Research Article

Serum Erythropoietin Concentration In Normal And Preeclamptic Pregnancies

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Abstract

Background: Preeclampsia is a multisystem disease and a threat to the well-being of both the mother and her newborn; it contributes significantly to the causes of maternal and perinatal morbidity and mortality. An increase in maternal plasma of erythropoietin in women with preeclampsia may be of placental origion and a reflection of an underlying placental hypoxic condition.
Aims: To compare serum erythropoietin concentrations among patients with and without preeclampsia and to investigate the association between serum erythropoietin levels and preeclampsia.
Methods: This case-control study involved one hundred pregnant women in their third trimester of singleton pregnancy with gestational age (28-40wk). Fifty patients were with preeclampsia (study group) and fifty patients were with normal healthy pregnancies (control group). For both groups maternal blood samples were collected for Erythropoietin concentration measured by ELISA method. Statistical analysis was performed to compare maternal serum erythropoietin levels in preeclamptic women and normal heathy pregnant women, and to evaluate the association between serum erythropoietin and preeclampsia.
Results: Mean erythropoietin level for the preeclamptic group was (41.66±26.76) ranging from 10.716-159.121(mIU/ml) with a median of 36.101 mIU/ml, while for the control group, the mean value was (28.71±14.38) ranging from 6.482-65.228 (mIU/ml) with a median of 26.741 mIU/ml. Erythropoietin levels were significantly (P=0.003) higher among preeclamptic patients compared with controls.
Conclusion: Women with preeclampsia have significantly higher levels of serum erythropoietin compared to normal healthy pregnancy.

Key words: erythropoietin, normal pregnancy, preeclampsia

INTRODUCTION

Preeclampsia is a multisystem disorder of pregnancy that can manifest clinically with hypertension and proteinuria after 20wk of gestation in previously normotensive women with or without accompanying symptoms, abnormal maternal laboratory test results, intrauterine growth restriction, or reduced amniotic fluid volume.[(1)] In literatures, little attention is devoted to the role of erythropoietin and the mechanisms regulating its secretion in pregnancy. Erythropoietin concentration has been proved to increase 2-4 fold in the course of pregnancy, and plateau is achieved after 20 weeks of gestation.[(2-4)] The etiology of this rise is not clear, but few theories have been raised. The first theory deals with the problem of anemia in pregnant women. Renal erythropoietin production is stimulated by tissue hypoxia. Most frequent reason for hypoxia is anemia, but also insufficient tissue blood flow, impaired gas exchange in the lungs and increased haemoglobin's affinity for oxygen.[(2, 4, 5)] The second theory is the role of placenta as an important, extrarenal source of erythropoietin production, which may be even higher.[(6, 7)] Conflicting data regarding the

link between increased blood serum erythropoietin concentration in pregnant women and the occurence of preeclampsia. One hypothesis assumes that elevated erythropoietin concentration in the blood of patients with preeclempsia is caused by reduced renal perfusion, which results in local relative hypoxia and compensatory increase of renal erythropoietin secretion.[8,9] Another theory links intensified hormone secretion to anemia which is caused by hemolysis, often accompanying preeclampsia. According to Hershkovitz et al., increased blood serum erythropoietin concentration in these women results from reduced placental blood flow and its reduced oxygenation, which induces a compensatory local erythropoietin secretion by placenta that results in increased total erythropoietin pool in blood serum of patients with preeclampsia.[8]

PATIENTS AND METHODS

A prospective case-control study was conducted at Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital in Baghdad from the 1st of May 2014 till the 1st of May 2015.

The study was approved by the Arab Board Committee for Medical Specialization. Informed verbal consent was obtained from all pregnant women before enrolling them in the study.

All participants (100) were Iraqi pregnant women in their third trimester of singleton pregnancy, their gestational age ranged from (28 to 40) weeks, the gestational age was determined by a reliable last menstrual period, confirmed by sonographic examination within the first 20 weeks of gestation.

