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The Relationship Between the Incidence of Second and Third Trimester Hemoglobin and the Incidence of Preterm Birth and Birth Weight

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Abstract

Objectives: Changes in maternal hemoglobin during pregnancy affect preterm delivery and liver birth weight. The aim of this study was to investigate the relation between the second and third trimester hemoglobin levels and the incidence of live birth weight and preterm delivery.

Methods: Six hundred patients at Milad hospital in 2011 were evaluated in this study. The second and third trimester hemoglobin levels were measured, in addition to investigating the relationship between the maternal hemoglobin level and the incidence rate of low birth weight and preterm delivery. Finally, the relation between the second and third trimester hemoglobin levels and education, job, history of abortion, and the use of calcium, folic acid, iron, and multivitamin pills was evaluated as well.

Results: The results indicated that the second trimester maternal hemoglobin levels were high in patients with preterm delivery and low birth weight. The relative risk of preterm delivery in the second trimester of pregnancy was 1.89 times higher in the high hemoglobin group compared to the normal hemoglobin group (CI = 1.15-3.01), and it was 1.16 times higher in the third trimester. Based on the results, the relative risk of low birth weight in the high hemoglobin group was 2.7 times the normal one (CI = 1.15-5.01), and it was 1.03 higher in the third trimester.

Conclusions: In general, high hemoglobin, especially in the second trimester, is associated with a higher risk of subsequent preterm delivery and low birth weight. Hence, it is recommended that women with high hemoglobin levels in their second trimester should be check up timely to reduce the undesirable effects of pregnancy.

Keywords: Receiver operating characteristic surface, Second and third trimester hemoglobin, Preterm delivery, Low birth weight

Introduction

The purpose of pregnancy-related care is healthy pregnancy in terms of physical and favorable mental health for the mother, the infant, and the family (1). Preterm birth and low birth weight are the unfavorable outcomes of pregnancy (2). The prevalence of preterm birth is 10%-11% in Iran. The incidence of low birth weight is 10% and 7.6% in Iran and the United States, respectively. These unfavorable outcomes are among the major causes of perinatal morbidity and mortality and preterm birth such that preterm birth comprises 69%-83% of neonatal mortality. Neonatal mortality in neonates weighing 1500-2500 g is 5-30 times higher compared with normal weight infants. Different factors influence the incidence of unfavorable pregnancy outcomes that are considered as risk factors. One of the possible risk factors that has received much attention in recent years is the level of blood factors including hemoglobin and hematocrit. Previous evidence indicates the relationship between high- and low-level hemoglobin and unfavorable pregnancy outcomes such as preterm birth and low birth weight (3).

Preterm birth occurs after the beginning of 20 weeks of pregnancy up to 37 completed weeks after the first of the last menstrual cycle (2). The approximate prevalence of preterm birth is reported at 10%-11% in Iran (4). Preterm birth is the cause of 75% of perinatal mortalities, and 50% of neurological disorders are observed in preterm neonates. The causes of preterm birth are complicated and multidimensional and even not completely known (5). Most studies have shown that anemia could be a predisposing factor of preterm birth, directly and indirectly. Corticotropin-releasing hormone synthesis increases because of tissue hypoxia in anemic women, causing maternal and fetal stress, and thus preterm birth. In recent years, the relation between high maternal hemoglobin and the incidence of preterm birth has received attention (6).

According to Alden et al study (1), low birth weight (under 2500 g) is one of the most important determinants of neonatal mortality and is considered as one of the most important indices of the World Health Organization (WHO). The prevalence of low birth weight is reported at 7.6% in the United States (7) and 7.7-10% in Iran (8).

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Key Messages

- The importance of adequate plasma volume expansion in allowing adequate fetal growth is attested by several studies that showed an increased incidence of low birth weight in association with either a high maternal hemoglobin concentration.

Numerous reports have noted the combination of high hemoglobin and hematocrit levels and its relation with the increased risk of preterm birth and low birth weight. It seems that high blood viscosity might reduce placental blood flow and lead to placental infarctions, and as a result, stop the intrauterine growth of the fetus (9).

Nonetheless, contradictions exist in this regard and the hemoglobin level is only used to diagnose maternal anemia in Iran. Moreover, the discovery of new risk factors requires more extensive studies and may even lead to increased sensitivity of selected screening programs. Therefore, the present study aimed to explore the relationship between the levels of the second and third trimester hemoglobin and unfavorable pregnancy outcomes in women who referred to Milad Hospital in Tehran in 2011.

