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The Relation Between the Incidence Rate of Second and Third Trimester Hemoglobin and the Incidence of Preeclampsia and Gestational Diabetes: A Cohort Study

Majid Rostami Mogaddam[1], Nastaran Safavi Ardebili[2*], Nourossadat Kariman[3]

Abstract

Objectives: Changes in maternal hemoglobin during pregnancy affect the incidence rate of preeclampsia and gestational diabetes mellitus (GDM). The present study aimed to investigate the relation between the second and third trimester hemoglobin and the incidence of preeclampsia and gestational diabetes.

Materials and Methods: A total of 600 patients who referred to Milad hospital in 2011 participated in this study. Second and third trimester hemoglobin levels were measured. The association between the level of maternal hemoglobin and the incidence rate of preeclampsia and gestational diabetes was evaluated. In addition, the association between the second and third trimester hemoglobin level and education, job, history of abortion, as well as the use of calcium, folic acid, iron, and multivitamin pills was evaluated.

Results: The results indicated that the second and third trimester maternal hemoglobin levels were high in patients with gestational diabetes and preeclampsia. Further, the relative risk of GDM was 2.12 times higher in the high hemoglobin group during the second trimester of pregnancy compared to the normal hemoglobin group (CI = 1.14-3.94) and it was 1.47 times higher in the third trimester (CI = 0.78-2.7). Furthermore, the relative risk for preeclampsia in the high hemoglobin group was 2.33 times more than normal one (CI = 1.16-4.66) and in the third trimester, it was 1.33 higher (CI = 0.66-2.66).

Conclusions: The high hemoglobin, especially in the second trimester is associated with a higher risk of subsequent preeclampsia and GDM. Hence, women with high hemoglobin in their second trimester are at greater risk of developing GDM and preeclampsia. Therefore, early detection and prevention reduce undesirable effects.

Keywords: ROC surface, Second and third trimester hemoglobin, Gestational diabetes, Preeclampsia

Introduction

Healthy pregnancy in terms of physical health and favorable mental health for the mother, infant, and family is the purpose of pregnancy-related cares (1). Prevalence of gestational diabetes is 2%-5% in the world with an approximate 40% increase during 1989-2002 (2). Gestational diabetes and preeclampsia are among the major causes of perinatal morbidity, mortality, and preterm birth. In addition, diabetes is the most common endocrine disorder in pregnancy and responsible for a large group of perinatal complications such as fetal death, large for gestational age, damage during childbirth, and neonatal hypoglycemia (1). The level of blood factors like hemoglobin and hematocrit is a possible risk factor and thus a high level of hemoglobin can increase the incidence of preeclampsia and gestational diabetes in the afflicted women compared to those with a normal hemoglobin level (3). Since iron supplements are prescribed as a routine practice for pregnant women from the 20th week of pregnancy, it seems that in women with high hemoglobin levels, this may cause increased blood viscosity and consequent complications including preterm birth, low birth weight (LBW), preeclampsia, and gestational diabetes (4-6). High maternal hemoglobin level is considered as a test for early diagnosis of preeclampsia and gestational diabetes (6).

Gestational diabetes is a type of diabetes which first develops during the pregnancy by varying degrees of intolerance to carbohydrates (3). Prevalence of this type of diabetes is 2%-5% in the world. Larijani et al reported its prevalence as 4.5% in Tehran (7). Recent studies have indicated that the prevalence of gestational diabetes is increasing in all racial groups. Further, the World Health Organization (WHO) estimates that the incidence of diabetes in 2025 is 1.5 times more than its prevalence in 2000. Furthermore, since the trend of gestational diabetes

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[1]Department of Dermatology, Ardabil University of Medical Sciences, Ardabil, Iran. [2]Department of Midwifery, Ardabil Branch, Islamic Azad University, Ardabil, Iran. [3]Midwifery and Reproductive Health Research Center, Department of Midwifery and Reproductive Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Corresponding Author: Nastaran Safavi Ardebili, Tel: +984533728020, Email: n.safavi@iauardabil.ac.ir

prevalence follows the prevalence of type 2 diabetes, it is expected that the incidence of this disease to have an upward trend (8). Changes in insulin sensitivity develop during the first trimester as the fetus grows and thus insulin secretion increases due to insulin resistance. Accordingly, this state of resistance which is dependent on hormonal changes reaches its highest point. Physiological changes during the pregnancy can trigger gestational diabetes in susceptible people. Therefore, pregnancy is a diabetes-inducing condition and gestational diabetes is the most common metabolic disorder in this period (9). Moreover, gestational diabetes is accompanied by increased complications and unfavorable outcomes during the pregnancy and may cause long-term complications for the mother and infant (1).