Two groups were defined, the control group included fifty (50) healthy pregnant women presented for routine antenatal visits or pregnant women admitted for elective caesarean section and the study group included other fifty (50) pregnant women with preeclampsia at the time of admission. Preeclampsia was defined as blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and proteinuria ≥ 300 mg per 24 hour urine collection or dipstick reading of 1+ or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: thrombocytopenia (platelet count less than 100,000/microliter), renal insufficiency (serum creatinine concentrations greater than 1.1 mg/dL), impaired liver function (elevated blood concentrations of liver transaminases to twice normal concentration), pulmonary edema, and cerebral or visual symptoms.[10]

All patients were thoroughly examined after detailed history to assess maternal symptoms relating to preeclampsia like headache, visual disturbance, epigastric pain, nausea and/or vomiting and clinical enquiry about fetal movements. The groups were matched for maternal age, gestational age and parity.

Blood samples were collected with great care by standard peripheral venipuncture techniques. Five ml of the collected blood was sent for general investigations including: blood group and Rh, CBC, liver function test (including SGOT, SGPT, TSB, and S.ALKP), renal function test (including blood urea, serum creatinine), and serum uric acid. After sending the patient for general investigation she was allocated into either the study group or the control group, or she was excluded from the study. Patients with multiple pregnancies, with unsure date or have no early ultrasound examination, antepartum hemorrhage, chorioamnitis, premature rupture of membrane, Rh isoimmunization, intrauterine growth retardation or Intrauterine fetal death, fetal malformations, pregnant patient in labor, maternal chronic diseases (chronic anemia, diabetes mellitus, renal diseases, liver diseases, pulmonary disease, thyroid diseases, blood disease, cardiac disease), and maternal smoking were excluded from the study. Another 2ml of blood was collected for quantitative determination of serum erythropoietin levels by enzyme linked immunosorbent assay (ELISA), using Demeditec Diagnostics EPO ELIZA GmbH • Lise-Meitner-Straße 2 • D-24145 Kiel (Germany).

To assay the specimen in duplicate, 400 µL of human serum was required. The specimens were collected between 7:30 a.m. to 12:00 noon, two ml of whole blood without anticoagulant was collected and allowed to clot between 2-8°C, the serum was promptly separated, and stored at –15°C or lower. Serum samples frozen at -15°C were stable for up to 12 months. Prior to use, all specimens were allowed to come to room temperature (22°C to 28°C) and mixed by gentle inversion or swirling, avoiding grossly hemolyzed or grossly lipemic samples. In the general population, serum erythropoietin values were ranged from 3.22 to 31.9 mIU/mL when measured with the DEMEDITEC EPO ELISA kit.

Statistical analysis:

Analysis of data was carried out using SPSS-22 - version 22 Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).The significance of difference of different means was tested using

Students-t-test for difference between two independent means. The significance of difference of different percentages was tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. In addition to correlation the r^2 was calculated (The coefficient of determination). Statistical significance was considered whenever the P value for the test of significance was equal or less than 0.05.

RESULTS

The study represents a case–control study on 100 pregnant Iraqi women, in their third trimester. Fifty cases were with preeclampsia (study group) and the other 50 cases were normal healthy pregnant women (control group). Table 1 shows the characteristics of preeclamptic patients and the controls..

Regarding maternal age, the mean maternal age for preeclamptic women was (28.42± 5.50) ranging from 16 -40 years, while the mean maternal age for the control group was (27.94 ± 5.99) ranging from 16-37 years, there was no statistically significant difference between the two groups (p value= 0.678). Regarding parity, the mean of parity for preeclamptic women was (2.34± 1.64), while the mean of parity for the control group was (2.10 ± 1.58) there was no statistically significant difference between the two groups (p value= 0.458). Regarding gestational age, the preeclamptic group had a mean gestational age of (34.12 ± 2.69) while the control group had a mean gestational age of (34.82± 2.45) there was no statistically significant difference between the two groups (p value=0.177). Regarding blood pressure for both groups, the mean systolic blood pressure was significantly (P=0.0001) higher among preeclamptic patients compared with controls (166.60±11.29 versus 117.32±4.85) respectively. Diastolic blood pressure was significantly (P=0.0001) higher among preeclamptic patients compared with controls as the preeclamptic group had a mean diastolic blood pressure of (110.08±7.37) while the control group had a mean diastolic blood pressure of (72.42±3.53).

