

## Iron status parameters in preeclamptic women in Gaza, Palestine

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### Abstract:

Preeclampsia (PE) is a turmoil in the pregnancy appeared with the onset of hypertension and considerable amount of proteinuria. Extra serum iron is a causative component of oxidative stress concerned in the pathogenesis of preeclampsia. This study is a case control, conducted in 2018, and aimed to determine the iron status in preeclamptics as compared to normotensive pregnancies in Gaza strip. About 100 pregnant women with gestational age between 26 to 36 weeks. Fifty of them were preeclamptics and an equal number were without preeclampsia, aged between 18 to 35 years. Interview questionnaires were used to take sociodemographic and clinical data. Anthropometric evaluation and biochemical analysis were conducted. The SPSS version22 was used for data analysis. There was no statistically difference in the gestational age, gestational number and hemoglobin levels in the cases and controls ( $p \geq 0.05$ ). In contrast, the body mass index (BMI), systolic, diastolic blood pressure (BP), and uric acid (UA) levels were significantly higher in preeclamptics ( $P < 0.001$ ). As well, the majority of cases were have +2 proteinuria on dipstick testing. Further, serum iron and ferritin levels were significantly higher in preeclamptics. On the other hand, ferritin levels had significant direct correlations with gestational number, previous preeclampsia, BMI, systolic BP, diastolic BP, UA, and proteinuria ( $P < 0.05$ ). Likewise, Iron had significant direct correlation with proteinuria ( $P < 0.05$ ). Preeclamptics have higher hematological parameters levels (iron & ferritin) as compared to normotensive women. However, Iron status of preeclamptic women should be assessed before giving iron supplements as these may cause more harm than benefit.

### Keywords:

Preeclampsia, Iron, Ferritin, Gaza Strip, Palestine.

## 1. Introduction

PE is the development of hypertension (HTN) and proteinuria and/or edema after 20<sup>th</sup> week of pregnancy. Eclampsia is PE plus convulsions or coma (Siddiqui et al., 2011). PE is one of the main reasons for maternal mortality and morbidity in growing nations. It is a common, partially known and multifactorial disease, roughly 5 to 7 % of all pregnant women suffer from it (Ziaei et al., 2008). The pathophysiological mechanism of PE is not clearly understood, a one explained mechanism stated that failure of the trophoblastic invasion of the spiral arteries which may be related to an elevated resistance of the uterine artery and lessened placental perfusion (Sukonpan and Phupong, 2005). Many complications are related to PE such as: oliguria, eclampsia, hemolysis, rose liver enzyme, pulmonary edema, and fettering of embryonic growth (Cunningham et al., 2010). Early recognition and quick management of the condition helps us in lessening its complications. Internationally, 2,87,000 ladies died during delivery in 2010 (Park, 2011). Because of this, Ways to diminish the risk of HTN issue in pregnancy have gotten significant consideration. Iron may likewise play a significant role in the pathophysiology of preeclampsia (Zafar and Iqbal, 2008). As reported in various studies; preeclamptic women have high serum levels of lipid peroxidation products in respect to typical pregnancy (Zafar and Iqbal, 2008). It has been proposed that lipid peroxidation may have a rule in the pathophysiology of the PE. Lipid peroxidation is encouraged by iron (Zafar and Iqbal, 2008). Demolition of red blood cells from ischemic placenta discharged iron species, which in order can start the lipid peroxidation process to cause endothelial cell destruction in preeclamptic women (Rayman et al., 2002). In addition, there is evidence that oxidative stress occurs in preeclampsia could be generated from iron or iron species (Rayman et al., 2002). Ongoing investigations in pregnant ladies have demonstrated that there is a significant relationship between a raised maternal serum ferritin, iron levels and abnormal transferrin metabolism with PE and eclampsia (Taheripanah and Farkush, 2007). Although many studies have been reported that Iron has a significant role in the emergence of preeclampsia due to its role in lipid peroxidation process, where this process plays a role in the etiology of the disease. But the gynecologists of Gaza strip describe iron supplements for all pregnant women who attended the clinics regardless of their serum iron status. This improper behavior leads to the possibility of preeclampsia among normotensive women and the possibility of increased severity and complications of preeclampsia among preeclamptic women. Thus, it seems important to pay attention to the iron status parameters in preeclamptics and as compared to normotensive pregnancies in Palestine in order to prove the significant differences in their levels between the two groups to provide advice to decision makers on the need to conduct serum iron parameters tests for all pregnant women before giving them iron supplements. Therefore, preeclampsia might be reduced through serial monitoring of serum iron status as a part of an antenatal check-up. In addition, Locally, to date, there were no previous studies related to this topic and it's the first time to accomplish this research among Palestinian population in Gaza strip. However, this study aimed to find out the iron status parameters in preeclamptics as compared to normotensive pregnancies in Gaza, Palestine.