Preeclampsia is one of the most prevalent problems of pregnancy and after hemorrhage and infection, is the third cause of maternal mortality. Additionally, it is regarded as one the most important causes of preterm childbirth, fetal growth restriction, and mortality during pregnancy. Preeclampsia is recognized by WHO as a global women health problem the cause of which is still unknown (10). Preeclampsia is an exclusively human disorder which is due to the advanced vascular disorders in women. Its prevalence is 5%-7% in the world and 20% in developing countries (2). As the most important pregnancy complication, preeclampsia leads to 15% of maternal mortalities and causes preterm birth and emergency cesarean section. In addition, it was considered the second cause of maternal mortality in Iran during 1997-2000. Since the hemoglobin level is only used to diagnose maternal anemia in Iran, this study sought to determine the relationship between the second and third trimester hemoglobin levels and the incidence rate of preeclampsia, as well as gestational diabetes in pregnant women who referred to Milad hospital (Tehran) during 2011.

Materials and Methods

Study Type and Participants

This analytical research was conducted as a prospective cohort study. Research population included 600 pregnant women in the second and third trimesters who referred to perinatal clinic and delivery block of Milad hospital to receive perinatal, delivery, and post-delivery services during 2011. The minimum sample size was determined 533 women based on the following formula and the confidence level of 95%, 25% (i.e., 25% relative error in the estimates), and prevalence of LBW (10%) and considering a 10% attrition rate, the final sample size included 600 patients.

Totally, 700 pregnant women were selected and written consent was obtained from the women in the second and third trimesters who met the inclusion criteria and were interested to participate in the study. A form of demographic information and obstetric history was administered by an interview. Data regarding the patients' weight and height were measured by a standard scale and a tape measure was attached to the scale. They were barefoot and with minimum clothes. Second and third trimester body mass indexes (BMIs) were calculated and blood pressure (BP) was recorded. Further, the levels of the second and third trimester hemoglobin were then obtained from the test results and recorded in the data form. Based on the hemoglobin levels, participants were divided into low, normal, and high hemoglobin groups. BP and unpredicted problems which might occur for the pregnant women were recorded in the information form. Finally, the type of delivery, gestational age, and infant weight were assessed in the delivery block and recorded in the form.

Inclusion criteria were singleton pregnancy, 18-35 years old, 13-26 week gestational age based on the first day of the last regular and reliable menstrual cycle or a second trimester ultrasound, three or less pregnancies, performing routine tests, receiving pregnancy and delivery care in Milad hospital, lack of any known underlying diseases including chronic BP, 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, LBW, fetal growth restriction, and stillbirth). Furthermore, the exclusion criteria encompassed known fetal anomaly, the incidence of polyhydramnios, oligohydramnios, placenta previa, placental abruption, abortion and fetal death in the current pregnancy, smoking, as well as the use of alcohol and other unusual medications during the pregnancy.

Data were collected in 11 months during March 2011-February 2012 and analyzed using the SPSS software, version 18. A 95% CI and a 0.05 maximum accepted error were employed. In line with the research goals, descriptive statistics including calculation of statistical indices, absolute and relative frequency distribution tables, mean and standard deviation were applied. Moreover, inferential statistics including chi-square, Fisher exact, one-way ANOVA, and Kolmogorov-Smirnov two-sample tests were utilized to compare the incidence rates of preterm birth and LBW.

Results

The results indicated that 70.5%-75.6% (second trimester-third trimester) of the patients in the low hemoglobin group, 69.6%-73.0% of them in the normal hemoglobin group, and 66.8%-69.5% in the high hemoglobin group had middle-school education. Based on the results of the Kruskal-Wallis test, there was no statistically significant difference between education and the three groups in the second (P = 0.92) and third (P = 0.27) trimesters (Table 1). Additionally, the participants' husbands in all three groups had middle-school education and no significant difference was found between their education and their women's hemoglobin level in the second (P = 0.41) and

Table 1. The Average Age and BMI in Different Hemoglobin Groups

		Hemoglobin (g/100 mL)			*P* Value
		<11	11-12.4	≥12.5	
Average age	2nd trimester	27.5±3.97	87.3±42.27	27.07±3.95	0.61
	3rd trimester	27.1±3.44	27.47±4.14	27.16±3.84	0.64
1st trimester BMI	2nd trimester	24.75±4.63	24.84±4.29	25.41±4.48	0.36
3rd trimester BMI	2nd trimester	29.41±4.31	29.75±4.17	30.19±4.09	0.37
	3rd trimester	29.64±5.01	29.92±4.14	27.77±4.05	0.87

third (*P* = 0.92) trimesters. As regards employment, the majority of the participants in all the groups were housewives and no significant difference was observed between employment and the three hemoglobin groups in the second (*P* = 0.26) and third (*P* = 0.52) trimesters. In addition, the majority of husbands were self-employed and there was no meaningful difference between employment and the 3 hemoglobin groups in the second (*P* = 0.08) and third (*P* = 0.84) trimesters. Further, results represented no significant difference between the second (*P* = 0.23) and third (*P* = 0.16) trimester hemoglobin levels and the number of pregnancies.