Table 1: Characteristics of preeclamptic patients and the controls.

	Preeclampsia	Normotensive	P value
Age (years)	28.42±5.50 (16-40)	27.94±5.99 (16-37)	0.678
Parity	2.34±1.64 (0-6)	2.10±1.58 (0-6)	0.458
Gestational age (weeks)	34.12±2.69 (28-40)	34.82±2.45 (28-40)	0.177
SBP (mmHg)	166.60±11.29 (143-191)	117.32±4.85 (108-129)	0.0001*
DBP (mmHg)	110.08±7.37 (94-120)	72.42±3.53 (67-80)	0.0001*

-Data were presented as Mean±SD (Range)

***Significant using t-test for two independent means at 0.05 level.**

Regarding hematological and biochemical laboratory data for preeclamptic patients and the controls (table 2), there were statistically significant higher levels of hemoglobin and hematocrit among preeclamptic patients compared with the controls as the p values were 0.0001 and 0.0001 respectively, while there was a statistically significant lower platelet count among preeclamptic patients compared with the controls (p=0.0001). Blood urea, serum creatinine and serum uric acid were significantly higher among preeclamptic group compared with the controls as p values were 0.0001, 0.036 and 0.0001 respectively.

Table 2: Hematological and biochemical laboratory data for preeclamptic patients and the controls.

	Preeclampsia	Normotensive	P value
Hemoglobin (g/dl)	11.42±0.20 (11.07-11.73)	11.27±0.10 (11.09-11.41)	0.0001*
Hematocrit (%)	35.02±0.35 (34.27-35.64)	33.24±0.45 (32.60-33.99)	0.0001*
Platelets (x109/l)	191.19±4.28 (184.2-199.1)	213.83±33.30 (117.3-273.4)	0.0001*
Blood urea (mg/dl)	28.42±2.81 (23.1-33.0)	26.28±1.71 (22.9-30.0)	0.0001*
Serum creatinine (mg/dl)	0.67±0.21 (0.28-1.02)	0.59±0.16 (0.29-0.99)	0.036*
Uric acid (mg/dl)	5.30±0.48 (4.41-6.05)	4.91±0.39 (4.29-5.73)	0.0001*

***Significant using t-test for two independent means at 0.05 level.**

Regarding erythropoietin level (table 3), there was a significantly (P=0.003) higher level of erythropoietin among preeclamptic patients compared with controls, as the mean value was (41.66±26.76) for the preeclamptic group ranging from 10.716-159.121(mIU/ml) with a median of 36.101 mIU/ml, while for the control group, the mean value was (28.71±14.38) ranging from 6.482-65.228 (mIU/ml) with a median of 26.741 mIU/ml.

Table 3: Mean erythropoietin (mIU/ml) for preeclamptic patients and the controls.

Erythropoietin (mIU/ml)	Groups	
	Preeclampsia	Normotensive
Mean	41.66±26.76	28.71±14.38
Standard Error of Mean	3.784	2.034
Range	10.716-159.121	6.482-65.228
Percentile 05th	14.289	9.376
25th	22.397	18.497
50th (Median)	36.101	26.741
75th	55.923	38.765
95th	88.389	58.751
99th	159.121	65.228
P value	0.003*	

***Significant using t-test for two independent means at 0.05 level.**

Figure 1 shows the exploratory graphic distribution of erythropoietin data among the two groups.

