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THE ASSOCIATION BETWEEN FETAL HEMOGLOBIN AND PREECLAMPSIA

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ABSTRACT

Background: Preeclampsia is a leading cause of maternal morbidity and mortality worldwide, and early diagnosis is essential to reduce adverse maternal and neonatal outcomes. Fetal hemoglobin (HbF) has been proposed as a potential biomarker involved in the pathogenesis of preeclampsia through its effects on placental and maternal vascular function. **Aim of study:** To evaluate the association of maternal serum levels of fetal hemoglobin in the diagnosis of preeclampsia and its severity. **Patients and methods:** This case-control study was conducted in the Obstetrics and Gynecology Department at Baghdad Teaching Hospital from 1 January to 1 November 2024 and included 100 pregnant women between 20 and 36 weeks of gestation. Participants were divided into two groups: 50 women with preeclampsia (23 mild/moderate, 27 severe) and 50 normotensive controls. Maternal serum HbF levels were measured and compared between groups, and diagnostic performance was evaluated using different cut-off values. **Results:** Mean serum HbF levels were 1.25 ± 0.19 µg/ml in severe preeclampsia, 0.87 ± 0.23 µg/ml in mild/moderate preeclampsia, and 0.42 ± 0.17 µg/ml in controls ($p < 0.001$). An HbF cut-off of 0.75 µg/ml for diagnosing preeclampsia yielded a sensitivity of 84%, specificity of 80%, positive predictive value (PPV) of 80.7%, and negative predictive value (NPV) of 83.3%. For severe preeclampsia, a cut-off of 0.85 µg/ml showed a sensitivity of 74.1%, specificity of 69.9%, PPV of 85.7%, and NPV of 75.8%. **Conclusion:** Elevated maternal serum fetal hemoglobin is significantly associated with both the occurrence and severity of preeclampsia, and HbF appears to be a promising, simple, and accessible biochemical biomarker for the diagnosis and risk stratification of preeclampsia.

INTRODUCTION

Preeclampsia is the second-most common cause of maternal death globally and raises the risk of stroke, eclampsia, and organ failure. Preterm labor, intrauterine growth restriction, low birth weight, and stillbirth are examples of serious adverse outcomes.[1][2] Early diagnosis of preeclampsia, is key factor in improving adverse neonatal and maternal outcomes by earlier referral to specialized care; and hence, earlier initiation of treatment (e.g. aspirin and LMWH), and maternal education regarding lifestyle and dietary recommendations.[3][4] The diagnosis is based on three cornerstones: maternal risk factors, biophysical parameters, and biochemical parameters.[5] The diagnosis of PE is based on three cornerstones: maternal risk factors, biophysical parameters, and biochemical parameters.[6] Certain biomarkers, such as C-reactive protein, plasma fibrinogen, and CA-125 were shown not only to be predictive of preeclampsia, but also correlated with its severity.[7]

Fetal hemoglobin (HbF) has been implicated in the pathogenesis of preeclampsia a hypertensive disorder of pregnancy characterized by maternal endothelial dysfunction. While the exact mechanisms remain under investigation, the role of HbF is increasingly recognized due to its influence on placental function and maternal vascular health.

Recently studies have shown that free Hb is a potential key factor in the pathogenesis of preeclampsia and suggests a method for its prediction/diagnosis and a possible treatment, which based on the recent findings on the involvement of fetal hemoglobin (HbF) and the heme and radical scavenging protein A1M (alpha-1-microglobulin). Gene and protein profiling studies have

independently shown that increased amount of free HbF (extra cellar unbound HbF) is accumulated in the vascular lumen of placenta. The placenta is an extra-medullary hematopoietic organ providing the fetus with hematopoietic stem cells throughout gestation, what stimulate the production of free HBF in the placenta has not been clarified; but recent studies have shown that the inflammation seen in preeclampsia can induce hematopoiesis.[8]

The present study aims to evaluate the utility of fetal hemoglobin as a biochemical parameter in the diagnosis and severity classification of PE.

PATIENTS AND METHODS

Study Design and Setting

This is a case-control study conducted in the Baghdad Teaching Hospital's Obstetrics and Gynecology Department from first of January to first of November, 2024.

Research Specimen

Two groups of 100 pregnant women in their second and third trimesters (20–36 weeks of gestation) were included in the study.

Inclusion criteria were pregnant women with a single viable fetus at a gestational age of 20–36 weeks.

Exclusion criteria were the following.