Materials and Methods

The analytical research was carried out as a prospective cohort study. The research population consisted of 600 pregnant women in their second and third trimesters who referred to the perinatal clinic and delivery block of Milad Hospital in 2011 to receive perinatal, delivery, and post-delivery services. The minimum required sample size was set at 533 subjects according to the following formula and a confidence level of 95%, a 25% relative error in the estimates, and a 10% prevalence of low birth weight. Considering a 10% attrition rate, the sample size was set at 600 subjects.

After obtaining written consent forms from women in the second and third trimesters who met the inclusion criteria and were interested in participating in the study, a total of 700 samples were selected and included in the study. A form of demographic information and obstetric history was completed through interviews. The weight and height of the subjects were measured by a standard scale and a tape measure attached to the scale. The subjects were barefoot with minimum clothes. The second and third trimester body mass indices (BMIs) were calculated and blood pressure was recorded as well. Then, the second and third trimester hemoglobin levels were obtained from test results and recorded in the information form. The subjects were divided into low, normal, and high hemoglobin groups based on hemoglobin levels. The researcher and colleagues repeatedly visited the pregnancy care clinic by appointment with the subjects and recorded the blood pressure and unpredicted complications probably occurring for pregnant women in the information form. The type of delivery, gestational age, and neonates' weight were examined in the delivery block and recorded in the information form.

The inclusion criteria were having a singleton pregnancy, 18-35 years old, being in their 13-26 weeks of gestational age based on the first day of the last regular and reliable menstrual cycle or a second trimester ultrasound, having three or fewer pregnancies, preforming routine tests, and receiving pregnancy and delivery care in Milad Hospital. The other criteria included having no known underlying disease such as chronic blood pressure, cardiovascular diseases, chronic renal, hematologic, thyroid, diabetic, gastrointestinal and neurological (epilepsy) diseases, thalassemia, and no history of unfavorable pregnancy outcomes (i.e., preeclampsia, gestational diabetes, preterm birth, low birth weight, fetal growth restrictions, and stillbirth). On the other hand, the exclusion criteria were known fetal anomaly, the incidence of polyhydramnios, oligohydramnios, placenta previa, placental abruption, abortion and fetal death in the current pregnancy, smoking, and the use of alcohol and other unusual medications during pregnancy.

Data were gathered from March 2011 to February 2012 and then analyzed using SPSS 18. The confidence interval was set at 95% and the maximum accepted error was 0.05. Descriptive statistics including statistical indices, absolute and relative frequency distribution tables, as well as means and standard deviations were used to achieve the research goals. Moreover, inferential statistics including chi-square, Fisher exact, one-way ANOVA, and Kolmogorov-Smirnov two-sample tests were applied to compare the incidence rates of preterm birth and low birth weight.

Results

The results of the study showed that 70.5%-75.6%, 69.6%-73.0%, and 69.5%-66.8% (2nd trimester - 3rd trimester) of individuals in the low, normal, and high hemoglobin groups had middle school education, respectively. The results of the Kruskal-Wallis test indicated no statistically significant difference between education and the three hemoglobin groups in the second ($P=0.92$) and third ($P=0.27$) trimesters. The husbands of the subjects in the three hemoglobin groups also had middle school education with no significant difference between their education and women's hemoglobin levels in the second ($P=0.41$) and third ($P=0.92$) trimesters. Most subjects in all three groups were housewives with no significant difference between employment and the three hemoglobin groups in the second ($P=0.26$) and third ($P=0.52$) trimesters. Most husbands in the three groups were self-employed with no significant difference between employment and the three hemoglobin groups in the second ($P=0.08$) and third ($P=0.84$) trimesters. Based on the findings, no significant difference was found between the second ($P=0.23$) and third ($P=0.16$) trimester hemoglobin levels and the number of pregnancies. Participants' ages and BMI are provided in Table 1.

Table 1. Average Age and BMI in the Three Hemoglobin Groups

		Hemoglobin (g/100 mL)			*P* Value
		<11	11-12.4	≥12.5	
Average age	2nd trimester	27.7±3.95	27.42±3.87	27.5±3.97	0.61
	3rd trimester	27.16±3.84	27.47±4.14	27.1±3.44	0.63
1st trimester BMI	2nd trimester	25.41±4.48	24.84±4.29	24.75±4.63	0.36
3rd trimester BMI	2nd trimester	30.19±4.09	29.75±4.17	29.41±4.31	0.37
	3rd trimester	29.77±4.05	29.92±4.14	29.64±5.01	0.87

Note. BMI: body mass index.

