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The Prediction of Preeclampsia and Its Association With Hemoglobin and Hematocrit in the First Trimester of Pregnancy

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Abstract

Background: Hypertensive disorders in pregnancy are one of the most serious complications and their early diagnosis is one of the most important goals of prenatal care.
Objectives: The objective of this study was to determine the association of first trimester Hemoglobin (Hb) and Hematocrit (Hct) with preeclampsia.
Patients and Methods: This descriptive-analytic, prospective study was performed on 1376, less than 12 weeks of gestation, singleton pregnancies, visited for their prenatal care in health and medical clinics of the Qazvin province during years 2013 and 2014. At first, demographic data were recorded in a questionnaire and then all pregnant cases were referred to one of the three reference laboratories for their first trimester routine tests. After hemoglobin and hematocrit date collection, women were categorized in three groups: Hb $<$ 11, Hb $\geq$ 12.49 and 11 $\leq$ Hb $<$ 12.49, and based on Hct, two groups: Hct $<$ 38% and Hct $\geq$ 38. The analysis was done by χ^2 (chi-square) and t-test with SPSS 16. Receiver operator characteristics (ROC) curve and Youden's index were utilized for finding the optimum cut off for each. P values of $<$ 0.05 were considered significant.
Results: Preeclampsia incidence was 5.1% in our study. Mean Hb was 12.38 $\pm$ 1.69 g/dL in the preeclampsia group and 11.8 $\pm$ 1.18 in the non-preeclampsia group, and mean Hct was 37.74 $\pm$ 5.15% in the preeclampsia group and 35.45 $\pm$ 3.58% in the preeclampsia group and 35.45 $\pm$ 3.58% in the non-preeclampsia group, (P = 0.016) (P = 0.001). Furthermore, 43 out of 68 patients with preeclampsia (10.9%) had high hemoglobin (Hb $\geq$ 12.5 g/dL). We found a significant association between the 1st trimester Hb, Hct and preeclampsia (P $<$ 0.001, P $<$ 0.001). Assessed relative risk in high Hb group was 5.82 (3.14 - 10.18: CI 95%), and likewise 7.41 in high Hct group (Hct $>$ 38%) (4.41 - 12.044: CI 95%). According to Youden's Index, optimum cut-off for 1st trimester Hb was 12.65 and for Hct, this was 38.05%.
Conclusions: The association of the 1st trimester high Hb and Hct with preeclampsia was revealed in this study, therefore it could be used as a prediction factor for early preeclampsia diagnosis.

Keywords: Preeclampsia, First Trimester, Hemoglobin, Hematocrit

1. Background

Hypertensive disorders complicate 5% - 10% of all pregnancies, and together they are one member of the deadly triad-along with hemorrhage and infection that contributes greatly to maternal morbidity and mortality (1, 2). Annual maternal mortality from preeclampsia is 75000, the etiology of which has remained unresolved in spite of intensive research (3). The world health organization reported that 16% of maternal deaths have been due to hypertensive disorders in developed countries (4). Preeclampsia universal prevalence is 5% - 7% and up to 20% in developed countries (5). The incidence is markedly influenced by race and ethnicity and thus by genetic predisposition (1). Other factors include environmental, socioeconomic and seasonal influences (6). The prevalence is reported 6.5% in Iran (7-9). The incidence of preeclampsia was 5% in white, 9% in Hispanic and 11% in African American women as indicated by a study in 2012 (10). The incidence was reported as 3% - 10% among nulliparous populations whereas variable in multiparas by a study in 2014 (11). The etiology has remained unsolved, although the latent pathophysiologic changes are subtle at first, then speed up along pregnancy and finally present clinically (1). In spite of its unknown etiology, documents have demonstrated the possibility of angiogenic factors imbalance (12, 13). Preeclampsia is a multisystemic conceptual disorder with endothelial dysfunction (14). Increased blood concentration, has been a diagnostic clue for preeclampsia diagnosis for a century (15). Endothelial cell activation causes interstitial plasma leakage and generalized vasoconstriction through

which, blood concentration increases (1). There are limited studies, with different results and restrictions about the association of 1st trimester blood indices and preeclampsia. On the other hand, early diagnosis is an important goal in prenatal care, however there is no reliable predictive test. The variability of clinical, biophysical and biochemical predictive tests for preeclampsia, reflects their low accuracy. Phaloprakarn's study, revealed 1st trimester Hb and Hct increase in preeclampsia (16). Another study in 2013, demonstrated the association of 1st trimester Hb and Hct with preeclampsia incidence (17). However, there are some other researches, presenting this association with 1st trimester anemia and attenuated Hb and Hct (18, 19). Other researches have assessed this relationship during the 2nd and 3rd trimester of gestation (20, 21).