Based on the results, 85.6% (second trimester) and 86.0% (third trimester) of the participants had no history of abortion and no significant relationship was detected between abortion and hemoglobin level. Furthermore, there was no significant association between hemoglobin level and duration of taking folic acid, iron pills, calcium, and multivitamin pills (folic acid: second trimester: *P* = 0.63, third trimester: *P* = 0.15; iron pills: second trimester: *P* = 0.34, third trimester: *P* = 0.05; calcium: second trimester: *P* = 0.89, third trimester: *P* = 0.28; multivitamin pills: second trimester: *P* = 0.57, third trimester: *P* = 0.22).

A number of 47 (8.6% of the whole sample) women out of 600 women under investigation in the second trimester developed gestational diabetes of whom 22 (14.3%) patients were in the high hemoglobin group (≥12.5, *P* = 0.01). The relative probability of developing gestational diabetes in the high hemoglobin group was 2.12 times greater compared to the normal hemoglobin group (CI = 1.14-3.94). Moreover, such a risk was 0.33 times greater in the low hemoglobin group compared to the normal hemoglobin group (CI = 0.07-1.4). Forty-nine (8.2% of the whole sample) of the women under study in the third trimester were afflicted with gestational diabetes of whom 31 (9.6%) were in the high hemoglobin group (≥12.5, *P* = 0.01). Additionally, the relative risk for developing gestational diabetes in the high hemoglobin group was 1.47 times greater than that of the normal hemoglobin group (CI = 0.78-2.7) and it was 0.71 times greater in the low hemoglobin group compared to the normal hemoglobin group (CI = 0.16-3.2).

As regards preeclampsia, 39 (7.1% of the whole sample) women in the second trimester suffered from it, of whom 18 (11.7%) were in the high hemoglobin group (≥12.5). In addition, the relative probability of developing preeclampsia was 2.33 times greater in the high hemoglobin group compared to the normal hemoglobin group (CI = 1.16-4.66) and it was 0.95 times greater in the low hemoglobin group compared to the normal hemoglobin group (CI = 0.31-2.9).

Similarly, 40 (6.7% of the whole sample) women in the third trimester were afflicted with preeclampsia of whom 23 (7.1%) were in the high hemoglobin group (≥12.5). The relative risk for developing preeclampsia in the high hemoglobin group was 1.33 times greater than that of the

Table 2. Absolute and Relative Frequency Distribution of Pregnant Women Referring to Milad Hospital of Tehran During the 2nd and 3rd Trimesters With Gestational Diabetes and Preeclampsia

		Hemoglobin (g/100 mL)			Total
		<11	11-12.4	≥ 12.5	
Developing gestational diabetes (2nd trimester hemoglobin)	Yes: No. (%)	76 (4.97)	293 (7.92)	132 (7.85)	501 (4.91)
	No: No. (%)	2 (6.2)	23 (3.7)	22 (3.14)	47 (6.8)
	RR (95% CI)	0.33 (0.07-4.1)	1	12.2 (14.1-94.3)	
Developing gestational diabetes (3rd trimester hemoglobin)	Yes: No. (%)	39 (1.95)	221 (2.93)	291 (4.90)	551 (8.91)
	No: No. (%)	2 (9.4)	16 (8.6)	31 (6.9)	49 (2.8)
	RR (95% CI)	0.71 (0.16-2.3)	1	47.1 (0.78-7.2)	
Developing preeclampsia (2nd trimester hemoglobin)	Yes: No. (%)	74 (9.94)	299 (6.94)	136 (3.88)	509 (9.92)
	No: No. (%)	4 (1.5)	17 (4.5)	18 (7.11)	39 (1.7)
	RR (95% CI)	0.95 (0.31-9.2)	1	33.2 (16.1-66.4)	
Developing preeclampsia (3rd trimester hemoglobin)	Yes: No. (%)	37 (2.90)	224 (5.94)	299 (9.92)	560 (3.93)
	No: No. (%)	4 (8.9)	13 (5.5)	23 (1.7)	40 (7.6)
	RR (95% CI)	86.1 (0.58-1.6)	1	33.1 (0.66-66.2)	

normal hemoglobin group (CI = 0.66-2.66) and in the low hemoglobin group, it was 1.86 times greater compared to the normal hemoglobin group (CI = 0.58-6.1) (Table 2).