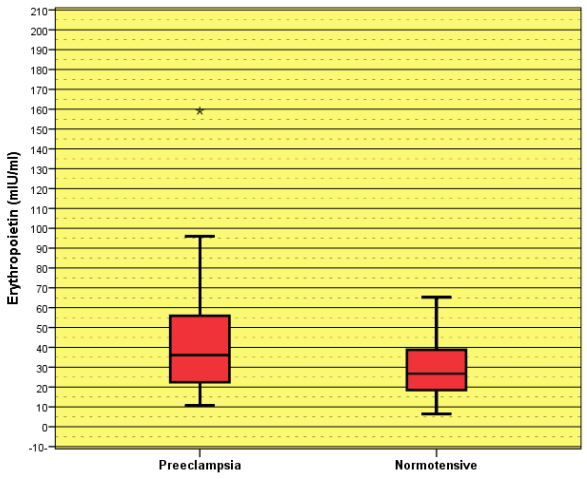

Figure 1: The Box Plot distribution of erythropoietin (mIU/ml) for preeclamptic patients and the controls.

Table (4) summarizes the correlation between erythropoietin level and different parameters (age, parity, gestational age, systolic blood pressure, diastolic blood pressure, hematological and biochemical laboratory data) in each group, there was no correlation between erythropoietin level and any of the previously mentioned parameters as the r was < 0.3.

Table 4: The correlation between erythropoietin level and different parameters (demographic, systolic blood pressure, diastolic blood pressure, hematological and biochemical data) among preeclamptic patients and the controls.

		Erythropoietin (mIU/ml)	
		Preeclampsia	Normotensive
Age (years)	r	-0.082	0.075
	P	0.572	0.604
Parity	r	-0.221	-0.029
	P	0.122	0.841
Gestational age	r	0.122	-0.015
(weeks)	P	0.400	0.920
SBP (mmHg)	r	-0.270	0.116
	P	0.058	0.422
DBP (mmHg)	r	-0.262	0.273
	P	0.066	0.055
Hemoglobin	r	-0.043	-0.070
(g/dl)	P	0.767	0.630
Hematocrit (%)	r	0.097	0.075
	P	0.505	0.606
Platelets (x109/l)	r	-0.136	0.001
	P	0.347	0.999
Blood urea	r	0.148	-0.210
(mg/dl)	P	0.305	0.144
Serum creatinine	r	0.080	-0.169
(mg/dl)	P	0.579	0.241
Uric acid (mg/dl)	r	-0.045	-0.106
	P	0.759	0.464

***Correlation is significant at the 0.05 level**

****Correlation is significant at the 0.01 level.**

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DISCUSSION

Preeclampsia is a multisystem disease and a threat to the well-being of both the mother and her newborn; it contributes significantly to the causes of maternal and perinatal morbidity and mortality.[11, 12] Preeclampsia affects 5-8% of pregnant women in the whole world with a perinatal and neonatal mortality rate of 10%.[13,14] Preeclampsia has a complex pathophysiology, although the exact pathogenesis is unknown. Invasion by the trophoblast appears to be incomplete, this will lead to alterations in placental perfusion and an insufficient transport of nutrients.[15,16] Increased uterine arterial resistance causes chronic placental ischemia and oxidative stress which induces the release of free radicals, oxidized lipids, cytokines and serum soluble vascular endothelial growth factor 1 into the maternal circulation,[16] so the net result of these is tissue hypoxia and hypoxia is one of the stimulant factors for erythropoietin release.[17] Controversy exists in the literature regarding the association between erythropoietin levels and preeclampsia,. Main hypotheses for erythropoietin release in preeclampsia are: the first theory is a decreased perfusion to the kidneys occurs; with relative hypoxemia, this leads to increased production of erythropoietin. The second theory is the hemolysis that may occur in women with preeclampsia, leading to anemia which may lead to increased erythropoietin production.[18] The third theory is the local placental release of erythropoietin. There are known erythropoietin receptors in placental tissue; it is believed that erythropoietin sustains survival, proliferation and differentiation of trophoblastic cells.[19]

According to current study maternal age, parity and gestational age for the studied groups showed no statistically significant difference, this to eliminate the effect of bias of these parameters on erythropoietin level. There was no correlation between erythropoietin level and any of the previously mentioned demographic parameters as r values for each were less than 0.3 (table 4).