2. Objectives

There is no reliable, accurate and cost-benefit screening test for preeclampsia and the vast amount of strategies for its prevention or modification have not been effective. Since pregnancy volume expansion and ferrous supplementation have not begun in the 1st trimester, Hb level in this time is more reliable than in the 2nd and 3rd trimester. Likewise, a low cost, accessible and easy test like complete blood count (CBC) is necessary in the 1st trimester. Therefor we would rather study the association and predictive value of 1st trimester Hb and Hct for preeclampsia prediction.

3. Patients and Methods

This descriptive-analytic and prospective cohort study was performed from September 2013 to May 2014 at five medical centers of the Qazvin province. Sample size was assessed as 1500 cases with 95% confidence interval, 25% relative accuracy and 10% elimination probability.

Obtaining Qazvin university ethics committee permission and consent from each case, 18 - 40 year-old singleton, less than 12-week of gestation parous mothers were visited for their 1st prenatal care and included in the study by accessible sampling. They were eliminated if hemoglobinopathies (thalassemia and sickle cell), alcohol abuse, smoking, any cardiac disorders, chronic hypertension, renal or pulmonary disorders and diabetes were present.

At first, demographic data, including maternal age, gestational age, height, education and parity were recorded by a midwife in a questionnaire prepared by the researcher at the medical center. The questionnaire's validity and reliability were assessed by content validity and retesting, respectively. Pregnant mothers were referred to particular university-controlled laboratories in Qazvin province. If this was done somewhere else, they were omitted from the research. Hemoglobin (Hb) and Hematocrit (Hct) recording in the questionnaire were done after the tests. The mothers were followed up for prenatal care according to the protocol released by the ministry of medicine and health. Ferrous and multivitamin supplementations were prescribed in each prenatal visit and finally the mother was referred for termination to Kowsar hospital, and if she were terminated somewhere else, she would be eliminated from the study. Other elimination factors included: intrauterine fetal death, fetal anomaly, amniotic fluid disorders, preterm labor, placental abruption and placenta previa. If she had to be terminated, due to high blood pressure and preeclampsia, obstetrical data were recorded in the questionnaire. Preeclampsia diagnosis was made according to William's obstetrics 2014 criteria (systolic blood pressure more than 140 and diastolic more than 90 mmhg with proteinuria, which is an objective index, reflecting the vast endothelial damage by the disorder, determined by more than 300 mg, 24 hours proteinuria or urinary creatinine ratio of 0.3 or more, or more than 30 mg proteinuria in a random sample (1, 22)).

As in the study of Phaloprakarn, mothers were categorized in three groups after data collection: $Hb < 11$, $Hb \geq 12.49$ and $11 \leq Hb < 12.49$, and based on Hct, two groups were made $Hct < 38\%$ and $Hct \geq 38$ (9). Data analyses were performed by SPSS 16, chi-square (χ^2) and T-test. Logistic regression was used for determining preeclampsia relative risk. receiver operator characteristics (ROC) curve and Youden's Index were utilized to find the cut-off. P values of < 0.05 were considered significant.

4. Results

As shown in Figure 1, from the total of 1500 participants, 126 were eliminated and finally 1376 were studied.

The mean age was: 25.64 ± 5.58 years. In our research, preeclampsia incidence was 5.1%, mean Hb 11.88 ± 1.22 g/dL and mean Hct $35.58 \pm 3.67\%$. Overall, there were 660 nulliparous women, among which only 32 developed preeclampsia, and amongst 713 (51.9%) multiparous women, 36 developed the disorder. This difference was not significant. As a matter of education, 836 (60.1%) had not graduated from high school, 443 (32.9 %) had high school diploma and 95 (7.1%) had university degrees, which presented no significant difference in developing preeclampsia. Mean body mass index was 24.68 ± 4.50 kg/m^2; eight participants (11.8%) were lower than 18.5 kg/m^2, most of them (31 cases) were placed in the higher than 25 kg/m^2 group.

