

Original Research Article

Effect of maternal hemoglobin and iron status on fetal hemoglobin, iron status, growth and maturity

Mohammad Moaaz Kidwai*, V. R. Anand, Deepika Gulathi

Department of Pediatrics, Mata Chanan Devi Hospital, New Delhi, India

Received: 26 October 2021

Revised: 24 November 2021

Accepted: 25 November 2021

*Correspondence:

Dr. Mohammad Moaaz Kidwai,
E-mail: moaaz06@gmail.com

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ABSTRACT

Background: Iron deficiency anemia during pregnancy is a major health issue in India. However, the status of iron stores in infants born to iron depleted mothers remains controversial and inadequately investigated. The present study is therefore an attempt to understand whether maternal anemia and iron stores have any significant effect on iron status and growth of fetus.

Methods: This is a prospective, cross-sectional, hospital based study conducted at Mata Chanan Devi Hosital, Janakpuri, New Delhi. Hemoglobin and iron profile of 100 newborns and their mothers were taken. Mothers were divided into anemic and non anemic group to see the effect of maternal anemia on fetus.

Results: A total of 100 newborns and their mothers were analysed. Cord hemoglobin and iron profile was significantly reduced in anemic compared to non anemic group. Birth weight of newborn was significantly reduced only in moderately anemic group as compared to non anemic group but there was no difference seen in length and head circumference.

Conclusions: Maternal serum ferritin levels should be measured for the diagnosis of occult iron deficiency in the fetus so that timely measures can be taken to prevent iron deficiency anemia in the newborn.

Keywords: Fetal hemoglobin, Fetal anemia, Anemia of pregnancy, Cord ferretin, Low birth weight

INTRODUCTION

Fetal growth restriction is an important predictor of its immediate and future health. One of the micronutrients needed for optimal growth of the fetus and the focus of this study is iron. Increased dietary iron requirements during pregnancy are difficult to achieve through diet alone and low iron stores increases the likelihood of preterm birth and low birth weight (LBW).^{1,2} Thus, the prevalence of iron deficiency (with and without anemia) is reported to increase during each trimester.^{3,4} During pregnancy, the maternal body requirement for iron increases to approximately 1000 mg, on average. Maternal iron deficiency anemia continues to be a major preventable cause of unfavourable perinatal outcome in our country. And it is associated with pregnancy wastage,

intra uterine fetal growth retardation and/or an untimely onset of labour.⁵ National family health survey (NFHS-3) of India reveals the prevalence of anemia to be 70% in pregnant women.⁶ Despite the high rate of Iron deficiency anemia (IDA) in pregnancy, it is rare to see newborns suffering from clinically significant anemia. This is because fetus extracts iron from the mother even when her iron stores are low. Yet they are the same healthy non anemic babies who suffer from IDA often severe enough to cause intellectual impairment. This is because neonates of anemic mothers although not anemic, lack iron stores which is needed for normal erythropoiesis after birth. Several studies have documented that the hemoglobin and iron profile at birth bear no relationship with corresponding parameters of iron status in mother.⁷ However, the status of iron stores in infants born to iron

depleted mothers remains controversial and inadequately investigated.⁸ Moreover, in studies from the west, the sample size has been generally small and moderate to severe degrees of maternal anemia, such as are encountered in India, were not seen and therefore not included those studies.⁷ The present study is therefore an attempt to understand whether maternal anemia and iron stores have any significant effect on iron status of fetus and on fetal outcome in terms of growth (birth weight, length and head circumference) and maturity (gestation age).

METHODS

Study design, location, population and sample size

Current study is a prospective, cross-sectional, hospital based study, conducted over a period of one year (January 2017 to February 2018) at Mata Chanan Devi Hospital, C1 Janakpuri, New Delhi. The sample size was of 100 newborns and their respective mothers delivered at Mata Chanan Devi hospital.