## 2. Materials and Methods

### 2.1 Study Population, Sample Size, and Sampling site

This study was a case-control, conducted between June and October 2018. The total samples of this study were consisting of 100 age-matched pregnant women who have gestational age between 26 to 36 weeks. 50 preeclampsia women were selected according to gynecologists reports. 50 healthy pregnant subjects were taken as a control group, having uncomplicated pregnancies and were normotensive throughout gestation and without proteinuria. Samples of this study were randomly collected from the obstructive departments of Nasser Medical Complex in Khanyounis governorate, Primary Health Care Centers in Rafah, and Khanyounis governorates, Emirates crescent hospital in Rafah governorate and Alshifa Medical Complex in Gaza governorate. The formal letter of approval to collect the samples from the governmental clinics and hospitals was obtained from the Palestinian ministry of health. Every participant in the study was given a consent form about the study and was received the report of the results of their biochemical examinations after the end of the study.

### 2.2 Questionnaire interview

The study population was asked to fill out a questionnaire related to their health and smoking habits. A meeting interview was used for filling in a questionnaire. The questionnaire consisted of two issues: sociodemographic

data (name, age, sex, education status and so on...) and clinical data (having health problem, gestational age and so on...).

### 2.3 Anthropometric measurements

The researchers measured the body weight using SECA type weighing scale in kg, and height in centimeter using SECA stadiometer, and the BMI was calculated by dividing the weight by the square of height in meter. According to the world health organization classification; BMI is classified (Altaher et al., 2018).

### 2.4 Blood sampling and biochemical analysis

About 3ml of venous blood was collected from each participant under aseptic precaution in a plain tube. Then the serum was separated by centrifugation at room temperature at 4000 round/minute for 10 minutes and was used for estimation of UA, Iron and ferritin levels. Serum concentration of UA is estimated by phosphotungstic acid method, iron was estimated using ferrozoin method using Bio-System and ferritin was estimate using immuno enzymometric Assay (TOSOH-A1A-360). All biochemical tests were conducted in the clinical chemistry laboratory of university college of science and technology in Khanyounis. Hemoglobin concentration results were obtained from medical records of pregnant women at both clinics and hospitals.

### 2.5 Data analysis

The SPSS program software (V. 22.0) was utilized to the analysis of data. Descriptive statistics, Chi-Square test, t-test & ANOVA test were applied. The statistically significant result was considered when the P-value was less than 0.05 at the confidence intervals 95%.

## 3. Results

### 3.1 Clinical and biochemical characteristics of the study subjects

Variables	Subject		P-Value
	Case (mean ±SD)	Control (mean ±SD)	
<b>Age (years)</b>			
	28.34±6.96	27.58±4.59	<b>0.091</b>
<b>Gestational age (weeks)</b>			
	34.86±3.90	33.58±5.03	<b>0.159</b>
<b>Gestational Number</b>			
	3.20±2.62	2.41±1.12	<b>0.143</b>
<b>BMI (kg/m<sup>2</sup>)</b>			
	31.339±4.95	27.07±5.19	<b>0.000**</b>
<b>Systolic BP (mm Hg)</b>			
	145.0±14.93	105.2±10.73	<b>0.000**</b>
<b>Diastolic BP (mm Hg)</b>			
	95.5±12.04	79.07±6.24	<b>0.000**</b>
<b>Uric acid (mg/dl)</b>			
	4.81±1.74	3.40±0.70	<b>0.000**</b>
<b>Proteinuria (mg/24 hrs.):</b>			<b>0.000**</b>
Normal	5 (10.0%)	50 (100.0%)	
+	17 (34.0%)	0 (0.0%)	
++	28 (56.0%)	0 (0.0%)	
<b>Count</b>	50	50	
<b>%</b>	100.0%	100.0%	