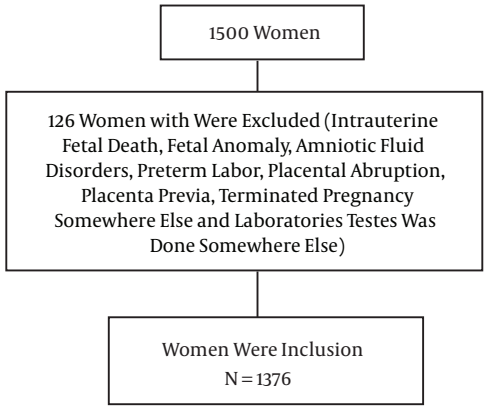

Figure 1. Participation Flowchart

However no significant difference in developing preeclampsia was found among them (Table 1).

Table 1. Demographic Characteristics of the Study Population by Preeclampsia

Variables	Preeclampsia N = 68 (5.19%)	No Preeclampsia N = 1308 (94.9%)	P Value
Age, y	25.89 ± 5.48	25.63 ± 5.6	0.705
Education			0.448
Under diploma	44 (66.7%)	792 (59.7%)	
Diploma	17 (25.8%)	426 (33.3%)	
University	5 (7.6%)	90 (7%)	
BMI, Kg/m^2			0.136
< 18.5	8 (11.8%)	79 (6%)	
18.5 - 24.9	29 (42.6%)	663 (50.7%)	
> 25	31 (45.5%)	566 (44.3%)	
Parity			0.901
Nulli-parous	32 (47.1%)	628 (48.1%)	
Multi-parous	36 (52.9%)	677 (51.9%)	

Mean Hb was 12.38 ± 1.69 g/dL in the preeclampsia group and 11.8 ± 1.18 g/dL in non-preeclampsia group, with a significant difference (P = 0.016).

Among 395 participants in Hb > 12.5 g/dL group, 43 (10.9%) developed preeclampsia. χ^2 test, revealed a significant association between 1st trimester Hb and developing preeclampsia (P < 0.001) (Table 2).

Estimated relative risk in high Hb group, compared with normal Hb group, was 5.82 (3.14 - 10.78; CI 95%).

Mean Hct was 37.74 ± 5.15% in the preeclampsia group and 35.45 ± 3.58 % in the preeclampsia group and 35.45 ± 3.58 % in the non-preeclampsia group (P = 0.001). Comparing the two groups, relative risk was estimated as 7.41 (4.41 - 12.44; CI 95%).

Comparing high and normal Hb group with Bonferroni's correction, a significant difference was indicated (P = 0.004), although Fisher's exact test, could not demonstrate a significant difference amongst the two groups in developing preeclampsia (P = 0.091). The logistic regression model revealed, 1.43 increment, per one g/dL Hb increase in developing preeclampsia (P = 0.001) (1.15 - 1.79, OR: 1.43; CI 95%).

We found no association between age, BMI and parity with preeclampsia in this model.

The ROC curve has been utilized to determine an appropriate cut-off for 1st trimester Hb and Hct. On the basis of Youden's index, it was 12.65 g/dL for Hb. As indicated by Table 3, with this cut-off, 1st trimester Hb test sensitivity was calculated as 60% specificity 78%, positive predictive value 13.07% and negative predictive value 97.30%, to predict preeclampsia (Figure 2).

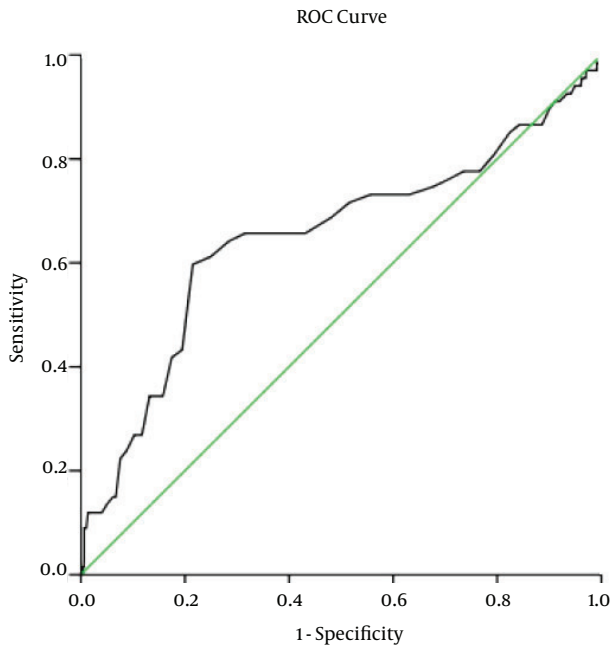

Figure 2. Receiver Operator Characteristics Curve of Hemoglobin During the First Trimester of Pregnancy in Diagnosis of Preeclampsia (Area Under the Curve 0.65)