Inclusion criteria

Inclusion criteria for current study were; mothers with term pregnancy (37- 42 weeks gestation), singleton deliveries and newborns born to the above selected mothers with term pregnancy.

Exclusion criteria

Exclusion criteria for current study were; mothers with history of any ongoing chronic illness, medication, illicit drug and obstetric complications known to affect birth weight and/or gestation, extremely low birth weight newborns (birth weight<1500 gram) and any perinatal risk factor leading to stress induced alteration of serum ferritin levels and babies with any major congenital anomaly or stigmata of congenital infection.

Procedure

The purpose and design of the study was explained to the patients or the consenting family members. The parents or consenting family members were informed that they can ask to withdraw from the study at any time without having reasons for the same.

The confidentiality of information obtained was maintained and revealed only to doctor/auditor involved in study and to regulatory authorities. History and examination: detailed information was obtained from the mothers regarding previous obstetric history and presence of any antenatal risk factors in pregnancy. The gestation was confirmed postnatally by classifying the newborn by new ballard scoring system. Anthropometric evaluation: birth weight of less than 2.5 kg was taken as LBW and less than 1.5kg was taken as very low birth weight (VLBW). Birth weight and length measurements were

made at the time of birth and head circumference was recorded after 24 hours of birth. Investigations: maternal blood sample was taken at the time of first stage of labor for hemoglobin (Hb) and iron profile which included serum ferritin, percent transferrin saturation (TS), serum iron, serum total iron binding capacity (TIBC).

Cord blood sample for the same was taken just after the second stage of labor from the placental end of the cord without milking it. The mothers were divided into two groups; anemic and non anemic, for the purpose of statistical evaluation. Also, anemic mothers were divided into mild, moderate and severe anemia according to hemoglobin level. Mothers with hemoglobin more than or equal to 11 g/dl were classified as group A-no anemia and hemoglobin <11 g/dl as group B-anemia.⁹

Statistical analysis

Statistical analysis was performed using SPSS for windows, version 17. The normality was tested by Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for non-normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test between anemic and non-anemic groups. All data was expressed as mean±SD. The correlations among maternal hemoglobin iron status, cord hemoglobin, iron status, fetal growth and maturity was analysed by Pearson's correlation analysis. Multiple regression analysis was carried out to determine any significant relationship between maternal anemia and neonatal anemia. The "t" test was applied to compare the two groups-anemic and non anemic. A probability value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

In this study a total of 100 newborns were analysed. Of them 61 were delivered by caesarean section (LSCS) and 39 by normal vaginal delivery (NVD). A total of 16 preterm babies were included in this study. 59 of the newborns were male and 41 were female as shown in (Table 1). A total of 86 babies were normal weight, one was large birth weight and 13 were LBW. Only one newborn had head circumference less than 31 cm with frequency being 1% and two newborns had length less than 44 cm with frequency being 2%.

Table 1: Demography of newborns.

Parameters	N	%
Male	59	59
Female	41	41
Born by LSCS	61	61
Born by NVD	39	39
Term delivery	84	84
Preterm delivery	16	16

Hematological parameters of mother

Among the maternal hematological parameters the maternal serum ferritin was the least affected one. Rest others like hemoglobin, serum iron, TIBC and transferrin saturation were largely affected as seen in (Table 2).

Table 2: Maternal hematological parameters.

Mother's parameters	N	%
Hb%	Abnormal <11 g%	83
	Normal ≥11 g%	17
S. Ferritin	Abnormal <12 µg/l	9
	Normal	91
S. Iron	Abnormal <67 µg/dl	80
	Normal	20
TIBC	Abnormal >350 µg/dl	75
	Normal	25
TS	Abnormal <15%	67
	Normal	33

Incidence of anemia in pregnancy in this study

The total incidence of anemia in third trimester of pregnancy in our study which was 46% is shown in (Table 3). Maximum patients were of the mild anemia group. Strikingly, there was no patient of the severe anemia.

