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IRON STATUS IN FULL TERM GROWTH RESTRICTED NEONATES

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ABSTRACT

Introduction: Iron transport across placenta occurs against concentration gradient and is energy dependent process. Growth restricted fetuses have increased iron demand due to accelerated erythropoiesis. This study was carried out tofind out iron status and RBC indices in term growth restricted neonates **Method:** Prospective analytical blinded study at a tertiary care hospital. 30 full term Asymmetrical Small for Gestation Age (ASGA) and 30 Full Term Appropriate for Gestation Age (AGA) infants were enrolled in the study. Cord blood was collected and analyzed for Serum Ferritin and RBC indices. Stored body iron (SBI) and Total body iron (TBI) were calculated. **Results:** Both the groups were comparable for maternal age, BMI, hemoglobin, iron supplementation & antenatal care. ASGA infants had significantly lower cord serum ferritin levels (Mean ferritin 283ng/ml[SD=157] *vs* 147ng/ml[SD=96.2], p<0.0001) and it showed linear correlation with birth weight (r=0.403, p=0.002) &Ponderal index (r=0.478, p<0.001). There was no significant difference in cord Hb& PCV between the two groups. RBC indices, MCV & MCH were higher in ASGA babies (Mean MCV 110fl [SD=5.91] vs. 114fl [SD=6.94]; p=0.011 and Mean MCH 35.5[SD=2.95] vs. 37[SD=1.67], p=0.022). Estimated SBI and TBI were significantly low in ASGA babies; SBI of 26.03mg (SD=18.13) vs. 66.81mg (SD=20.72), p<0.001 and TBI of 128mg [SD=23.37] vs 199.5mg [SD=37.72], p<0.001. **Conclusion:** Term ASGA neonates have significantly poor iron status. Microcytosis was not a feature of neonatal iron deficiency. This study supports rationale of early iron supplementation for term ASGA neonates. However further studies are required to determine exact timing and dosages of iron supplementation.

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INTRODUCTION

In pregnancies complicated by utero-placental insufficiency there is decreased nutrient and oxygen transport across the placenta. Chronic fetal hypoxemia leads to compensatory fetal erythropoiesis with increase fetal erythropoietin and increase in red cell mass.(1) Increased erythropoiesis would logically put increased demand for iron these fetuses. Normally, iron transport from the mother to the baby is an energy dependant process and it takes place against a concentration gradient. (2) Therefore fetal iron deficiency is extremely rare even in babies born to iron deficient mothers, unless the maternal iron deficiency is extremely severe.(2) There is however, limited knowledge as to how intra uterine growth restriction affects iron transport across placenta.

Knowledge about iron status in Neonate is important to decide timing of postnatal iron supplementation. In addition to it's predominant role in erythropoiesis, iron is important for normal cardiac and skeletal muscle functioning, intestinal motility and brain growth.(2) Neonates born with low iron stores are likely to be at higher risk for postnatal iron deficiency. Cord blood Ferritin level is a reflector of iron status in the neonate. The present study was carried out to find iron status of growth restricted babies since there is not much data in this subset of babies.

MATERIALS AND METHODS

Aims and objective

1. To determine umbilical cord serum ferritin levels and RBC indices of Full-term growth restricted neonates (ASGA) and compare them with term appropriate for gestation (AGA) neonates.
2. To determine stored body iron and total body iron in the subjects and compare between ASGA's and AGA's.

Study design

This study was designed as prospective analytical cohort study

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Subjects and method

Inclusion criteria: Consecutively born 30 Full term Asymmetrically small for gestation age (ASGA) growth restricted neonates and 30 full term appropriate for gestation (AGA) neonates were selected after obtaining parental consent.

Exclusion criteria

- Infants whose mother had hemoglobin < 10 gm %
- Mothers baby blood group incompatibilities (ABO, Rh)
- Mothers with Ante partum hemorrhage.
- Infants born to mothers with fever, leukocytosis or bacterimia.
- Congenital anomalies
- Multiple gestations
- Babies presenting with Bleeding / shock / anemia at birth
- Symmetrical small for gestational age

Gestational age was determined using maternal dates (LMP) and serial antenatal USG and was confirmed after birth with New Ballard Score. Babies were enrolled under the two groups as follows:

Group 1: Babies were termed as asymmetrically small for gestation (ASGA), based on Ponderal index calculated at birth. (1)

Group 2: Full term infants who were AGA (appropriate for gestational age).

Umbilical cord blood sample was obtained for following tests.

1. Cord Hemogram including RBC indices
2. Cord serum Ferritin levels.

The ferritin quantitative test is based on a solid phase enzyme-linked immunosorbent assay (ELISA). The assay system utilizes one rabbit anti-ferritin antibody for solid phase (micro titer wells) immobilization and a mouse monoclonal anti-ferritin antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution.

Quantitative Data was analysed using Student 't' test and qualitative data was analysed using Correlation coefficient of Pearson. P value < 0.05 was considered significant.