χ^2 test demonstrated significant difference in 1st trimester Hct in the preeclampsia group, compared with the non-preeclampsia group (P < 0.001). Utilizing the ROC curve (Figure 3), the appropriate cut-off for Hct was obtained as 38.05%, therefore its sensitivity was calculated as

Table 2. Frequently Distribution of the Studied Population in Three Groups of Hemoglobin and Preeclampsia

Preeclampsia	Hb < 11 N = 228	11 < Hb < 12.49 N = 681	Hb > 12.5 N = 395	P Value
Yes	11 (4.4)	14 (2.1)	43 (10.9)	< 0.001
No	218 (95.6)	667 (97.9)	352 (89.1)	< 0.001

64%, specificity 80%, positive predictive value 15.14% and negative predictive value 97.65%, in predicting preeclampsia (Table 3).

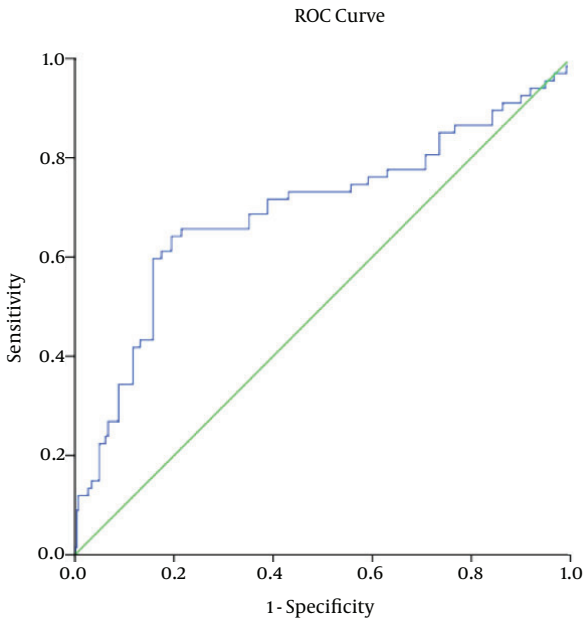

Figure 3. Receiver Operator Characteristics Curve of Hematocrit During the First Trimester of Pregnancy for the Diagnosis of Preeclampsia (Area Under the Curve 0.69)

Table 3. Distribution of the Study Population by Preeclampsia and Cutoff Point of Hemoglobin and Hematocrit

Variables	Preeclampsia	No preeclampsia	P Value
Hemoglobin			< 0.001
< 12.6	27 (40.3)	971 (78.5)	
> 12.6	40 (59.7)	266 (21.5)	
Hematocrit			< 0.001
< 38.05	24 (35.8)	996 (80.5)	
> 38.05	43 (64.2)	241 (19.4)	