The finding showed that the mean ± standard deviation (SD) of age among the hypertensive women was 28.34±6.96 years whereas; the mean ± SD of age was 27.58±4.59 among normotensive women. However, there is no statistically significant difference between the study subjects with respect to mean ± SD of age in years (P=0.091). The following figure shows the percent distribution of the study subjects according to their location of collection (figure 1), About 44.0% of subjects were collected from Nasser medical complex (Specifically: Mubarak

Obstetrics Hospital) in Khanyounis governorate, while 36.0% of them were collected from primary health care centers (PHC) clinics in Rafah and Khanyounis governorates, whilst 15.0% of them were collected from Alshifa medical complex in Gaza governorate and only 5.0% of them were collected from Emirate's crescent hospital in Rafah governorate.

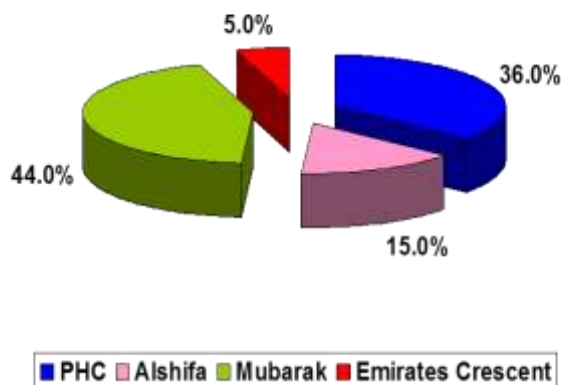


Figure 1: Percent distribution of the study subjects by the location of collection

The table below reveals the clinical and biochemical characteristics of cases as compared to controls (Table 1). The gestational age and gestational number were higher in the preeclamptics compared to normotensives ( $34.86 \pm 3.90$  Vs.  $33.58 \pm 5.03$  and  $3.20 \pm 2.62$  Vs.  $2.41 \pm 1.21$  respectively) but these differences did not reach the statistically significant levels. Furthermore, the mean  $\pm$  SD of BMI was significantly higher in preeclamptics than normotensives ( $31.339 \pm 4.95$  kg/m<sup>2</sup> Vs.  $27.07 \pm 5.19$  kg/m<sup>2</sup>,  $p < 0.001$ ). Likewise, the means  $\pm$  SD of systolic and diastolic blood pressure were significantly higher in hypertensive women as compared to normotensive women ( $145.0 \pm 14.93$  mm Hg Vs.  $105.2 \pm 10.73$  mm Hg and  $95.5 \pm 12.04$  mm Hg Vs.  $79.07 \pm 6.24$  mm Hg respectively,  $p < 0.001$ ). As well as, the mean  $\pm$  SD of serum UA levels was significantly higher in cases in comparison to controls ( $4.81 \pm 1.74$  mg/dl Vs.  $3.40 \pm 0.70$  mg/dl,  $p < 0.001$ ). Also, the majority (56.0%) of cases had +2 proteinuria on dipstick testing.

Table 1 Comparison of clinical and biochemical characteristics between cases and controls

$P < 0.05$ : Significant, \*\* Highly statistically significant

### 3.2 Hematological parameters of the study subjects

The table below shows the comparison of hematological parameters between both groups (Table 2). There was no statistical difference in the hemoglobin levels in the cases and controls ( $p \geq 0.05$ ). In contrast, the mean  $\pm$  SD of serum ferritin levels were significantly higher among preeclamptics compared to normotensives which were highly statistically significant ( $84.32 \pm 7.03$  Vs.  $57.26 \pm 4.94$  ng/ml,  $P < 0.01$ ). Likewise, the mean  $\pm$  SD of serum iron were significantly higher in cases compared to controls ( $132.88 \pm 10.03$   $\mu$ g/dl Vs.  $56.46 \pm 5.55$   $\mu$ g/dl,  $P < 0.001$ ).

