Hemoglobin level during the first trimester of pregnancy in gestational diabetes

Poziom hemoglobiny w pierwszym trymestrze u ciężarnej z cukrzycą ciążową

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Abstract

Objective: *The objective of this study was to determine the relationship between the hemoglobin levels during the first trimester of pregnancy with gestational diabetes incidence in pregnant women.*

Materials and methods: *This is a prospective cohort study on 700 pregnant women with gestational ages of 1-13 weeks. Sampling was performed using the convenience method. For each pregnant woman, the hemoglobin level of the first trimester of pregnancy was measured. All the cases were followed up to delivery due to gestational diabetes.*

Results: *Hemoglobin levels were categorized into three groups (<1.1, 1.1-1.24, ⩾1.25 g/L). The data were extracted using the SPSS, and analyzed with descriptive and inferential statistics. Statistical tests revealed a significant difference among the three groups in hemoglobin levels and gestational diabetes incidence (p<0.001). Women with higher hemoglobin levels were at an increased risk of developing gestational diabetes (RR=3.94, 95% CI=1.73-8.95).*

Conclusion: *It appears that hemoglobin level during the first trimester of pregnancy may be considered as a selective screening factor for gestational diabetes.*

Key words: **first trimester** / **gestational diabetes** / **hemoglobin** /

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Streszczenie

Cel pracy: *Celem pracy była ocena związku pomiędzy poziomem hemoglobiny w pierwszym trymestrze u ciężarnej z cukrzycą ciążową.*

Materiał i metoda: *Prospektywne kohortowe badanie przeprowadzono na 700 kobietach w 1-13 tygodniu ciąży. U każdej kobiety badano poziom hemoglobiny w pierwszym trymestrze ciąży. Wszystkie przypadki kontrolowano aż do porodu ze względu na cukrzycę.*

Wyniki: *Wyznaczono trzy grupy w zależności od poziomu hemoglobiny (<1.1, 1.1-1.24, ⩾1.25g/L). Uzyskane dane analizowano przy pomocy SPSS stosując statystykę opisową i wnioskowanie statystyczne. Testy statystyczne wykazały istotną różnicę pomiędzy trzema grupami w poziomie hemoglobiny i częstości występowania cukrzycy ciążowej (p<0.001). Kobiety z wyższym poziomem hemoglobiny były w grupie zwiększonego ryzyka rozwoju cukrzycy ciążowej (RR=3.94, 95%CI=1.73-8.95).*

Wnioski: *Wydaje się, że poziom hemoglobiny w pierwszym trymestrze ciąży może być selektywnym czynnikiem skriningowym cukrzycy ciążowej.*

Słowa kluczowe: **pierwszy trymestr** / **cukrzyca ciążowa** / **hemoglobina** /

Introduction

Diabetes is counted among the most important healthcare and socio-economic challenges of the contemporary world [1-2]. Gestational diabetes is a subtype of diabetes, manifesting as carbohydrate intolerance of varying degrees, occurring for the first time during pregnancy [2- 3].

The worldwide prevalence of gestational diabetes is 2-5% [3-4]. Recent studies have indicated that the prevalence of gestational diabetes is increasing in all ethnic groups, rising by about 40% from 1989 to 2002 [5-8]. The first trimester of pregnancy is accompanied by changes in insulin sensitivity and, as the embryo develops, insulin secretion is augmented due to insulin resistance. This resistance reaches its peak during the third trimester, what is caused by hormonal changes. The physiologic changes of pregnancy may result in gestational diabetes in individuals who are prone to it [9- 12]. Hence, pregnancy is considered to be a diabetogenic state and gestational diabetes is the most frequent metabolic disorder during this period [13-14]. Gestational diabetes is associated with increased complications and undesirable outcomes of pregnancy, and may result in long-term complications for both the mother and the newborn [15-17]. Early diagnosis of patients with gestational diabetes is of utmost importance, because appropriate therapy may minimize maternal and neonatal complications [9, 18-19]. Few studies have dealt with high hemoglobin levels and increased incidence of gestational diabetes [3, 17]. Although high level of maternal hemoglobin is erroneously considered to herald health and its impact on the outcome of pregnancy does not receive as much attention as that of anemia [15, 18, 20], there is considerable evidence in developed countries indicating that the complications of increased hemoglobin may be as detrimental, if not worse, as low hemoglobin levels [19, 21]. Some researchers, however, believe that high concentrations of maternal hemoglobin have never been definitely proven to be a risk factor for pregnant women [22].