1. Twin or higher-order pregnancies.
2. Past medical history of other conditions (autoimmune diseases, cancer, thyroid, kidney, liver, hematological disorders, epilepsy, diabetes and chronic hypertension).
3. History of ovulation induction, in vitro fertilization, or infertility.
4. History of blood transfusion or other blood component transfusion during the current pregnancy.
5. The patient who gave birth to a child with congenital anomalies (e.g., chromosomal abnormalities or birth malformations).
6. Smoking
7. Presentation with eclamptic fits.
8. Intrauterine fetal demise.
9. History of antepartum hemorrhage (APH).
10. External cephalic version

Approval and ethical consideration

Administrative permissions were granted by the Council of the Iraqi Board of Medical Specialization, with approval from the Obstetrics and Gynecology Department of Baghdad Teaching Hospital. Before data collection, verbal consent was obtained from all participants. Data were collected anonymously, with names replaced by identification codes.

Diagnostic criteria for preeclampsia

The diagnosis of PE was done according to the ACOG criteria (Practice bulletin no. 222).[9]

An among of 8ml of venous blood was drawn from each patient, the sample was separated as the following.

Three milliliter was drawn to serum separator tube (SST) and allow samples to clot for two hours at room temperature or overnight at 4°C before centrifugation for 15 minutes at 1000 ×g. the supernatant serum was removed and assay immediately or aliquot and store samples at -20°C or -80°C. Avoid repeated freeze-thaw cycles using Human fetal hemoglobin (HbF) ELISA Kit (Catalogue no. CSB-E09598h).

Five milliliters were collected in separate tubes for biochemical parameters (Hb, platelet count, ALT, AST, blood urea, serum creatinine, serum uric acid, LDH, and RBS).

Statistical analysis

Data entry was done using Microsoft Excel 2019. Data was recorded into different quantitative and qualitative variables for the purpose of analysis. Analysis was done using statistical package for social sciences (SPSS version 26). Data was summarized using measures of frequency (mean), dispersion (standard deviation), tables and graphs. Independent sample t-test was used to test for statistical significance between continuous variables. Fischer's exact test was used for categorical variables. Analysis of variance (ANOVA) was used to compare the means between three groups. Post-hoc Tukey's test was used after ANOVA. A two-tailed p value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance. ROC analysis was conducted in order to evaluate the role of serum hemoglobin F as a biomarker for preeclampsia.

The study sample

The study included one hundred participants (50 cases and 50 controls).

Basic characteristics of the studied sample

No significant difference was detected between cases and controls regarding age, gravidity, parity and gestational age as shown in table (1).

Table 1: Basic characteristics of the studied sample.

Variable	Cases		Controls		P value
	Mean	SD	Mean	SD	
Age	30.2	7.31	29.4	8.5	0.508
Gravidity	4.8	3.3	5.1	3.4	0.268
Parity	2.8	2.5	3.3	2.5	0.233
GA	33.5	0.9	34.2	0.7	0.789

Distribution of preeclampsia cases according to severity

Among 50 cases of preeclampsia 27 (54.0%) cases had severe preeclampsia while 23 (46.0%) had mild, moderate preeclampsia as shown in Figure(1).