Assessments revealed that 85.6% (2nd trimester) and 86.0% (3rd trimester) of the subjects had no history of abortion and no significant relationship could be found between abortion and the hemoglobin level. In addition, there was no significant relationship between the hemoglobin level and the duration of taking folic acid, iron pills, calcium, and multivitamin pills (folic acid: 2nd trimester, $P=0.63$; 3rd trimester: $P=0.15$; iron pills: 2nd trimester, $P=0.34$; 3rd trimester, $P=0.05$; calcium: 2nd trimester, $P=0.89$; 3rd trimester: $P=0.28$; multivitamin pills: 2nd trimester, $P=0.57$; 3rd trimester, $P=0.22$).

Of the examined women in the second trimester, 88 (16.1% of the whole sample) cases developed preterm birth of whom, 36 women (23.4%) were in the high hemoglobin group (≥12.5). The relative risk of developing preterm birth in the high hemoglobin group was 1.89 times (89%) greater than the normal hemoglobin group (CI = 1.15-3.01), and in the low hemoglobin group, the risk was 0.71 times greater than the normal hemoglobin group (CI = 0.32-1.6).

Of the women examined in the third trimester, 96 (16.0% of the whole sample) cases developed preterm birth of whom, 54 women (16.8%) were in the high hemoglobin group (≥12.5). Based on the results, the relative risk of developing preterm birth in the high hemoglobin group was 1.16 times greater than the normal hemoglobin group (CI = 0.73-1.84). In addition, the risk was 1.19 times greater in the low hemoglobin group compared to the normal hemoglobin group (CI = 0.49-2.8).

Out of the women under study in the second trimester, the highest percentage of healthy pregnant women (92.7%) belonged to the 11-12.4 (normal) hemoglobin group while most subjects with low birth weight were in the high hemoglobin group. The relative risk of developing low birth weight in the high hemoglobin group was 2.7 times greater in comparison with the normal hemoglobin group (CI = 1.5-5.01), and in the low hemoglobin group, the risk was 0.80 times greater compared with the normal hemoglobin group (CI = 0.33-1.9).

Out of the women under investigation in the third trimester, the highest percentage of healthy pregnant women (90.2%) belonged to the low hemoglobin group while most subjects with low birth weight were in the 11-12.4 (normal) hemoglobin group. The relative risk of developing low birth weight in the high hemoglobin group was 1.03 times greater compared with the normal hemoglobin group (CI = 0.60-1.79), and in the low hemoglobin group, the risk was 1.09 times greater when compared with the normal hemoglobin group (CI = 0.36-3.32) (Table 2, Figure 1 B).

The results showed that second trimester hemoglobin with sensitivity and specificity levels of 0.59 and 0.50,

Table 2. Absolute and Relative Frequency Distribution of Pregnant Women Referring to Milad Hospital in Tehran Divided by Three Hemoglobin Groups in the 2nd and 3rd Trimesters With Preterm Birth and Birth Weight

		Hemoglobin (g/100 mL)			Total
		<11 (Low)	11-12.4 (Normal)	≥12.5 (High)	
Childbirth (2nd trimester hemoglobin)	Term: (%) number	118 (76.6)	272 (86.1)	70 (89.7)	460 (83.9)
	Preterm: (%) number	36 (23.4)	44 (13.9)	8 (10.3)	88 (16.1)
	RR (95% CI)	1.89 (1.15-3.01)	1	0.71 (0.32-1.6)	
Childbirth (3rd trimester hemoglobin)	Term: (%) number	268 (83.2)	202 (85.2)	34 (82.9)	504 (84.0)
	Preterm: (%) number	54 (16.8)	35 (14.8)	7 (17.1)	96 (16.0)
	RR (95% CI)	1.16 (0.73-1.84)	1	1.19 (0.49-2.8)	
Birth weight (2nd trimester hemoglobin)	≤2490	27 (17.5)	23 (7.3)	7 (9.0)	57 (10.4)
	≥2500	127 (82.5)	293 (92.7)	71 (91.0)	491 (89.6)
	RR (95% CI)	2.7 (1.5-5.01)	1	0.80 (0.33-1.9)	
Birth weight (3rd trimester hemoglobin)	≤2490	33 (10.2)	25 (10.5)	4 (9.8)	62 (10.3)
	≥2500	289 (89.8)	212 (89.5)	37 (90.2)	536 (89.7)
	RR (95% CI)	1.03 (0.60-1.79)	1	1.09 (0.36-3.32)	

Note. RR: Relative riskss; CI: confidence interval.