As illustrated in Figure 1, 12.55 g/100 mL of the hemoglobin in the third trimester and 11.85 g/100 mL in the second trimester are regarded as proper cut-off points for diagnosing gestational diabetes (Table 3).

Discussion and Conclusions

Various factors are involved in the incidence of unfavorable pregnancy outcomes which are referred to as the risk factors. One of the possible risk factors which has received attention is the level of blood factors like hemoglobin and hematocrit. Research on this field is limited and findings are contradictory (3-6). Determining the level of hemoglobin and hematocrit is currently a routine test in pregnancy. Further, anemia is diagnosed with low hemoglobin count and iron supplement treatment is prescribed accordingly. Furthermore, since it is a routine

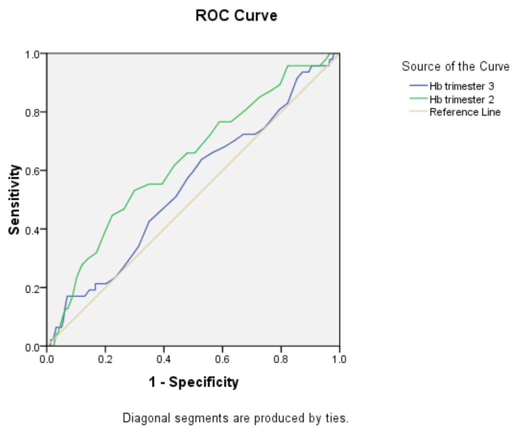

Figure 1. The ROC Curve of Second and Third Trimester Hemoglobin for Diagnosing of Gestational diabetes in Pregnant Women Referring to Milad Hospital (Tehran).

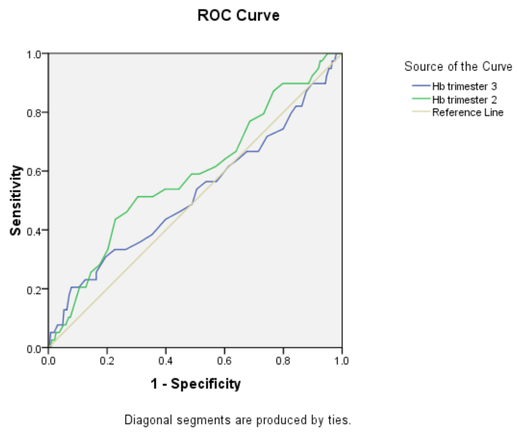

Figure 2. The ROC Curve of Second and Third Trimester Hemoglobin for Diagnosing the preeclampsia in Pregnant Women Referring to Milad Hospital (Tehran).

practice for all the pregnant women from the 20th week of pregnancy, it seems that this may cause increased blood viscosity and consequent complications in individuals with high hemoglobin levels (4, 6). Therefore, this study attempted to examine the relationship between the second and third trimester hemoglobin levels and the incidence of preeclampsia and gestational diabetes.

The normal plasma hemoglobin level is 2 ± 13 g/dL during non-pregnancy times and 2 ± 12 g/dL during pregnancy. Hemoglobin level slightly decreases in pregnancy due to a rise in blood volume (9). First and third trimester hemoglobin <11 g/dL and second trimester hemoglobin <10.5 g/dL are considered pregnancy anemia (9). Findings of Amburgey et al demonstrated that pre-pregnancy hemoglobin concentration increased significantly in women with preeclampsia and that there was a reverse relationship between maternal hemoglobin concentration and birth weight (11). Therefore, given the high prevalence of preeclampsia in women with first pregnancy and its maternal, fetal, and neonatal complications, prevention of the preeclampsia as an important health priority is a necessity for reducing maternal mortality and improving pregnancy final outcome (12). However, preventing preeclampsia is only possible when it is treated at early stages and before irreversible changes. Accordingly, early and appropriate diagnostic tests are required for successful treatment. An increase of 45% in plasma volume during pregnancy and an increase of 18%-33% in red cell mass reduces hemoglobin and hematocrit concentrations, especially in the second trimester. Failure in plasma volume increase leads to higher blood viscosity or increased hemoglobin and hematocrit levels (9). Normal hemodynamic changes during pregnancy do not occur in women with preeclampsia due to the plasma volume increase in the second trimester. Considering vascular spasms and non-occurrence of pregnancy-related hypervolemia in women with preeclampsia, it is possible that hemoglobin and hematocrit levels increase in these patients. Several studies suggested hemoglobin and hematocrit level as an early diagnostic test for preeclampsia (13). Research on 142 women with first pregnancy revealed that maternal hemoglobin concentration increased in women with preeclampsia (11). Findings of another study conducted on 874 pregnant women in Thailand indicated that 62 women (7.1%) developed preeclampsia of whom 49 had high hemoglobin level while 65 women (7.4%) developed gestational diabetes of whom 36 had high hemoglobin level (3). Moreover, based on the results of this study, preeclampsia (relative risk [RR] = 3.3, CI = 95%) and gestational diabetes (RR = 3.3, CI = 95%) were significantly related to high hemoglobin level. Similarly, a study in Iran implemented on 266 pregnant women represented that an increased hematocrit level in the first and third trimesters had a statistically significant relationship with the incidence rate of preeclampsia (14).