Table 3: Frequency of anemia in pregnant women.

Category	N	%	Mean Hb
No anemia Hb >10.9 g/dl	54	54.0	11.64
Mild anemia 10-10.9 g/dl	25	25.0	10.55
Moderate anemia 9-7 g/dl	21	21.0	9.03

Cord hematological parameters

A total of 28 babies had cord haemoglobin less than 15 g%. Out of these 28 all had cord iron, TIBC or Transferrin saturation in the abnormal range as shown in the table, thus there were a total of 28 neonates with iron deficiency anemia as shown in (Table 4). Also, we found that none of the neonates had cord ferritin less than 20 µg/l (cut off value for calling iron deficiency anemia), this can be explained by the fact the mothers included in our study had received iron and folic acid supplementation, had regular follow up and there were no mothers with severe anemia in our study.

Hematological parameters in different grading of anemia

Pregnant women with mild and moderate anemia had lower iron stores as compared to the non anemic group and which was statically significant with p value < 0.001. The difference between the mild and moderate anemia group was also found to be statically significant with p<0.001 as shown in (Table 5).

Table 4: Cord hematological parameters.

Serum cord parameters	N	%
Hb%	Abnormal <15g%	28
	Normal 15-24g%	72
S. Ferritin	Abnormal <20µg/l	0
	Normal 25-200µg/l	100
S. Iron	Abnormal <150µg/dl	60
	Normal 150-250µg/dl	40
TIBC	Abnormal >400	31
	Normal 100-400	69
TS	Abnormal <20%	15
	Normal 20-45%	85

Effect of maternal anemia on cord hematological parameters

There is a statically significant reduction in cord haemoglobin and cord iron status in anemic group as compared to non anemic group. This reduction was more in moderately anemic group (Table 6).

Effect of maternal anemia on cord heoglobin

As shown in (Table 6) it was seen that there was a fall in cord hemoglobin of about 2 g/dl from the non anemic to the moderately anemic group. And also, the percentage of low cord hemoglobin is more in the anemic group of pregnant women (30.1%) as compared to the non anemic group (17.6%). But the cord hemoglobin at birth was not found to be significantly low in the anemic group when compared to the non anemic group.

Effect of maternal anemia on cord iron profile

Significant difference was found in all of the cord iron profile parameters except for TIBC between the anemic and non anemic group (Table 8).

Effect of various gradings of maternal anemia on anthropometry

It was seen that in mild anemia the difference of birth weight was not significant as compared to non anemic mothers, but in moderately anemic mothers the difference

was significant as compared to non anemic mothers ($p=0.002$). Also, there was a gradual decline in the neonatal anthropometry with the increase in severity of anemia. This effect was more seen in birth weight and length, the head circumference was the least affected. But this reduction was not significant.

Table 5: Maternal hematological parameters in various grades of anemia in pregnant women.

Parameters	Non anemic	Mild anemia	Moderate anemia	P value
Hb%	11.64±0.61	10.55±0.29	9.03±0.69	<0.001
S. Ferritin	56.27±124.84	28.57±10.19	17.14±6.30	<0.001
S. Iron	60.49±22.41	43.88±17.61	29.48±6.14	<0.001
TIBC	388.78±78.98	417.68±94.96	480.24±107.60	<0.001
TS	16.17±6.37	11.20±5.18	6.33±1.53	<0.001

Table 6: Cord hematological parameters in various grades of maternal anemia.