Table 3. Area Under the Curve, Cut-off Point, Sensitivity and Specificity of Hemoglobin Measurements in the Second and Third Trimester of Pregnancy in Diagnosis of Preterm Birth and Birth Weight

	Hemoglobin	Area Under the Curve	Cut-off Point	*P* Value	Sensitivity	Specificity
Preterm birth	3rd trimester	0.523	12.35	0.499	0.58	0.43
	2nd trimester	0.588	11.85	0.009	0.59	0.50
Low birth weight	3rd trimester	0.501	12.55	0.972	0.53	0.50
	2nd trimester	0.576	11.95	0.060	0.60	0.52

respectively, was significantly effective in predicting preterm birth with an 11.85 cut-off point ($P=0.009$) (Table 3, Figure 1 A).

Discussion and Conclusion

Preterm birth and low birth weight are among the unfavorable pregnancy outcomes (2) and the major causes of perinatal morbidity and mortality and low birth weight. Numerous factors are involved in the incidence of unfavorable pregnancy outcomes considered as risk factors. One of these risk factors, which has gained attention in recent years, is the level of blood factors such as hemoglobin and hematocrit. Research in this area is limited and findings are contradictory (9-12). Currently, determining the levels of hemoglobin and hematocrit is one of the routine pregnancy tests. Anemia is diagnosed by low hemoglobin counts, and iron supplement treatment will be prescribed accordingly. Considering that it is a routine practice for all pregnant women from the 20th week of pregnancy, it seems that this may lead to increased blood viscosity and consequent complications in women with high hemoglobin levels (9,12). Accordingly, the purpose of the present study was to assess the relationship between the second and third trimester hemoglobin levels and the incidence of preterm birth and low birth weight.

The normal level of plasma hemoglobin is 2 ± 13 g/dL and 2 ± 12 g/dL during non-pregnancy times and pregnancy, respectively (2). The hemoglobin level slightly decreases during pregnancy because of the rise in blood volume (11). The first and third trimester hemoglobin levels <11 g/dL and the second trimester hemoglobin levels <10.5 g/dL are considered as pregnancy anemia (2,5). High maternal hemoglobin levels, as well as high maternal iron stores in the first half of pregnancy are reported as risk factors for preterm birth and low birth weight (9,10,13). Preterm birth is one of the main health problems that is the major cause of neonatal morbidity and mortality after inborn abnormalities such that 75% of perinatal morbidities and mortalities are caused by preterm birth (5). The prevalence of preterm birth is 5% and 25% in developed and developing countries, respectively (14).

At least, 18 million low weight neonates (14% of all births) are born each year across the world. One of the set goals at the World Summit for Children in 2004 was to lower the prevalence of low birth weight to less than 10% by 2004. However, according to WHO 2004 reports, the dilemma remains unsolved in the 21st century (15). Other causes of low birth weight include unfavorable socioeconomic conditions, mothers aged under 18 or above 35 years, a history of pregnancy complications such as abortion, low birth weight, poor maternal nutrition, poor weight gain during pregnancy, short height, low maternal hemoglobin, and hematocrit. Moreover, other causes were gestational blood pressure, urinary tract infection during pregnancy, smoking and drinking alcohol, second and third trimester bleeding, and hydramnios (16). The findings of Amburgey et al revealed that pre-pregnancy hemoglobin concentrations increased significantly in women with preeclampsia and there was