5. Discussion

In this study, preeclampsia incidence was 5.1%. However, this incidence was 6.7% in Safavi's study on 700, 18 - 35 years-old singleton pregnant women during year 2011 (9). This study revealed a significant difference between mean 1st trimester hemoglobin in preeclampsia and non-preeclampsia group ($P < 0.001$). The same was also demonstrated in Safavi's study ($P = 0.002$) (9). In a research about high 1st trimester Hb influence on pregnancy outcome in 2008, Phaloprakarn suggested that it could be significantly associated with preeclampsia ($P < 0.001$) (16). Bouzari's study was about the influence of 1st and 2nd trimester Hb on preeclampsia, which was found to be higher in the high Hb group. (Mean: 12.82 $\pm$ 1.2 g/dL), compared with the normal Hb group (mean: 12.3 $\pm$ 1.39 g/dL) ($P = 0.016$) (17). Aghamohamadi studied high 1st trimester Hb as a risk factor for preeclampsia, in 2011, where there were 14 patients with preeclampsia (2.75%) in the normal Hb group and 21 (4.2%) in the high Hb group, with a significant difference ($P = 0.045$) (23). All studied mentioned above, are compatible with our research. This study also demonstrated a higher Hct in the preeclampsia group (37.74 $\pm$ 5.15) compared with lower Hct in the non-preeclampsia group (35.45 $\pm$ 3.58), with a significant difference ($P < 0.001$). In Safavi's study mean Hct in the preeclampsia group was 39.06 $\pm$ 2.98 and in the non-preeclampsia group 37.77 $\pm$ 3.52. χ^2 test showed a significant association between high 1st trimester Hct and preeclampsia development ($P = 0.001$)(9). Bouzari's study also revealed higher mean 1st trimester Hct (37.30 $\pm$ 3.70) in the preeclampsia group compared to the control group (36.54 $\pm$ 3.45), with a significant difference ($P = 0.021$) (17). Both of these studies were in agreement with our study. In this research, relative risk of developing preeclampsia in the higher Hb group (1st trimester Hb $\geq$ 12.5 g/dL) compared to the normal Hb group was calculated as 5.82 (3.14 - 10.78), which is compatible with the calculated relative risk in Phalorakarn's study [3.8; CI: 95%, (2 - 7.1)] (16) and that of Safavi's study [4.52; CI: 95% (1.74 - 11.74)](9). Using logistic regression analysis, Aghamohammadi demonstrated increased preeclampsia relative risk [2.46; CI: 95% (1 - 6.9)] in the higher Hb group (23). This study determined the relative risk of developing preeclampsia as 7.4 CI 95%, (4.41 - 12.44) in the higher Hct group (Hct $\geq$ 38%), which was calculated [3.54;

CI: 95%, (1.65 - 7.58) in Safavi's study (9). Hemoglobin and Hct measurement are obtained from fresh whole blood, which could be influenced by plasma volume with hydration or dehydration. In fact, for calculating the ratio of erythrocyte volume to whole blood, Hct would be a more valuable parameter than Hb (19). Inspite of our research, Goudarzi presented more preeclampsia development with lower 1st trimester Hb in 2012 (P = 0.024) (20). The result of Karaflahin's study (24) was the same as Goudarzi's (20), therefore they recommended the necessity of family planning preconception evaluation to reduce unfavorable pregnancy outcomes (24). Jack's study revealed no association among blood indices, and pregnancy outcome, likewise there would be no significant difference in HB and Hct of any of the three trimesters in relation to preeclampsia (25). Hemoglobin and Hct increment in preeclampsia could be the result of compensatory mechanisms of deoxygenation in plasma as a result of placental secretion (21). Utilizing the ROC curve, our research revealed Hb cut-off of 12.26 g/dL in the 1st trimester, which could be a predictor of preeclampsia with 60% sensitivity, 78% specificity, 13.07% positive predictive value and 97.30% negative predictive value. With Safavi's study, the cut-off point was 12.5 g/dL with 85% sensitivity, 43.03% specificity, 9.63% positive predictive value and 97.57% negative predictive value in preeclampsia prediction, which is compatible with our results (9). Our study showed the 1st trimester Hct cut-off of 38.05%. With 64% sensitivity, 80% specificity, 15.14% positive predictive value and 97.65% negative predictive value in predicting preeclampsia, likewise Mello's study was in agreement with ours in reporting 1st trimester Hct role in early preeclampsia prediction with 63% sensitivity, 90% specificity 36% positive predictive value and 92% negative predictive value (26). Safavi's study calculated 1st trimester Hct cut-off of 38% with 77.5% sensitivity, 50.7% specificity, 10.1% positive predictive value and 96.95% negative predictive value in preeclampsia prediction. The two mentioned studies were compatible with ours. It appears that 1st trimester Hb and Hct could be an alarming sign for developing preeclampsia in the next conception weeks, therefore by early high risk population detection, prenatal care could be managed more frequently and more accurately and more precisely in order to prevent fetal, infantile and maternal complications. This research demonstrated the association of 1st trimester Hb and Hct increment with preeclampsia development. According to the results, Hb $\geq$ 12.5 g/dL and Hct $\geq$ 38.05 in the 1st trimester indicate high risk and necessitate, more frequent prenatal care. More widespread researches, including the association of routine prenatal tests and supplements like iron, calcium, magnesium and zinc with preeclampsia is recommended.

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Footnotes

Authors' Contribution: Hamideh Pakniat, study design and analysis of data and SPSS software application usage; Mahdi Azoor, data collection; Atie Bahman, academic writing; Farideh Movahed, manuscript submission.

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