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 gestational diabetes and preeclampsia

	Hemoglobin	Area Under the Curve	Cut-off Point	*P* Value	Sensitivity	Property
Gestational diabetes	3rd trimester	0.545	55.12	306.0	0.6	0.5
	2nd trimester	0.633	85.11	003.0	0.66	0.50
Preeclampsia	3rd trimester	523.0	45.12	632.0	0.56	47.0
	2nd trimester	587.0	95.11	069.0	0.59	51.0

Researchers compared hemoglobin levels of 444 women with preeclampsia with those of 15 825 healthy pregnant women and found that hemoglobin level was significantly higher in women with preeclampsia (15). Researchers reported that hemoglobin and its products are toxic and can cause oxidative stress, hemolysis, vascular spasms, renal damage, and endothelia and ultimately lead to a higher incidence of preeclampsia (16). A study in Iran during 2010-2011 performed on 650 pregnant women in the first to third trimesters indicated that 7.2% of women had preeclampsia and that their hemoglobin levels were significantly higher than those of the normal women ($P = 0.003$). Additionally, it was found that the hemoglobin level in the first trimester was significantly higher and lower than the second and third trimesters, respectively. In addition, first, second, and third trimester hemoglobin was found to help predict the incidence of preeclampsia (17).

Anaka et al studied 564 women and found that patients with HbA1C < 5.2 developed no gestational diabetes while all the patients with HbA1C > 6.1 developed gestational diabetes (18). Further, Amylidi et al investigated 208 patients and concluded that the risk of developing gestational diabetes increased in pregnant women with high first trimester HbA1C. Finally, they found that HbA1C level could help predict the potential prevalence of gestational diabetes (19).

The results of the current study demonstrated that the high maternal hemoglobin levels in the second and third trimester of pregnancy were associated with an increased risk of gestational diabetes and preeclampsia, which is in line with the results of Khoigani et al (14). Furthermore, Pakniat et al indicated that high levels of hemoglobin in the first trimester of pregnancy could be a predictive factor for the incidence of preeclampsia (20). Moreover, it was indicated that high levels of hemoglobin at the first trimester of pregnancy could be a risk for preeclampsia (21). According to Murphy et al, a high level of hemoglobin in the first and second trimester of pregnancy was associated with preeclampsia incidence rate (22). Tan et al indicated that the high maternal hemoglobin level at the first prenatal visit was independently predictive of gestational diabetes mellitus (GDM) among the Asian population (23). Additionally, it was demonstrated that the high maternal hemoglobin (>13 g/dL) at the initial prenatal visit was an independent risk factor for GDM in Chinese studies (24). The hemoglobin levels in the first and second half of pregnancy can predict preeclampsia and premature preterm rupture of the membranes (14). The results of the current study indicated that the higher hemoglobin of mothers in the second and third trimester of pregnancy increased the risk of GDM and preeclampsia. This is in conformity with the results of previous studies.

In addition, Gangor et al demonstrated there was no significant difference between the level of maternal hemoglobin in the second trimester and the incidence of gestational diabetes (25). However, Lao et al found that high maternal hemoglobin in early pregnancy could be an independent risk factor for gestational diabetes (24). Thus, further studies are needed to accurately assess the effect of maternal hemoglobin on undesirable pregnancy outcomes. Therefore, the results of this study seem to be helpful in reducing the adverse effects of pregnancy with careful care of women with high hemoglobin levels.

Conflict of Interests
Authors have no conflict of interests.

Ethical Issues
This research project was approved under No. p/5.90.1138.

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