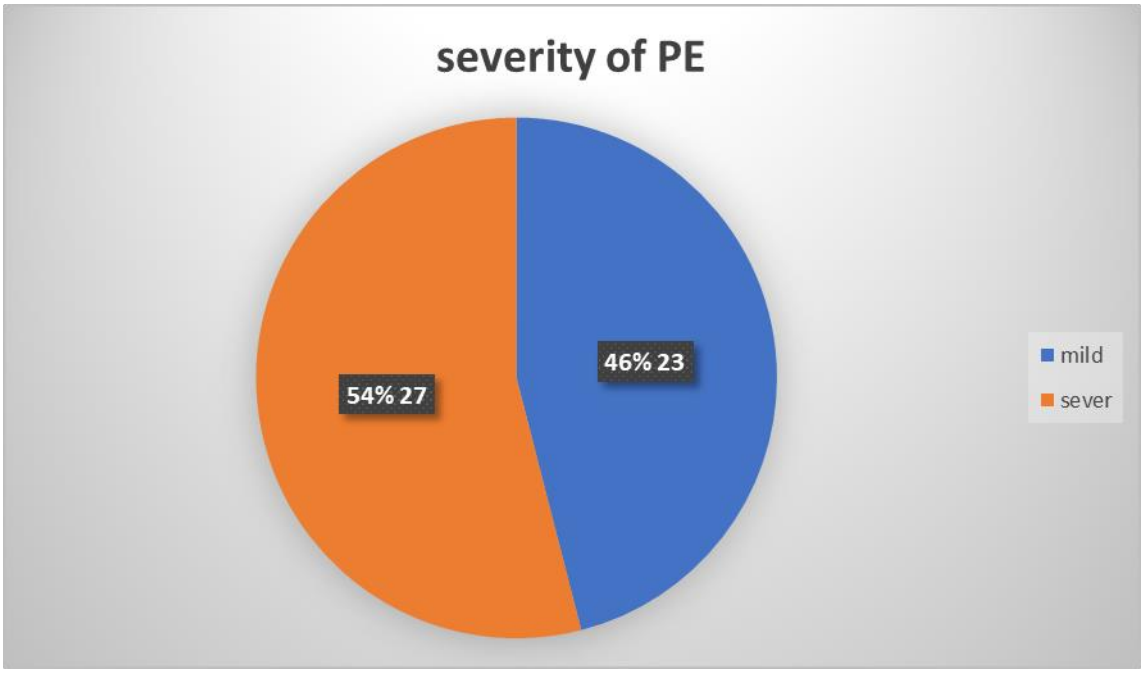

Figure (1): Distribution of preeclampsia cases according to severity.

Clinical and biochemical parameters of the studied sample

A statistically significant difference was detected between the 3 study groups regarding systolic and diastolic blood pressure, AST, ALT, serum creatinine, blood urea, urinary albumin, LDH, and platelet count as shown in table (2).

Table 2: Clinical and biochemical parameters of the studied sample.

Variables	Control	Mild	Severe	P value
	Mean ±SD	Mean ±SD	Mean ±SD	
Systolic blood pressure (mmHg)	117.3 ± 15.8	148.3 ± 19.3	167.8 ± 23.3	**<0.001**
Diastolic blood pressure (mmHg)	77.2 ± 11.4	103.5 ± 13.6	127.3 ± 26.5	**<0.001**
AST (IU/L)	38.5 ±8.99	43.04 ±9.41	45.27 ±9.10	**<0.001**
ALT (IU/L)	37.92 ±9.65	39.54 ±6.89	42.69 ±7.49	**<0.001**
Blood urea(mg/dl)	24.90 ±6.18	44.65 ±8.12	55.87 ±9.49	**<00001**
S. Creatinine (mg/dl)	0.53 ±0.37	0.96 ±0.42	1.23 ±0.49	**<0.001**
uric acid mg/dl	5.89 ±0.91	5.98 ±0.88	6.41 ±1.10	**<0.001**
Urinary albumin (++ or more)	3/50 (6.0%)	16/23 (69.5%)	25/27 (92.6%)	**<0.001**
LDH(IU/l)	192.08 ±37.56	301.47 ±58.45	498.11 ±78.30	**<0.001**
Platelet	163.90 ±66.21	142.45 ±67.11	121.56 ±68.58	**<0.001**

*ANOVA test. Post hoc Tukey analysis was significant between all groups.

Comparison of mean serum fetal hemoglobin values

Statistical comparison of mean serum fetal hemoglobin values revealed the following, Serum fetal hemoglobin levels were as the following: severe preeclampsia (1.25 ± 0.19), mild/moderate preeclampsia (0.87 ± 0.23), controls (0.42 ± 0.17). Statistical analysis revealed significant difference between all three groups.

Table 3: Comparison of mean serum Fetal hemoglobin values between cases with preeclampsia and controls.

Serum fetal hemoglobin (µg/ml)	Group			P value
	Severe preeclampsia	Mild/moderate PE	Control	
Mean ± SD	1.25± 0.19	0.87± 0.23	0.42 ± 0.17	<0.001

Association of Fetal hemoglobin with preeclampsia

The ROC analysis revealed that Fetal hemoglobin was significantly associated with preeclampsia (AUC = 0.808, P value <0.001); as shown in **Figure (3.2).** The optimum cut-off point with the highest (sensitivity + specificity) was determined to be 0.75 µg/ml as it had a sensitivity of 84%, specificity of 80%, PPV of 80.7%, NPV of 83.3%; as shown in **Table (4).**