Mean value	Non anemic	Mild anemia	Moderate anemia	P value	Non anemic vs. mild anemia	Non anemic vs. moderate anemia	Mild anemia vs. moderate anemia
Hb%	16.98±2.01	16.88±1.91	14.22±1.71	<0.001	0.975	<0.001	<0.001
Cord ferritin	91.23±30.39	84.91±29.00	51.95±32.26	<0.001	0.668	<0.001	0.001
Cord iron	154.72±47.26	149.63±39.72	91.24±38.05	<0.001	0.880	<0.001	<0.001
Cord TIBC	348.31±74.12	350.52±92.84	446.90±101.45	<0.001	0.924	<0.001	<0.001
Cord %TS	46.32±17.02	46.24±14.91	24.45±17.18	<0.001	1.000	<0.001	<0.001

Table 7: Correlation between maternal serum and cord haemoglobin.

Mother's Hb	Total	Cord Hb				P value
		Abnormal <15 g/dl		Normal 15-24 g/dl		
		N	%	N	%	
Abnormal <11 g/dl	83	25	30.1	58	69.9	0.383
Normal ≥11 g/dl	17	3	17.6	14	82.4	
Total	100	28	28	72	72	

Effect of maternal anemia on iron transfer to newborn

Ratio of maternal iron: cord iron in non anemic mothers was 1:2.56. Ratio of maternal iron: cord iron in moderately anemic mothers was 1:3.1. As shown in (Figure 1) we found that there was a higher uptake of iron by neonates of moderately anemic mothers as compared to non anemic mothers. These anemic mothers had lower serum iron levels when compared to non anemic mothers but their neonates had comparatively higher serum iron values.

DISCUSSION

All the patients in this study were booked cases for antenatal care and had received iron and folate supplementation except for 9 patients who were not

registered in our hospital for antenatal check-up and presented at the time of delivery. Out of these 9 mothers 6 had anemia at the time of admission for delivery of which 4 had mild anemia and two had moderate anemia. This highlights the importance of good Antenatal Check-up and iron supplementation in preventing anemia in pregnancy and its associated morbidity.

Table 8: Cord iron profile in anemic and non anemic group.

Parameters	Non anemic	Anemic	P value
Cord ferritin	91.23±30.39	69.86±34.45	0.001
Cord %TS	46.32±17.02	36.29±19.24	0.007
Cord TIBC	348.31±74.12	389.09±109.74	0.030
Cord iron	154.72±47.26	122.97±48.47	0.001

Incidence of anemia in mothers

In our study the incidence of anemia was found to be 46% out of which 25% had mild anemia and 21% had moderate anemia as shown in table 3. There were no cases of severe anemia. The prevalence of anemia in NFHS-3 was 53% and of severe anemia was 5%.¹⁰ This difference can be accounted for by the fact that our study was done in a private tertiary level institute where regular antenatal follow up was done.

Table 9: Effect of various grading of maternal anemia on anthropometry.

Parameters	Non anemic (N=54)	Mild anemia (N=25)	Moderate anemia (N=21)	P value
Birth weight	3.03±0.39	2.92±0.44	2.81±0.47	0.120
No of LBW	2 (3.7%)	4 (16%)	7 (33.3%)	0.002
HC	33.64±0.91	33.64±1.30	33.67±0.93	0.994
Lt	48.18±1.53	47.98±1.93	47.40±0.82	0.151

Correlation between maternal anemia and fetal iron stores and anemia

The reduction in cord hemoglobin was statically significant when we compared the non anemic group with the moderately anemic group with a $p < 0.001$. But when we compared the non anemic group with the mildly anemic group then the hemoglobin was reduced but was not statically significant. This may be due to the high number of mildly anemic mothers as compared to moderately anemic mothers and also the absence of severely anemic mothers from this study. The cord hematological parameters were significantly reduced and cord hemoglobin reduced but not significantly in the anemic group as compared to the non anemic group, and cord hemoglobin was significantly reduced only if the mother was moderately anemic. This can be explained by the fact that there were no severely anemic mothers in our study. In a study done by Jieshao et al it was shown that cord-blood serum ferritin was lower in neonates whose mothers had a low serum ferritin.¹¹ Also, in a study by Terefe et al the median hemoglobin level in newborn were significantly lower if mother had iron deficiency anemia as compared to non anemic mothers.¹² Thus, maternal anemia had a significant negative effect on fetal hematological parameters, especially if maternal anemia was moderate to severe and remained uncorrected till labour.

