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Original Article

Does Maternal Hemoglobin Consistently Associate with Iron Status at Birth? Evidence from a Cross-sectional Study in Indonesia

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ABSTRACT

Background: Maternal iron status is a vital determinant of feto-maternal iron transfer to ensure the adequacy of neonatal iron. Hemoglobin measurement is often used in pregnancy as an iron status parameter. However, evidence on the association between maternal hemoglobin and newborn iron status is still inconclusive. This study aims to assess the association between maternal hemoglobin and neonatal iron status.

Methods: We conducted a cross-sectional study involving 84 neonates and their mothers in three hospitals in Central Java, Indonesia. Maternal hemoglobin was measured as a proxy for maternal iron status. Neonatal iron status was measured using hematologic markers (red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, and red cell distribution) and biochemical markers (serum iron, soluble transferrin receptor/sTfR, and cord blood hepcidin). Neonatal iron status was compared between the two groups of maternal iron status followed by sensitivity analysis.

Results: Maternal hemoglobin was not significantly associated with neonatal hematologic markers or biochemical markers. Sensitivity analysis did not reveal any associations in multiple tests conducted by various categories.

Conclusion: Maternal hemoglobin was consistently not associated with neonatal iron status, as measured by both hematologic and biochemical markers. The use of maternal hemoglobin as a single parameter proxy for maternal and neonatal iron status is likely inaccurate and can potentially underestimate the actual maternal and neonatal iron status.

Keywords: Hemoglobin, Hepcidin, Iron status, Maternal, Newborn, sTfR

Introduction

The World Health Organization (WHO) estimated that more than 30% of the world's population, 33% of women of reproductive age, and about 38.2% of pregnant women suffer from anemia. Iron deficiency anemia (IDA) is the single major cause of those anemia cases (1-3). In Indonesia, data from 2018 Basic Health Research (*RISKESDAS 2018*), a national health survey conducted by the Ministry of Health, showed that the national prevalence of anemia in the pregnant women population was 48.9% (4). This denotes a significant hike compared to the finding from a similar national survey in 2013 according to which the national prevalence of anemia in the pregnant women population was 37.1% (5).

This substantial prevalence of maternal anemia may significantly affect the welfare of both mothers and newborns in Indonesia and other countries with a similar setting. Research shows that maternal iron deficiency is associated with adverse pregnancy outcomes, not only for mothers but also for newborns (6). These include premature birth, low birth weight, as well as maternal, perinatal, and neonatal death (7-8). Hypothetically, there can be a

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strong causal association between maternal Hemoglobin (Hb) levels and maternal and newborn outcomes. However, previous studies have reported inconsistent results(9, 10). According to a study, the effect of maternal anemia on infant iron status was reportedly minimal, except for mothers with severe anemia (8, 11). Another study in Brazil found no significant association between maternal and infant iron status in neonates born to mothers with anemia, iron deficiency, or non-iron deficiency (with normal Hb) (8).

The effect of iron deficiency at the end of the fetal and early life periods is well documented though empirical evidence on the association between maternal and neonatal iron status, as well as determinants of neonatal iron status is still lacking. Neonatal iron deficiencies may cause decreased cellular respiration in the hippocampus and frontal cortex, abnormal neurotransmitter concentrations, fatty acid profile changes, and impaired myelination (12). In the early life period, the disruption of iron homeostasis in the brain significantly impairs the oxidative metabolism of neural cells (13-14). Buntat *et al.* concluded that iron deficiency (low serum ferritin levels) in infants is significantly associated with a higher risk of impaired neurological development (15).

For infants, IDA is not merely a hematological disorder. Iron deficiency, even without anemia, has long-term consequences for child development and behavior. These disorders may be irreversible, particularly when at a critical age such as the first two years of life (16, 17). The maintenance of iron homeostasis during the early stage of life plays a crucial role in optimal infant growth and development (18). These processes likely depend on neonatal iron stores. Although the importance of neonatal iron status has been acknowledged, there is no neonatal iron status screening policy in Indonesia and many developing countries that share a similar setting. Currently, maternal Hb is the routine parameter used to determine maternal iron status in many developing countries, which indirectly assesses neonatal iron status.

Considering the lack of consistent evidence to support the association between maternal and neonatal iron status, the use of Hb as a proxy for maternal iron status may not accurately reflect neonatal iron status. Therefore, this study was conducted to analyze the associations between maternal Hb and neonatal iron status using the parameters of red blood count (RBC), Hb, hematocrit (Ht), mean corpuscular volume (MCV), red cell distribution width (RDW), serum iron (SI), infant soluble transferrin receptor (sTfR), and cord hepcidin.