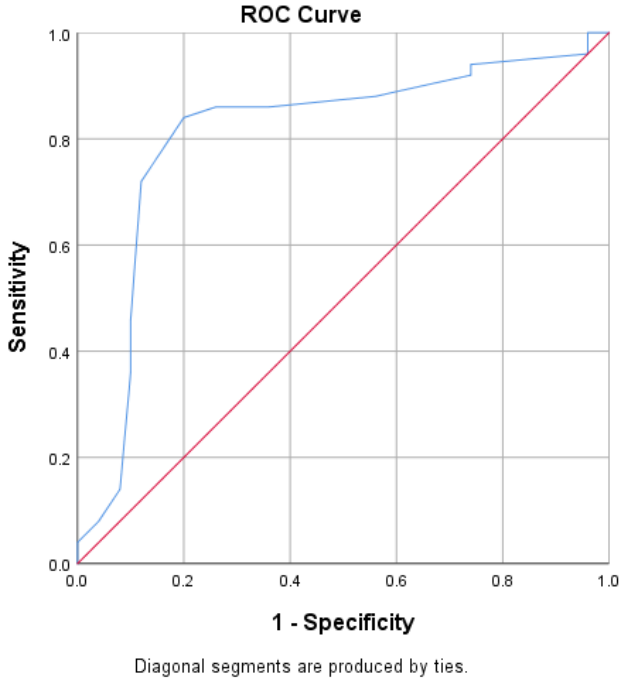

Figure (2): ROC analysis of association of fetal hemoglobin with preeclampsia.

Table (4): Accuracy of 0.75µg/ml as a cut-off point of Fetal hemoglobin in the differentiation between cases of preeclampsia and controls.

Fetal hemoglobin	Diagnosis		Total
	Preeclampsia	Controls	
≥0.75 (µg/ml)	42	10	52
<0.75 (µg/ml)	8	40	48
Total	50	50	100

Association of Fetal hemoglobin with severe preeclampsia

The ROC analysis revealed that Fetal hemoglobin was significantly associated with severe preeclampsia (AUC = 0.719, P value =0.001) as shown in **Figure (3.3)**. The optimum cut-off point with the highest (sensitivity + specificity) was determined to be 0.85(µg/ml); as it had a sensitivity of 74.1%, specificity of 69.9%, PPV of 85.7%, and NPV of 75.8%; as shown in **Table (5).**

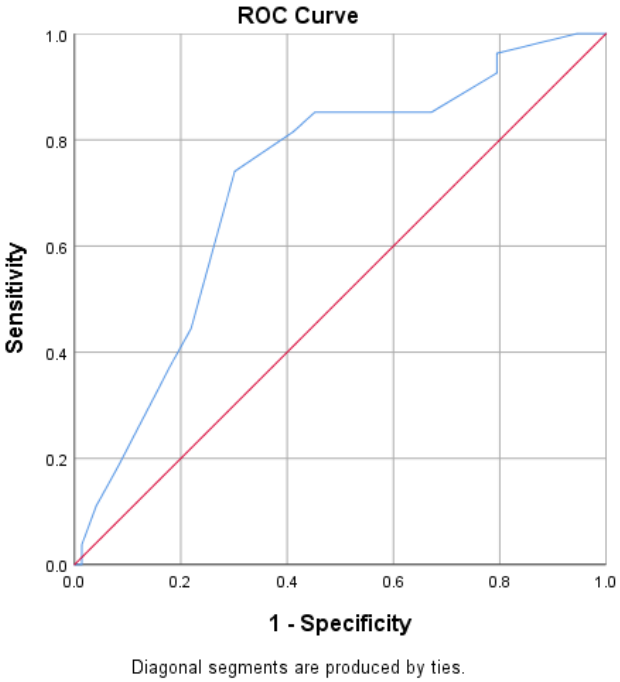

Figure (3): ROC analysis of association of Fetal hemoglobin with severe preeclampsia.

Table (5): Validity of 0.85 cut-off point of Fetal hemoglobin the differentiation between cases of severe preeclampsia and those with mild/ moderate preeclampsia/ controls.

Fetal hemoglobin	Group		Total
	Severe preeclampsia	Mild PE/ moderate PE/ controls	
≥ 0.85 µg/ml	36	6	42
< 0.85 µg/ml	14	44	58
Total	50	50	100

Correlation between serum HbF values and markers of severity

A statistically significant positive correlation was detected between serum hemoglobin F and each of systolic, diastolic BP, blood urea and serum creatinine. whereas a significant inverse correlation was detected with platelet count as shown in Table (6).

Table 6: Correlation between serum HbF value and markers of severity of preeclampsia.

