration gradient. It is uncertain whether the amount of iron transferred across the placenta is proportional to iron available in the mother or whether the foetus receives the iron preferentially as per its requirements. Many studies are done to find correlation between maternal iron status and neonatal status, but the results are conflicting.[7] Some studies reported that transfer of iron to foetus occur independent of maternal iron levels. In contrast, many later studies reported that maternal iron deficiency lead to low reserves of foetal iron stores.[8,9] Study by O'Brien et al concluded that transfer of dietary iron is regulated to maternal iron status.[5] Maternal iron status will determine how iron will be endowed to the foetus.

Physiological changes during pregnancy and neonatal life have impact on biochemical parameters used for assessing iron stores. Multiple parameters were used by several investigators to find correlation between maternal and neonatal iron stores. Various biochemical parameters used in the studies have low specificity resulting in conflicting reports.[8] Present study used multiple parameters to find correlation between maternal and neonatal iron indices. It's still unclear what the optimal parameter is for the assessment of iron status in the neonatal period. Serum ferritin is considered as deciding parameter as low ferritin levels can occur only in iron deficiency and the cut-off values for neonates recently established.[10]

In the current study population, there was significant positive correlation between maternal haemoglobin and neonatal ferritin concentrations at birth. There was significant correlation between maternal iron and neonatal iron concentrations at birth. A study by Singla et al showed that maternal haemoglobin had a linear correlation with haemoglobin and cord blood iron levels.[11] No correlation was observed between maternal ferritin 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.[12,13,14] The threshold of maternal ferritin concentration below which foetal iron accretion is affected was estimated as <12 µg/L.[15] In the present study, comparison of ferritin concentrations of babies born to mothers with ferritin level <12 µg/L and >12 µg/L, significant low ferritin concentrations were observed in the group with maternal ferritin levels <12 µg/L similar to that observed in the study done by Jaime-Perez et al.[15]

Transfer of iron to the foetus begins in the first trimester of pregnancy, but maximum transport occurs during last trimester of pregnancy. Consequently, iron stores in preterm will be less than the term counterparts. In this study, iron stores in preterm neonates were significantly less as compared to the term neonates on cord blood samples. Similar observations were made by Mukhopadhyay et al, Jansson et al and Messer et al.[16,17,18] Serum ferritin levels progressively increase with gestational age, with mean levels of 63 µg/L at 23 weeks to a mean value of 171 µg/L at 41 weeks.[10]

Optimal timing for administration of prophylactic enteral iron supplementation in preterm and very low birth weight infants is unclear.[19] The American Academy of Paediatric recommend 2 mg/kg per day of supplemental iron on milk feeding from 1 month of age and extending through 12 months of age.[20] In the present study, preterm neonates showed significant low haemoglobin levels compared to term neonates at 4 weeks. On analysis of samples at 4 weeks, neonates with low iron stores tend to have significantly lower stores at 4 weeks postnatal age. This observation may support early supplementation at 4 weeks of age particularly in preterm neonates.

CONCLUSION

Neonatal iron stores are affected in case of severe maternal iron deficiency indicated by ferritin levels less than <12 µg/L. Low levels of iron stores at 4 weeks in SGA neonates.

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