Methods

This cross-sectional study was conducted in three hospitals in Purbalingga District, Province of Central Java, Indonesia, from September to November 2015. This study was part of comprehensive research to assess factors associated with neonatal iron status. We consecutively recruited 84 newborns and their mothers for the research. The sample size was estimated by assuming α = 5%, and power = 80%, using the one-tailed test. The sample size was calculated for the main four independent variables of the study including maternal hepcidin, IL-6, sTfR, and umbilical cord clamping time. The largest sample size of those variables comprised 84 subjects and was used in this study. We included subjects with the following criteria: (i) vaginal delivery, (ii) single and term pregnancy, (iii) Apgar scores ≥7 at the first minute, and (iv) normal birth weight (≥2,500 to <4,000 grams), and (v) healthy mother without preeclampsia/hypertension, diabetes mellitus and other comorbidities. Subjects with major congenital abnormalities were excluded from the study. The study was reviewed and approved by the Health and Medical Research Ethics Commission, Faculty of Medicine, Diponegoro University/Dr. Kariadi Hospital, Semarang, Indonesia under No.48/EC/FKRSDK/2015. Written informed consent was obtained from the parents of the newborns.

We used both hematologic and biochemical markers to indicate neonatal iron status. Hematologic markers consisted of RBC, Hb, Ht, MCV, and RDW, while biochemical markers involved SI, sTfR, and umbilical cord hepcidin. The neonatal blood specimens were taken immediately after birth, while the cord blood sample was taken from the umbilical cord artery immediately after placental delivery. The Hb was used as a parameter of maternal iron in this study. Maternal blood specimens were drawn from the veins of mothers at the time of admission for the delivery process (before birth). Hematologic markers for mothers and newborns were measured using *Sysmex, XN-1000.* Serum iron was measured by IRON Flex® (Siemens). Both hepcidin and sTfR were measured using the ELISA method, DRG® Hepcidin ELISA (EIA-4705) and Human sTfR1 (Soluble Transferrin Receptor 1) ELISA Kit (AMS.E- EL-H6085), respectively. Demographic characteristics and data on family socioeconomic status (i.e., the educational level of the parents) were also collected.

To describe the basic characteristics of subjects, they were categorized into two groups based on the median maternal Hb, with a cut-off of 12.5 g/dL. The characteristics measured by a numerical scale were presented as mean, standard deviation, median, and minimum-maximum values and those measured by a categorical scale were presented as percentages. We compared basic characteristics between groups using an independent t-test or Mann-Whitney test, and the Chi-square test was used to ensure the homogeneity of basic characteristics in subjects.

To assess the association between maternal and neonatal iron statuses, the infant hematologic and biochemical parameters were compared between the two maternal iron status groups (median maternal Hb with a cut-off of 12.5 g/dL) using an independent t-test or Mann-Whitney test. To assess the consistency of the association between maternal and neonatal iron statuses, sensitivity analyses were performed by categorizing maternal Hb into different groups based on (i) anemic (Hb < 11 g/ dL) and non-anemic groups, and (ii) quartile groups 1, 2-3, and 4 (Q 1, Q 2-3, Q4). Similarly, parametric tests such as independent t-test and one-way ANOVA or a non-parametric test (Mann-Whitney or Kruskal-Wallis test) were used. Moreover, we used Pearson's or Spearman's correlation tests to explore the correlations between maternal and neonatal iron status on a numerical scale. The significance level was set at 0.05, and a p-value <0.05 was considered statistically significant.

Results

We collected data from 84 newborn-mother pairs. Table 1 shows the characteristics of maternal and neonatal subjects based on the median maternal hemoglobin group with a cut-off 12.5 g/dL. There were 43 subjects with Hb level<12.5 g/dl (lower-level maternal Hb group) while 41 subjects had Hb level≥12.5 g/dl (upper-level maternal Hb group). There was no difference in the characteristics of maternal subjects between the groups. The maternal age was relatively similar between groups (around 26 years old). The group with upper-level maternal Hb contained a slightly larger proportion of mothers with higher education and slightly smaller percentages of passive smoke than the lower-level maternal Hb group. There was no significant difference in the characteristics of maternal subjects between groups, including the nutritional status, and blood pressure. All the maternal subjects received iron supplementation as prescribed by the Indonesian government policy. Regarding newborn characteristics, male newborns were more frequently found in the upper-level maternal Hb group compared to the lower group, though this difference was not statistically significant. The average birth weight of the newborns was identical in all groups (around 3200 grams).