Parameters	r	P value
Systolic BP	0.63	<0.001
Diastolic BP	0.53	<0.001
AST	0.362	0.372
ALT	0.462	0.473
S. creatinine	0.184	0.005
LDH	0.262	0.342
Platelet	-0.493	<0.001

DISCUSSION

In the present study maternal age was (30.2 years ± 7.31 in cases group vs. 29.4 years ± 8.5 controls. p value = 0.508 without significant difference being detected between cases. This is in discordance with studies have consistently reported that advanced maternal age is a significant risk factor for preeclampsia. For instance a large study in Finland found that women over 35 years old had higher rates of preeclampsia and associated complications, including higher rates of cesarean deliveries and poorer neonatal outcomes.[10] A Chinese study by **Mengting et al.** noted that the incidence of preeclampsia among women aged ≥35 was significantly higher than in younger cohorts, reinforcing the notion that advanced maternal age is linked to increased risk across different populations.[11] The lack of significant difference in age between both groups may be attributed to the reason that the study did not involve participants in the extremities of reproductive age, which are risk factors for preeclampsia.

In the current study parity was (2.8 ± 2.5 in cases group vs. 3.3 ± 2.5 in control group, P = 0.233) without significant difference being detected. The association between primiparity and preeclampsia is well established. For instance a systematic review indicated that primiparous women have a significantly higher risk of developing preeclampsia with an odds ratio of approximately 2.42 compared to multiparous women.[12] The lack of significant difference in parity may be attributed to the limited sample size of this study, as larger studies are needed in order to detect such associations.

The present study found that a 0.75 µg/ml cutoff point of fetal hemoglobin had a sensitivity of 84%, specificity of 80% in the assessment of preeclampsia. For the determination of severity, a 0.85 µg/ml cutoff had a 74.1% sensitivity and 69.9% specificity for the assessment of severity of preeclampsia.

The study by **Abdelsalam et al.** included 60 pregnant women (20 with severe preeclampsia, 20 with mild preeclampsia, and 20 controls). The study reported that fetal hemoglobin level was higher in preeclampsia patients. Severe preeclampsia cases showed higher level of fetal hemoglobin when compared to mild preeclampsia cases. The mean value was 0.6µg/ml, 1.7 and µg/ml, 2.7 µg/ml, the control, mild PE and severe PE groups, respectively. Moreover, a cutoff value of 0.8 µg/ml had 82.5% sensitivity and 85% specificity for the diagnosis of preeclampsia.[13]

The study by **Elrefaie et al.** included 100 pregnant women with preeclampsia/ eclampsia and 100 normotensive controls. The optimal fetal Hb cutoff value for predicting preeclampsia was 2.00 µg/ml,, as it demonstrated a sensitivity of 70.0%, specificity of 65.0%, PPV of 71.0%, NPV of 65.0%, and overall accuracy of 86.0%. For predicting eclampsia the optimal fetal Hb cutoff was 2.40 µg/ml,, yielding a sensitivity of 88.0%, specificity of 84.0%, PPV of 90.0%, and NPV of 82.0%, and overall accuracy of 86.0%.[14]

The study by **Anderson et al.** included 96 participants (60 with preeclampsia and 36 controls). The study reported that the mean concentration of HbF was 1.38 µg/ml, in PE,and 0.45 µg/ml, in the controls with the difference being statistically significant. For determining the predictive accuracy, the study used HbF/ total Hb ratio and revealed that it had a sensitivity of 78%.[15]

The study by **Ibrahim et al.** included 50 women with preeclampsia. The study reported that serum HbF was significantly higher in cases with severe preeclampsia than controls. A cutoff point of 9.2 µg/ml,had 75% sensitivity, 68% specificity, 69% PPV, 72% NPV and 72% overall accuracy.[16]

The study by **Vijaya et al.** included 100 pregnant women (56 women developed preeclampsia and 44 did not develop preeclampsia). The study found that a serum HbF cutoff level of 1.92 µg/ml,could predict future preeclampsia with a sensitivity of 98.2% and specificity of 97.7%.[17]

Another notable finding of the present study is that serum HbF significantly correlated with markers of severity (systolic BP, diastolic BP, urea creatinine and platelet count). In other words, higher values of serum HbF were significantly linked to rising blood pressure, urea, creatinine; and decreasing platelet count. This is in concordance with the study by **Elrefaie et al.** who also reported positive significant correlation between the fetal Hb and blood urea and serum creatinine.[14] This serves as further contribution in solidifying the hypothesis linking serum HbF to the severity of preeclampsia.

CONCLUSION

Elevated maternal serum fetal hemoglobin is significantly associated with both the occurrence and severity of preeclampsia, and HbF appears to be a promising, simple, and accessible biochemical biomarker for the diagnosis and risk stratification of preeclampsia.

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