It has been shown that the Sr.Ferritin levels reflect the storage form of iron with each 1 mcg/L, equal to 8 to 10 mg of stored iron. Exact iron stores can be calculated from values of Sr.Ferritin and babies body weight.(3) We calculated TBI as the sum of two components, Hb iron (HbI) and body storage iron (BSI), according to the method previously used in infants,(4)

HbI was calculated as
HbI = 3.47 ×BV×Hemoglobin×Bodyweight;
where HbI is expressed in mg, 3.47 is the iron content (mg)/g Hb, BV is blood volume in L/kg body which we assumed to be 0.080 at birth , Hb is Hemoglobin concentration at birth (g/L) and body weight is birth weight (kg). (4)

BSI was estimated from plasma ferritin concentration and the regression equation determined by Saarinen and Siimes (5)
BSI = (log10 plasma ferritin - 1.345) / 0.0439× body weight;
where BSI is expressed in mg, plasma ferritin in mcg/L, and body weight is birthweight (kg).

Study approval was obtained from institutional ethics committee.

RESULTS

Mothers in both the groups were comparable for age, BMI, Hemoglobin, iron supplementation & antenatal care received.

Anthropometric indices showed significantly lighter, shorter babies with lower head circumference in ASGA group. (Table 1).

Table 1 Anthropometric measures of both groups

	Mean (SD)		p value
	AGA	aSGA	
WEIGHT (grams)	2913 (341)	2227 (231)	0.0001
PONDERAL INDEX (gm/cm3)	2.29 (0.2)	1.88 (0.1)	0.0001
LENGTH (cm)	50.1 (1.66)	49.1 (1.87)	0.035
HC (cm)	33.6 (1.19)	32.6 (1.06)	0.001

Table 2 cord blood Investigations

	Mean (SD)		p value
	AGA	aSGA	
PCV	49.5 (7.62)	49.8 (6.9)	0.86
MCV	110 (5.91)	114 (6.94)	0.011
MCH	35.5 (2.95)	37 (1.67)	0.022
MCHC	32.5 (2.1)	32.4 (1.55)	0.78
Ferritin	283 (157)	147 (96.2)	<0.001
Low Ferritin (<76 mcg/L)	1 (3%)	15 (50%)	<0.001

Table 3 Comparision of estimated stored body iron (BSI) & total body iron (TBI) in newborn

	Mean (SD)		p value
	AGA	ASGA	
BSI (mg)	66.81(20.72)	26.03 (18.13)	< 0.001
TBI (mg)	199.5 (37.72)	128 (23.37)	< 0.001

BSI = stored body iron, TB I= total body iron, SD = standard deviation

Statistically significant positive correlation was observed with Low Cord Ferritin and

- Lower birth weights (p=0.002, r=0.403)
- Lower values of Ponderal Indices (p<0.001, r=0.478)
- Corelation coefficient of cord ferritin with weight is 0.403 (p0.002) &pondral index is 0.478 (p<0.001).

DISCUSSION

Iron, the fourth most abundant element, is nutritious, noxious, nonsoluble, and yet necessary for the most basic functions of mammalian life. Neonates during third trimester have approximately70 to 75 mg/kg body iron (6) most of which is complexed in hemoglobin. The iron is distributed between erythrocyte hemoglobin (50 to 55 mg/kg), liver, spleen, bone marrow, and kidney storage (10 mg/kg) and non storage iron such as myoglobin, cytochrome c, and catalase (7 mg/ kg). (5;6)It has been shown that the Sr.Ferritin levels reflect storage form of iron with each 1 mcg/L, equal to 8 to 10 mg of stored iron.(2) Low serum ferritin concentrations are seen only in iron deficiency; however elevated Serum ferritin can be seen in acute inflammation, or infection where it behaves as an acute phase reactant. It may also be elevated in neoplasia or hemochromatosis.(3;7) Serum ferritin concentration has been used as a standard measurement of iron stores in infants, children and adults(7).

It has been long held, but unfounded, belief that neonatal iron deficiency occurs only secondary to severe maternal iron deficiency. Furthermore, it is compounded by the fact that maternal deficiency is highly unlikely event because pregnant women receive prenatal iron supplementation.(2) The mechanism by which fetal iron demand and placental iron status regulate maternofetal iron transport has only recently been elucidated. Human placental iron transport is mediated by the transferring receptor located on the basal (fetal) and apical (maternal) membranes of the syncytiotrophoblast. This receptor-mediated system pumps iron against an ever increasing gradient from mother to the fetus. Mammals with hemochorial placentas use this system, in contrast to other mammalian species that accrete iron by placental erythrophagocytosis.(8)

In the present study, babies ASGA babies had significantly lower Cord Ferritin levels as compared to AGA babies (p< 0.0001) Lower birth weights &Ponderal Indices revealed direct correlation with lower Cord Ferritin level. These findings support the hypothesis that reduced iron stores and frank iron deficiency does occur in fetuses and newborns born to iron - sufficient mothers due to impaired placental function secondary to placental vascular disease or to increased fetal iron demand that exceeds the capacity of placental iron transport.(9;10). Proposed algorithm of iron deficiency in term growth restricted neonates is depicted in fig1