Table 2 compares maternal and neonatal iron status parameters between lower and upper-level maternal Hb groups. We found no significant difference in all hematologic markers (RBC, Hb, Ht, MCV, and RDW) and biochemical markers (SI, sTfR, and hepcidin) between these groups, as indicated by p-value > 0.05.

Table 1. Characteristics of maternal and neonatal subjects

Characteristics	Median maternal Hb cut-off groups		p-value
	<12.5 g/dL (43)	≥12.5 g/dL (41)	
A. Maternal			
Mean age (SD), years	26.2 (5.45)	27.0 (5.32)	0.450[a]
Level of education, n (%)			
≥ Senior high	19 (44.2)	21 (51.2)	0.519[c]
< Senior high	24 (55.8)	20 (48.8)	
Passive smoking, n (%)			
No,	25 (58.1)	22 (53.7)	0.679[c]
Yes	18 (41.9)	19 (46.3)	
Hemoglobin, g/dL			
Median (range)	11.7 (8.80-12.50)	13.4 (12.60-15.10)	0.000[b]
Mean (SD)	11.48 (0.96)	13.6 (0.76)	
B. Neonates			
Gender, n (%)			
Male	17 (39.5)	21 (51.2)	0.282[c]
Female	26 (60.5)	20 (48.8)	
Mean birth weight, grams (SD)	3.150.5 (349.19)	3.231.6 (254.32)	0.226[a]

Notes: Statistical tests using 95% CI; a=independent t-test; b=Mann-Whitney test; c=Chi-square test

Table 2. Analysis of neonatal iron status based on maternal Hb groups

Neonatal iron status	Median maternal Hb group		p-value
	Hb < 12.5 g/dL (n=43)	Hb ≥ 12.5 g/dL (n=41)	
A. Hematological markers Mean RBC (SD), 10^6/ mm^3	4.8 (0.50)	4.9 (0.53)	0.336[a]
Mean Hb (SD), g/dL	17.3 (1.65)	17.6 (1.80)	0.494[a]
Mean Ht (SD), %	48.6 (4.47)	50.3 (5.41)	0.125[a]
Mean MCV (SD), fL	101.7 (5.42)	102.69 (5.05)	0.388[a]
Median RDW (range), %	16.4 (15.20-19.40)	16.8 (15.50-19.90)	0.193[b]
B. Biochemical markers Mean SI (SD), µg/dL	112.7 (52.99)	113.39 (52.82)	0.952[a]
Mean sTfR serum (SD), nmol/L	35.13 (8.95)	37.12 (8.56)	0.253[a]
Hepcidin Mean (SD) Median (range)	3.83 (1.71) 3.0 (1.58-6.85)	4.3 (1.61) 4.6 (1.66-6.90)	0.258[b]

Notes: Statistical tests using 95% confidence intervals; a=independent t-test; b=Mann-Whitney test

In light of this poor association, we conducted sensitivity analyses by comparing neonatal iron status using different classifications of maternal iron status to further assess the association between maternal and neonatal iron status. In Table 3, the maternal subjects were divided into anemic and non-anemic groups using a maternal Hb level of 11 g/dL as the cut-off point. We found that three were no significant differences in all neonatal hematological markers (RBC, Hb, Ht, MCV, and RDW), SI, sTfR, and hepcidin) between the anemic and non-anemic groups. For biochemical markers, the mean neonatal SI (96.8±49.87) was lower in the anemic group than in the non-anemic group (115.7± 52.88).

Moreover, the mean sTfR (33.4±10.40) was higher in the non-anemic group than in the anemic group (36.6±8.46). However, neither of these differences was statistically significant (p>0.05).

Table 4 shows the findings of another sensitivity analysis that tests the association between maternal Hb and neonatal iron status. Maternal Hb was classified into three quartile groups (Q 1, Q 2-3, or Q 4). Similarly, no significant difference in hematologic and biochemical markers was found between maternal Hb quartile groups (p>0.05). We found that SI was inversely associated with maternal Hb, while cord hepcidin increased linearly with maternal Hb. However, these associations were not statistically significant.