Considering this controversial issue, we decided to conduct a study in order to determine the relationship between the hemoglobin levels during the first trimester of pregnancy with the incidence of gestational diabetes in women referred to the Milad Hospital, Tehran in 2010.

Method

This is an analytical, prospective, cohort study conducted with convenience sampling from October 2009 to August 2010. Sample size was determined as follows: 700 people with a confidence interval of 95%, relative accuracy of 25% and a probability of exclusion of 10%.

The Ethics Committee at the International Branch of Shahid Beheshti University of Medical Sciences approved of our study (license number 116/995). Once all the necessary authorizations were acquired, the researchers referred to the Milad Hospital, Tehran, in order to explain the nature and objectives of the study and to recruit 700 pregnant women who were referred to the pregnancy care clinics and fulfilled the inclusion criteria. All women gave their written informed consent. Data were collected using a questionnaire containing personal data and obstetric history. The validity and reliability of the questionnaire were assessed using content validity and test re-test, respectively. Researchers completed the questionnaires through interviews with the cases. Complete blood counts (CBC) were obtained from all cases to measure the hemoglobin level of the first trimester. In addition, glucose challenge test (GCT) with 50 g of glucose was performed as the national routine test for pregnant women in 24-28 weeks of gestational age. For those women who had blood sugar levels higher than 140 mg/dL on the GCT, oral glucose tolerance test (OGTT) was performed at the laboratory of the Milad Hospital in order to establish a diagnosis of gestational diabetes, and the results were extracted by the researchers and recorded on data sheets.

Based on hemoglobin level, the samples were categorized in three groups of Low (<1.1 g/L), Normal (1.1-1.24 g/L) and High (≥1.25 g/L) [20].

All cases were followed up to the delivery due to developing gestational diabetes and the supplements, duration of intake and their types were recorded on each visit. The inclusion criteria were: a pregnant woman with a single fetus, aged 18-35 years with a gestational age of 1-13 weeks (calculated using the first day of the last regular menstruation or a sonography report during the first trimester), a parity of 3 or less, lack of known systemic diseases, and lack of gestational diabetes during previous pregnancies.

The Carpenter and Coustan criteria were used for diagnosing diabetes – fasting blood sugar of 95 mg/dL, 1-hour, 2-hour, and 3-hour blood sugar levels of 180, 155, and 130 mg/dL, respectively, following oral consumption of 100 g of glucose).

The researcher and 3 trained colleagues determined the type of delivery, gestational age and neonatal weight in the labor room and recorded the information on data sheets. The reliability of data measurement and recordings was assessed by 4 midwives using the inter rater consistency.

The exclusion criteria were: development of known fetal anomalies, abortion, stillbirth, consumption of alcohol, cigarettes or non-routine drugs during the present pregnancy or receiving pregnancy care or tests in other centers. Hemoglobin levels were measured by a laboratory expert at the laboratory of the Milad Hospital by flow cytometry on a Sysmex XT 1800i cell counter (Adons Electronics, Japan). Blood sugar was measured using the GOD/PAP method and kits prepared by ParsAzmoon (licensed by Germany) on Hitachi 902 instruments manufactured in Japan. All the instruments were calibrated every morning by a laboratory expert and their accuracy and reliability were ascertained. Data analysis was performed using the SPSS software version 18 with statistical tests of Kruskal-Wallis, chi-square, one-way ANOVA, relative risk and logistic regression model. The confidence interval and level of significance were 95% and <0.05, respectively.

Results

From the 700 women who entered our study, a total of 100 were excluded due to lack of compliance (16 cases), abortion (15 cases), intrauterine fetal demise (9 cases), oligohydramnios (36 cases), polyhydramnios (4 cases), placenta previa (9 cases), placental abruption (8 cases), and neonatal anomalies (3 cases), thus leaving 600 women for investigation.

The demographic and obstetric characteristics of our cases are summarized in Table I: 343 (57.2%) of the patients fell in the age range of 25-30 years. Their mean age was 27.28 years, with a standard deviation of 3.94. 419 (69.8%) of the study participants had intermediate/high school education and 502 (83.7%) were housewives. 289 (48.2%) were primigravidas. BMI during the first trimester was within the normal range (19.8-26 kg/m^2) for 326 (54.3%) of the women. 516 (86%) did not have a history of abortion and 332 (55.3%) did not have a history of delivery. Analysis of the different groups (in terms of hemoglobin levels) did not indicate any significant differences among them regarding the above variables, as well as the type and duration of complement intake in pregnancy (p>0.05).