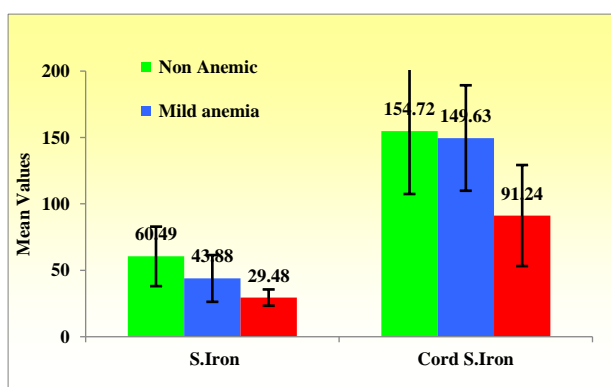


Figure 1: Ratio of serum iron to cord iron in various grades of maternal anemia.

Maternal serum ferritin levels as a predictor of iron deficiency in newborns

In our study it was shown that cord ferritin was significantly reduced in anemic mothers (with reduced

maternal ferretin levels) as compared to non anemic mothers. In a study done by El-Farrash et al it was seen that hemoglobin, RBC indices, and iron profile showed significant differences in the neonates born to anemic mothers compared to controls, particularly in moderate to severe anemia and linear correlations with maternal hemoglobin, iron, and ferritin levels were found ($p < 0.01$).¹³ And Terefe et al showed that newborns ferritin and hemoglobin levels showed significant correlation with maternal hemoglobin ($p = 0.018$; $p = 0.039$) and ferritin ($p = 0.001$; $p = 0.008$) levels.¹² Thus, maternal serum ferritin can be used as predictor of fetal iron deficiency. And serum ferritin levels, which are affected earlier than hemoglobin levels, should be measured for the diagnosis of occult iron deficiency in the fetus so that timely measures can be taken to prevent iron deficiency anemia.

Iron transfer to the fetus

We calculated the ratio of maternal serum iron and cord iron in both the anemic and non anemic groups as an indicator of iron transfer from the mother to the baby. The ratio of maternal serum iron and cord iron was 1:2.5 in non anemic group and 1: 3.1 in anemic group as shown in (Figure 1). It was seen that there was a higher rate of transfer of iron from mother to fetus when the mother was anemic as compared to non anemic mothers. In our study we also found that cord ferritin level at term is considerably higher than maternal serum ferritin levels regardless of presence of anemia in mothers. The serum ferritin was 56.27 ± 24.84 and cord ferritin 91.23 ± 30.39 in non anemic group with a ratio of 1:1.6 (cord ferritin: maternal serum ferritin). This ratio increased to 1:3.1 in moderately anemic group. This finding also suggests that fetus actively extracts iron from its mother.

In a study done by Ajayi et al it was seen that the mean cord ferritin concentration of 135.9 mcg/l ($77.6\text{--}238.2 \text{ mcg/l}$) was 3.6 times the maternal level of 38.1 mcg/l ($17.3\text{--}83.8 \text{ mcg/l}$) similar to what is seen in our study.¹⁴ It was also shown by Bhargava et al that there appears to be a compensatory mechanism to protect infants born to severely anemic mothers.¹⁵ These findings are similar to that of Agarwal et al which showed that anemic mothers with reasonably maintained ferritin and transferrin saturation levels provide sufficient iron for maintenance of cord hemoglobin, although foetal iron stores are likely to be depleted.¹⁶ Our study showed that there is an increased transfer of iron from mother to fetus in anemic

group as compared to the non anemic group which is in concordance with other studies. But the compensatory mechanism to protect the baby seen in severely anemic mothers, where the cord haemoglobin and ferritin levels were higher as compared to mildly anemic mothers could not be seen in our study due to the absence of severely anemic mothers in our study.