Table 3. Neonatal iron status based on anemic and non-anemic mothers

Neonatal Iron Status	Maternal anemia groups		p-value
	Anemia, Hb < 11 g/dL (n=12)	Non-anemia, Hb ≥ 11 g/dL (n=72)	
A. Hematological markers Mean RBC, 10^6/ mm^3 (SD)	4.7 (0.51)	4.9 (0.52)	0.235[a]
Mean Hb, g/dL (SD)	17.1 (1.93)	17.5 (1.69)	0.402[a]
Mean Ht, % (SD)	47.7 (4.84)	49.8 (4.99)	0.182[a]
Median MCV, fL (range)	99.9 (96.80-112.40)	102.3 (92.00-114.80)	0.609[b]
Median RDW, % (range)	16.2 (15.40-19.40)	16.8 (15.20-19.90)	0.145[b]
B. Biochemical markers Medan SI, µg/dL (SD)	96.8 (49.87)	115.7 (52.88)	0.251[a]
Mean sTfR, nmol/L (SD)	33.4 (10.40)	36.6 (8.46)	0.179[a]
Hepcidin Mean (SD) Median (range)	3.6 (1.72) 2.6 (1.80-6.85)	4.1 (1.66) 4.1 (1.58-6.90)	0.406[b]

Notes: Statistical tests using 95% confidence intervals; a=independent T-test; b=Mann-Whitney test

Table 4. Neonatal iron status based on maternal hemoglobin quartile groups

Neonatal iron status	Maternal hemoglobin quartile groups			p-value
	Quartile 1 (n=23)	Quartile 2-3 (n=41)	Quartile 4 (n=20)	
A. Hematological markers				
Mean RBC, $10^6/mm^3$ (SD)	4.8 (0.45)	4.9 (0.57)	4.9 (0.50)	0.965 [a]
Mean Hb, g/dL (SD)	17.3 (1.57)	17.5 (1.82)	17.5 (1.77)	0.919 [a]
Mean Ht, % (SD)	48.4 (3.87)	49.7 (5.30)	50.2 (5.51)	0.463 [a]
Mean MCV, fL (SD)	100.6 (6.31)	102.4 (4.64)	103.47 (4.81)	0.184 [a]
Median RDW (range), %	16.4 (15.30-19.40)	16.7 (15.20-19.90)	16.75 (15.70-18.30)	0.730 [b]
B. Biochemical markers				
Mean SI, μg/dL (SD)	121.9 (59.64)	111.0 (46.03)	107.1 (57.99)	0.621 [a]
Mean sTfR, nmol/L (SD)	33.95 (9.89)	37.0 (8.75)	36.7 (7.30)	0.281 [a]
Hepcidin, ng/mL				
Mean (SD)	3.7 (1.71)	4.1 (1.57)	4.4 (1.80)	0.421 [b]
Median (range)	2.7 (1.69-6.85)	4.02 (1.58-6.63)	4.9 (1.66-6.90)	

Notes: Statistical tests using 95% CI; a=one-way ANOVA; b=Kruskal-Wallis test

We conducted the final sensitivity analysis by testing the correlation between maternal Hb and neonatal iron status. Consistent with our previous findings, there were no correlations between maternal and neonatal iron status, as outlined in Table 5. The correlation coefficient for all hematological and biochemical markers was relatively small, indicating weak and non-significant correlation between maternal and neonatal iron status ($p<0.05$).

The correlation between maternal and neonatal iron status was also graphically represented using a scatter plot as displayed in Figure 1.

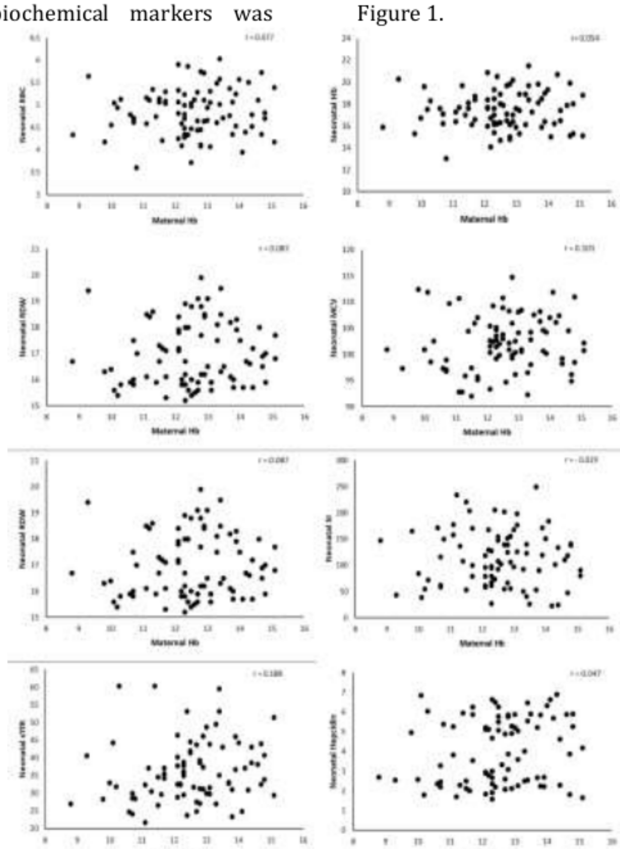

Figure 1. Scatter plots (correlation graph) for maternal and neonatal iron status