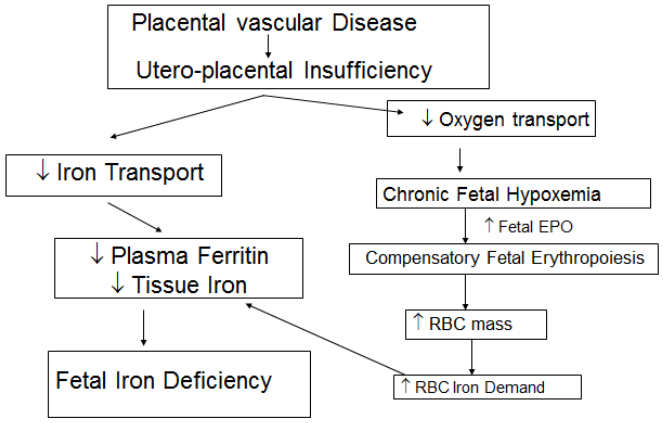

Fig 1 Flowchart showing proposed mechanism of iron deficiency in term growth restricted neonates

The fetus accumulates iron at a rate of 1.35 mg/kg of fetal weight in the third trimester, maintaining an average iron content of 70 to 75 mg/ kg of body weight during the last trimester (7) Storage iron and total body iron both were statistically low in the ASGA group, suggesting that babies with growth restriction are total body iron deficient.

High MCV value in ASGA may be due to selective stimulation of HbF containing cells due to chronic hypoxic stimulus. The low incidence of polycythemia in infants in the setting of underlying uteroplacental vascular insufficiency would suggest that the growth retarded infants are total body iron deficient (1;11). Since cord ferritin level indicates fetal iron stores exclusively, estimation of this level can help in deciding timing of iron supplementation in ASGA babies.

In a previous study, Chockalingam UM, *et al* (1;10;11) showed that the babies born to mothers with utero-placental insufficiency and babies born to diabetic mothers have significantly less iron stores. Serum ferritin level is significantly low in these babies. These babies are physiologically also iron deficient as indicated by the higher serum transferrin levels.

Study carried out by Karaduman D *et al* (1;10-12), showed significantly lower levels of serum iron and total body iron stores in ASGA babies. Serum ferritin levels in the SGA and AGA groups were 58.36 +/- 20.1 ng/ml and 90.46 +/- 30.5 ng/ml, respectively. Ferritin levels were found lower in the SGA group ($p < 0.001$).

In a study from North India, Mukhopadhyay, K *et al* showed Cord serum ferritin levels were low in SGA group as compared to AGA [median (IQR): 68 (30,136) vs. 141 (63,259), $p = 0.007$]. The proportion of infants with 'low' cord ferritin (< 40 mug/l) were more in SGA [$p = 0.05$]. (1;10-13)However, the serum ferritin levels at 4 weeks were similar in both the groups ($p = 0.16$).

Chronic fetal hypoxia increases fetal iron requirements for secondary erythropoiesis seen in pregnancies complicated by diabetes and maternal smoking. In these conditions the iron supply to fetal organs such as liver, heart and brain are often reduced (1;6;9) Iron deficiency during the fetal or postnatal periods can alter brain structure, neurochemistry and cognitive functioning, and lead to long-term cognitive and motor impairment that cannot be corrected by iron supplementation(14-16) Newborn infants with the lowest quartile of cord ferritin concentrations (<76 µg/l) have impaired mental and psychomotor function at school age (7) Iron-deficient infants of diabetic mothers (IDM) with low neonatal ferritin concentrations (<35 µg/l) have impaired auditory recognition memory processing at birth compared with iron-sufficient IDM (ferritin >35 µg/l) (17). Pre-term infants with low serum ferritin concentrations (<75 µg/l) at 37 weeks post-conception had abnormal neurologic reflexes (18)

In our study we did not do follow-up iron studies. It would be preferable to do iron studies in these babies around 6 to 8 weeks, when erythropoiesis is expected to restart. Also it is preferable to check transferrin receptor saturation estimation as it is a better markers for iron status.

Term IDM, IUGR and infants of mothers who smoked during pregnancy and were born with low neonatal iron stores have significantly lower ferritin concentrations between 6 and 9 months of age. (19; 20), and thus enter their second postnatal year with a higher risk of becoming iron deficient (19) . The AAP currently recommends screening term infants for iron deficiency anemia between 9 and 12 months of age and high-risk infants including pre-term and low-birth-weight infants at an unspecified time point earlier than 9 months. There are no separate recommendations for growth restricted babies for screening or for early iron therapy (7). High-risk term infants could be identified more specifically by using the cord ferritin cutoffs from the current study and they could be potentially screened earlier.

Recommendation

Full Term ASGA need routine early iron supplementation. Further studies are required to decide exact timing and dosages of Iron supplementation in ASGA babies as they have low iron stores and rapid postnatal catch-up growth.

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