As Table II depicts, 49 (8.2%) of all cases developed gestational diabetes, among which 41 (83.67% of those afflicted) were in the High group (hemoglobin levels of 1.25 and higher). Using the chi-square test, a statistically significant relationship was discovered between high hemoglobin levels during the first trimester of pregnancy and developing gestational diabetes (p=0.001). The relative risk of developing gestational diabetes was 3.94 times higher for the High group compared to the Normal group (CI=1.74-8.95), while it was 1.03 times higher for the Low group compared to the Normal group (CI=0.12-8.17). Having performed the Bonferroni correction, the chi-square test indicated a significant difference between the High and Normal hemoglobin groups; i.e. gestational diabetes occurred more frequently in the High hemoglobin group (p<0.001). Comparison of Low and Normal hemoglobin groups with chi-square test failed to indicate any significant difference in terms of the occurrence of gestational diabetes (p=0.3).

Moreover, comparing the High and Low hemoglobin groups with chi-square test indicated a significant difference between the two groups in terms of the development of gestational diabetes (p=0.008). The incidence of gestational diabetes was 8.2% in our study, with confidence interval of 5-10%.

Table I. Demographic and obstetric characteristics of study cases.

Hemoglobin (g/L)					
Group	**<1.1 n(30)**	**1.1-1.24 n(217)**	**≥1.25 n(353)**	**Statistical Test**	**p value**
Age	28.23± 4.1	27.01 ±3.86	27.32± 3.97	One way ANOVA	NS
Education (Intermediate/High School)	(66.7%)	(74.7%)	(67.1%)	Kruskall-Wallis	NS
Occupation (Housewife)	11 (36.7)	78 (35.9)	123 (34.8)	Chi-square	NS
Number of Pregnancies	1.83± 0.69	1.7± 0.69	1.58± 0.67	Kruskall-Wallis	0.03
Number of Deliveries	0.7± 0.59	0.55± 0.61	0.44± 0.58	Kruskall-Wallis	0.01
Body Mass Index in First Trimester	24.31± 3.94	24.87± 4.4	25.11± 4.39	One way ANOVA	NS
Body Mass Index in Third Trimester	29.41± 3.87	29.56± 4.15	30.02± 4.17	One way ANOVA	NS

Table II. Distribution of absolute and relative frequency of pregnant women referred to the Milad Hospital in three hemoglobin groups and occurrence of gestational diabetes in 2010.

Hemoglobin (g/100 mL)				
Group	**<11**	**11-12.4**	**≥12.5**	**Total**
Gestational Diabetes	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Yes	29 (96.7)	210 (96.8)	312 (88.4)	551 (91.8)
No	1 (3.3)	7 (3.2)	41 (11.6)	49 (8.2)
Total	(100) 30	(100) 217	(100) 353	(100) 600
RR* (CI 95%)	1.03(0.12-8.71)	1 (Reference)	3.94(1.74-8.95)	

* Relative risk

Table III. Risk factors for gestational diabetes using logistic regression model

Indices Related Factors	RR	p value	Confidence Interval
Hemoglobin	1.76	0.001	1.26-2.46
Duration of Iron Intake during Pregnancy	1.37	0.03	1.02-1.84
Duration of Calcium Intake during Pregnancy	0.95	0.5	0.83-1.1
Fasting Blood Sugar in First Trimester	1.03	2	1.01-1.05
Fasting Blood Sugar in Second Trimester	1.05	0.001	1.03-1.08
Body Mass Index in First Trimester	1.05	0.4	0.92-1.2
Body Mass Index in Third Trimester	1.07	0.04	1-1.14

A ROC curve was used to determine the appropriate cut-off point for hemoglobin test during the first trimester of pregnancy. As Diagram 1 depicts, the ideal cut-off point for hemoglobin test of the first trimester was calculated to be 12.52 g/dL with the area under the curve equal to 0.67. According to the data of this table, first trimester hemoglobin has a sensitivity of 83.67%, specificity of 47.73%, and positive predictive value of 12.46% and negative predictive value of 97.05% for early diagnosis of gestational diabetes.