Table 5. Correlation analysis of maternal hemoglobin level and neonatal iron status

		Neonatal iron status							
		RBC [a]	Hb [a]	Ht [a]	MCV [a]	RDW [b]	SI [a]	sTfR [a]	Hepcidin [b]
Maternal hemoglobin	r	0.077	0.054	0.142	0.101	0.087	-0.029	0.188	0.047
	p-value	0.487	0.628	0.199	0.363	0.433	0.790	0.087	0.668

Notes: a=Pearson's test; b=Spearman's test; r=correlation coefficient

Discussion

The present study sought to assess the association between maternal and neonatal iron status using hematological and biochemical markers. Findings did not show any association between maternal iron status measured by maternal Hb and various hematological and biochemical markers of neonatal iron status. The sensitivity analyses confirmed the findings, as indicated by the absence of any association between maternal and neonatal iron status for any parameters when maternal iron status was classified in terms of maternal anemia, and maternal Hb quartiles, and the correlation of those parameters were measured on a numerical scale.

In this study, maternal hemoglobin was not associated with any hematologic and biochemical marker parameters used as proxies for neonatal iron status. Previous studies have reported divergent findings. Results of two studies revealed no association between maternal Hb and neonatal iron status in terms of both hematological and biochemical markers (17, 18). However, in other studies, newborns with anemic mothers had lower cord Hb and Ht compared to the non-anemic mothers, as well as lower sTfR, SI, and ferritin, particularly in severe cases of anemia (19-21).

The complex physiological changes emerging during pregnancy such as elevated plasma volume and erythropoiesis are arguably the most possible explanation for our findings. These changes wield a significant impact on hematological and biochemical parameters of maternal iron status, which may complicate determining the maternal iron status using Hb as a single parameter (8). For instance, Ht has been identified as a key factor in maternal blood status that I crucial for iron transfer to the fetus via the placenta (22). Consequently, the measurement of maternal Hb alone may not accurately reflect the maternal iron status. As suggested in a previous study, maternal Hb should be used along with other maternal iron status indicators such as Ht to accurately indicate maternal iron status, particularly in clinical practice (23).

Hemodilution, another physiological change during pregnancy, may also justify our findings. Hemodilution caused a relative reduction in maternal Hb and provoked physiological anemia in pregnancy. However, hemodilution also facilitates placental perfusion due to decreased blood viscosity (23, 24). Therefore, mild anemia in pregnancy does not automatically disturb the transfer of ferritin to the fetus (10, 25). In previous studies, the lowest incidence of low birth weight and prematurity was found at a maternal Hb concentration of 9.5-10.5 g/dL, a condition that is generally deemed as anemia in pregnancy (10, 26). However, this Hb level can still be considered optimal if the maternal MCV is >84 fL. Even when maternal Hb (9.5-10.5 g/dL) is anemic, the condition is still ideal for fetal growth.

To our knowledge, this is the first study in to assess the association between maternal and neonatal iron status using hematologic markers, SI, sTfR, and cord hepcidin in Indonesia. Our study lends credit to previous evidence from other countries that highlight the limitation of maternal iron status, particularly maternal Hb, as the proxy of neonatal iron status due to the lack of association. Our study had some limitations. Since we only recruited healthy mothers and infants as subjects, our findings would not be readily generalizable. Further, our results cannot be applied to pregnant women with specific diseases/disorders, which can interfere with the micronutrient feto-maternal transfer process, such as severe anemia, diabetes mellitus, chronic hypertension, pre-eclampsia/eclampsia, or heart failure.

Conclusion

In conclusion, our findings showed no association between maternal iron status as measured by maternal Hb, and neonatal iron status, as measured by both hematological and biochemical markers. This underlines the importance of using multiple parameters to measure maternal iron status as a proxy of infant iron status. That is, the use of maternal hemoglobin as a single parameter for maternal iron status potentially underestimates both deficiency and excess iron in pregnant women, which may adversely affect both maternal and neonatal outcomes. Practically, developing countries such as Indonesia, which are currently implementing iron supplementation programs for pregnant women, should carefully assess the risk and benefits of continuing this program due to the inherent inaccuracy of determining the feto-maternal iron association using a single parameter of maternal Hb. Consequently, there is an urgent need for another maternal iron status parameter that can accurately reflect the feto-maternal iron transfer. Future studies that explore a combination of parameters to reflect the maternal iron status more accurately and efficiently and investigate factors that influence the process of feto-maternal iron transfer are vital to the research agenda in this field.

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Conflicts of interest

The authors declare no conflicts of interests.

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