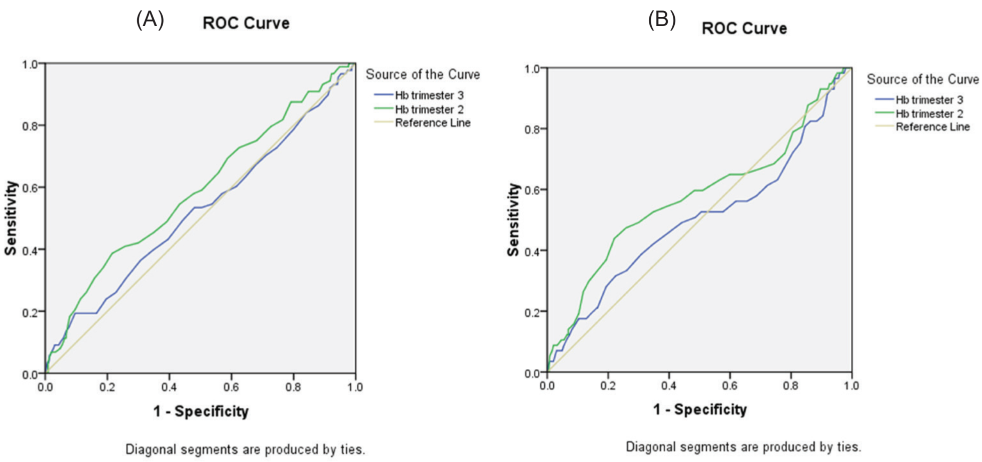

Figure 1. ROC Curve of the 2nd and 3rd Trimester Hemoglobin for the Diagnosis of (A) Preterm and (B) Low Birth in Pregnant Women Referring to Milad Hospital in Tehran. *Note*. ROC: Receiver operating characteristic.

a reverse relationship between maternal hemoglobin concentrations and birth weight (17).

Researchers showed that 59 (6.8%) out of 874 pregnant women developed preterm birth of whom, 27 cases were in the high hemoglobin group and 27 were in the normal hemoglobin group. Fifty-four and 28 women also developed low birth weight and small for gestational age, respectively (10).

It is argued that the increased average concentration of hemoglobin with pathologic blood pressure during the second trimester, smoking, and mother's age are important risk factors for preterm birth. Based on the results of a study (9), a high hemoglobin level was at least a contributing factor in the increased risk of high-risk pregnancies, and the hemoglobin concentration in women with normal pregnancy (9.66 ± 0.9 g/dL) was lower compared to women with unfavorable pregnancy outcomes (12.5 ± 1 g/dL).

The results of the present study demonstrated that the relative risk of developing preterm birth in the second trimester was 1.89 times (89%) greater in the high hemoglobin group in comparison with the normal hemoglobin group (CI = 1.15-3.01). The relative risk in the third trimester of developing preterm birth in the high hemoglobin group was 1.16 times greater compared with the normal hemoglobin group (CI = 0.73-1.84), and in the low hemoglobin group, the risk was 1.19 times greater when compared with the normal hemoglobin group (CI = 0.49-2.8).

The present findings also revealed that the relative risk of developing low birth weight in the second trimester was 2.7 times greater in the high hemoglobin group in comparison with the normal hemoglobin group (CI = 1.5-5.01). In the third trimmest, the relative risk of developing low birth weight in the high hemoglobin group was 1.03 times greater compared with the normal hemoglobin group (CI = 0.60-1.79), and the risk was 1.09 times greater in the low hemoglobin group in comparison with the normal hemoglobin group (CI = 0.36-3.32).

The findings of one study showed that the hemoglobin level in the first trimester significantly affected neonatal weight although no significant relationship was found between the hemoglobin level and neonatal weight in the second and third trimesters. However, maternal hemoglobin levels in the second and third trimesters were higher in relation to newborn infants under 2500 grams (18). On the other hand, other researchers noted a significant relationship between low hemoglobin levels in the third trimester and low birth weight (19). Some studies also reported a direct relationship between high hematocrit levels and unfavorable pregnancy outcomes (20,21). Based on the findings of another study, a low hemoglobin level in the third trimester can cause low birth weight and even increase neonatal mortality (19). It was shown that anemic mothers are 10% more likely to give birth to low weight infants and 20% more likely to develop preterm birth, and the likelihood of low birth weight and preterm birth reaches 60% in women with severe anemia (22). Moreover, maternal plasma changes in the final half of pregnancy increase hemoglobin concentrations, which is related to unfavorable pregnancy complications (23). Studies in India and Britain represented that there was a U-shaped relationship between hemoglobin levels and low birth weight (24,25). Other studies suggested that low hematocrit levels at the early stages of pregnancy and high hematocrit levels at the final stages of pregnancy are significantly related to high rates of preterm birth (26, 27). The results of the present study also showed that with increased maternal hemoglobin levels in the second trimester, the risk of developing preterm birth and low birth weight increases 1.89 and 2.7 times, respectively, and in the third trimester, the risk of developing preterm birth and low birth weight increases with higher or lower than normal hemoglobin levels, which is consistent with the findings of the above-mentioned studies. However, further research is needed to accurately examine the impact of maternal hemoglobin levels on unfavorable pregnancy outcomes.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Islamic Azad University of Ardabil (p/5.90.1138).

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