Risk factors for gestational diabetes were assessed using the logistic regression model. As Table 3 illustrates, our investigation indicates that for every 1 unit rise in hemoglobin level of the first trimester, there is a 1.76-fold increase in the risk of developing gestational diabetes. (Table III).

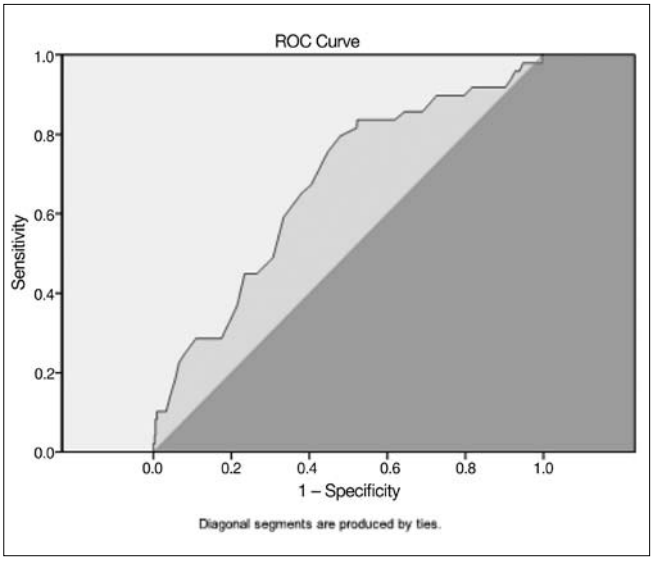

Figure 1. ROC curve for the first trimester hemoglobin in early diagnosis of gestational diabetes.

Discussion

The present study indicated that high levels of hemoglobin in the first trimester of pregnancy and progression of pregnancy are significantly related. Phaloprakarn et al., (2008) reported similar results (CI=2.0-7.1, RR=3.8) [3], as well as Lao et al., (2002) whose results were similar to those of our study (CI=1.08-2.78, RR=1.73) [22]. The findings of a study by Vasegh et al., indicated that high hemoglobin levels before 14 weeks of gestational age may be considered to be a risk factor for developing gestational diabetes, what may be accounted for by increased amounts of iron stored in these women.

On the other hand, Gungor et al., (2007) [23] did not observe a significant relationship between high hemoglobin levels of the first trimester and gestational diabetes. However, many confounding variables were not controlled in the Gungor

study and hemoglobin levels were assessed in 28-30 weeks of gestations, when the iron supplements received during the second half of pregnancy had probably obscured the true difference of hemoglobin level among the groups. Our study controlled the confounding variables appropriately and assessed hemoglobin levels during the first trimester.

The probable mechanism accounting for the relationship between excessive hemoglobin and development of gestational diabetes is that the increased iron may affect insulin synthesis and secretion, as well as promote lipid oxidation, leading to a decreased glucose uptake and consumption in muscles and increased glucose synthesis in the liver. This condition creates a state of insulin resistance and makes the pregnant woman more prone to gestational diabetes. Furthermore, increased iron stores influence the oxidative stress and may result in lipid peroxidation and tissue injury through creation of highly toxic free radicals such as superoxide and hydroxide anions. Oxidative stress increases ferritin so that the higher levels of ferritin may neutralize free iron and reduce the oxidative injury. It appears that tissue deposition of iron promotes insulin resistance, increasing ferritin and establishing a vicious cycle of iron overload which renders the patient prone to glucose tolerance disorder. Iron deposition may simultaneously lead to subclinical hemochromatosis, thus compromising pancreas [24, 25].

It seems that high levels of hemoglobin during the first trimester may be a warning sign for development of gestational diabetes over the next weeks of pregnancy.

Occurrence of certain medical conditions, such as abortion before 20 weeks of gestation and the consequent exclusion of the person was among the limitations of the present study. The main advantage of the present study is its prospective methodology, with elimination of known risk factors and control of confounding variables for the development of gestational diabetes. In order to enhance the reliability and validity of test results, all tests were performed at the laboratory of the Milad Hospital by one person and with one instrument. As was mentioned in the method section, reliability and validity were assessed. Discovering a new risk factor for early diagnosis of gestational diabetes may contribute to early detection of pregnant women at risk. Moreover, timely treatment or referral of patients afflicted may reduce maternal, fetal and neonatal complications.

Conclusion

It appears that hemoglobin level during the first trimester of pregnancy may be considered as a selective screening factor for gestational diabetes.

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