Effect of maternal iron status on fetal maturity

We studied the mothers who delivered preterm and noted their hemoglobin levels to see how many were anemic. We found 16 mothers who delivered preterm (<37 weeks of gestation) with no obvious risk factors for a preterm delivery as shown in (Table 8). Out of the 16 mothers 12 had anemia. A study done by El-Guindi et al on severely anemic mothers showed a significant association between anemia and the frequency of preterm deliveries.¹⁷ Also, in a study by Sukrat et al it was suggested that maternal hemoglobin below 11 g% increases the risk of preterm birth.¹⁸ Kumar et al 2013 also showed that there was 11.5% increase in preterm deliveries in mothers who were anemic in their third trimester.¹⁹ Thus, it is seen that maternal anemia increases the risk of preterm deliveries.

Effect of maternal anemia on fetal growth

It was seen that there were a total of 13 babies with low birth weight, with the lowest value of 1.93 kg and mean value of 2.31 kg. There was no statistically significant difference in birth weight between anemic and non anemic group. But on comparing the non anemic group with the moderately anemic mothers statistically significant reduction as seen ($p=0.002$). The mean head circumference in non anemic group was 33.64 ± 0.91 cm and 33.65 ± 1.11 cm in the anemic group, showing no reduction in head circumference with a p value of 0.948 as seen in (Table 9). There was a reduction in length as anemia severity increased but this reduction was not significant. Singla et al did a study in which it was suggested that there exists a negative effect of maternal anemia during pregnancy on the different anthropometric parameters at birth.²⁰ In a study by Lee et al maternal hemoglobin level had significant positive correlations with gestational age ($r=0.258$), birth weight ($r=0.256$), birth length ($r=0.275$).²¹ In a study done by Teletar et al it was seen that the anthropometric measurements (height, weight, head circumference) of newborns of anemic and non-anemic mother groups showed a statistically significant difference ($p=0.036$, $p=0.044$, and $p=0.013$).²² Also, in a study done by Lelic et al it was seen that there was significant reduction in length of newborns of anemic mothers.²³ But in our study effect of maternal anemia on length was not significant due to absence of severely anemic mothers.

Correlation between maternal anemia and fetal growth

We found a positive correlation of birth weight and length with maternal hemoglobin and hematological

parameters, but this correlation was not found to be statically significant as shown in (Table 9). Head circumference was not significantly correlated with maternal hematological parameters as seen in (Table 9). A recent review done by Batool et al showed that 25 observational studies revealed anemia during pregnancy increased the risk for LBW compared to non-anemic women.²⁴ Thus, it is seen that there is a significant correlation between maternal anemia and neonatal anthropometry. But in our study only birth weight was significantly correlated, and length and head circumference were not, may be due to the fact that there were no severely anemic mothers in our study.

Limitations

Limitation of current study was that the effect of severe anemia on the fetus could not be studied due to absence of mothers with severe anemia in this study.

CONCLUSION

Thus, this study highlights the need for prophylactic iron therapy in pregnant women especially in Indian scenario where anemia is quite prevalent in low socio economic group due to lack of resources, as well as in the urban educated population due to lack of awareness. There is a need to closely monitor the children born to anemic mothers so as to diagnose and treat iron deficiency, not only anemia. These mothers should also be prescribed iron supplements after delivery so that we can effectively prevent iron deficiency anemia in successive pregnancies. Also, maternal serum ferritin levels, which are affected earlier than hemoglobin levels, should be measured for the diagnosis of occult iron deficiency in the fetus so that timely measures can be taken to prevent iron deficiency anemia in the newborn.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kidwai MM, Anand VR, Gulathi D. Effect of maternal hemoglobin and iron status on fetal hemoglobin, iron status, growth and maturity. *Int J Contemp Pediatr* 2022;9:62-8.