Also hemoglobin and hematocrit levels were significantly higher among preeclamptic women, possibly due to pathophysiology of hemoconcentration that develop in preeclampsia, resulting from generalized vasoconstriction that follows endothelial activation and leakage of plasma into the interstitial space because of increased permeability.[20] Our findings were in agreement to those reported by study findings of Ganai et al.[21] and Zafar et al.,[22] while

disagree with those observed by Ceyhan et al.[23] and Hershkovitz et al.[8] who reported no significant difference in hemoglobin and hematocrit levels between normal and preeclamptic pregnancies. Regarding platelet count, it was significantly lower in preeclamptic women compared to normal healthy pregnancies; our finding was in agreement with those obtained by Vamseedhar et al.[24] and Jaremo et al. [25]

In the present study, significantly higher levels of blood urea, serum creatinine and uric acid were observed in women with preeclampsia compared to normal healthy pregnancies (table 2). The explanation for these high levels of the previously mentioned parameters in preeclamptic group is probably due to the decrease in glomerular filtration rate that occurs with preeclampsia and the increased renal vascular resistance that is principally due to an increase in the afferent arteriolar resistance.[19] Increased uric acid is due to the reduction in uric acid clearance and the increased tubular reabsorption of uric acid in renal tubule, possibly due to the coupling to sodium reabsorption in the proximal tubule, which may be increased in the hypovolemic state of preeclampsia.[26] Also increased placental urate production compensatory to increased oxidative stress have been proposed as another contributing source of hyperuricemia noted in preeclampsia apart from reduced renal excretion.[26, 27] These findings were in agreement with magna et al.[28] and Tetteh et al.,[29] while Hershkovitz et al.[8] found the elevation in the previously mentioned parameters in preeclamptic patients were not significant.

In our study, erythropoietin levels (table 3) were significantly higher among preclamptic women compared to normal healthy pregnancies.These higher levels of erythropoietin didn't correlate with any of the previously mentioned hematological or biochemical parameters (table 4). This lack of correlation between erythropoietin level and laboratory results made the theory of hemolysis or renal hypoxia as a cause of elevated erythropoietin in preeclamptic patients is unlikely. So the increased levels of erythropoietin in women with preeclampsia may be mainly of placental origin.

Goldstein et al.[9] and Troeger et al.[30] demonstrated that erythropoietin levels were increased in preeclampsia and these increments were statistically significant and their findings were in agreement with the results observed in our study. On the other hand, Kaupke et al.[31] and Hershkovitz et al.[8] have found a tendency towards increased plasma erythropoietin concentrations in preeclamptic women as compared to those with normal pregnancies, although this was not statistically significant. This difference could be attributed to small sample size in their studies.

The tendency toward increased erythropoietin levels in preeclampsia may lead to the assumption that serum erythropoietin may serve as an early marker of preeclampsia in pregnant patient who are at high risk to develop preeclampsia. To confirm this assumption, further studies need to be performed at early midtrimester patients, a time when a crucial step in placental development occurs, as our study was performed in the third trimester.

Increased erythropoietin levels were suggested to have a role in humoral mechanisms in the placenta leading to vasoconstriction.[6] Hypertension was an associated side effect while using human recombinant erythropoietin in the treatment of anemic pregnant patients.[32]

Thus elevated erythropoietin levels in preeclamptic patients may be a causative factor in the pathophysiology of preeclampsia and not only a consequence of preeclampsia. Further studies are needed to evaluate the association between preeclampsia and erythropoietin as being a consequence or a causative agent in the pathogenesis of preeclampsia.

CONCLUSION:

Maternal serum erythropoietin levels are found to be significantly elevated in pregnant women with precclampsia compared to normal healthy pregnancy.

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