Table 2 Comparison of hematological parameters means between cases and controls

	Subject		P-Value
	Case (mean ±SD)	Control (mean ±SD)	
Hemoglobin (g/dl)	11.78±0.92	11.33±.74	0.464
Serum iron (µg/dl)	132.88±10.03	56.46±5.55	0.000**
Ferritin (ng/ml)	84.32±7.03	57.26±4.94	0.000**

*P < 0.05: Significant, \*\* Highly statistically significant*

In the other side, after applying chi-square test to verify the differences between cases group and control groups according to both iron and ferritin levels by normal range; the results show that 26.0% of cases had iron levels 138 (µg/dl) or more. While 8.0% of cases had ferritin levels 125(ng/ml) or more. However, there were statistically significant differences between the two groups according to iron and ferritin levels (p-value = 0.000 & 0.041 respectively) (Table 3).

**Table 3 Comparison of hematological parameters means between cases and**

	Subject		
	Case (n=50)	Control (n=50)	
<b>Serum iron (µg/dl)</b>			
Less than 137	37 (74.0%)	50 (100.0%)	0.04
138 and more	13 (26.0%)	0 (0.0%)	
<b>Ferritin (ng/ml)</b>			
Less than 124	46 (92.0%)	50 (100.0%)	
125 and more	4 (8.0%)	0 (0.0%)	
<b>total</b>	<b>%</b>	<b>50 (100%)</b>	<b>50 (100%)</b>

**controls**

*P < 0.05: Significant, \* Statistically significant, \*\* Highly statistically significant*

### 3.3 Correlation between hematological parameters with clinical and biochemical parameters of the study cases

Table 4 illustrates the correlation between hematological parameters of the study cases (hemoglobin, iron and ferritin) with clinical and biochemical parameters including: gestational age (weeks), gestational number, previous preeclampsia, BMI (kg/m<sup>2</sup>), systolic BP (mm Hg), diastolic BP (mm Hg), UA (mg/dl), proteinuria (mg/24 hrs.). Correlating case's group ferritin levels with their clinical and biochemical parameters revealed that ferritin concentration had significant direct correlations with gestational number (r=0.258, P = 0.023), previous preeclampsia (r=0.303, P = 0.007), BMI (r=0.246, P = 0.014), systolic BP (r=0.373, P = 0.000), diastolic BP (r=0.257, P = 0.010), UA (r=0.272, P = 0.006), and proteinuria (r=0.388, P = 0.000) (Table 4). In the other hand, iron also had significant direct correlation with proteinuria (r=-0.242, P = 0.015 (table 4.4). Furthermore, table 4.4 also showed that there was no correlation between Hb concentrations with clinical and biochemical parameters of preeclamptics (p ≥ 0.05 for all).

**Table 4 Correlation between hematological parameters with clinical and biochemical parameters**

Correlations	Hemoglobin (g/dl)	Iron (µg/dl)	Ferritin (ng/ml)
<b>Gestational age (weeks)</b>			
Pearson Correlation (r)	-0.002	0.117	0.113
Sig. (2-tailed)	0.982	0.245	0.262
<b>Gestational number</b>			
Pearson Correlation (r)	-0.012	-0.083	0.258*
Sig. (2-tailed)	0.915	0.471	<b>0.023*</b>
<b>Previous preeclampsia</b>			
Pearson Correlation (r)	0.080	0.005	0.303**
Sig. (2-tailed)	0.489	0.967	<b>0.007*</b>
<b>BMI (kg/m<sup>2</sup>)</b>			
Pearson Correlation (r)	0.063	0.150	0.246*
Sig. (2-tailed)	0.535	0.136	<b>0.014*</b>
<b>Systolic BP (mm Hg)</b>			
Pearson Correlation (r)	-0.016	0.174	0.373**
Sig. (2-tailed)	0.878	0.084	<b>0.000**</b>
<b>Diastolic BP (mm Hg)</b>			
Pearson Correlation (r)	-0.073	0.134	0.257**
Sig. (2-tailed)	0.471	0.183	<b>0.010*</b>
<b>Uric acid (mg/dl)</b>			
Pearson Correlation (r)	-0.111	0.024	0.272**
Sig. (2-tailed)	0.270	0.812	<b>0.006*</b>
<b>Proteinuria (mg/24 hrs.)</b>			
Pearson Correlation (r)	0.012	0.242*	0.388**
Sig. (2-tailed)	0.905	0.015*	<b>0.000**</b>

Correlation is significant at the 0.05 level. \* Statistically significant, \*\* Highly statistically significant

#### 4. Discussion

According to our knowledge, This study is the first study estimates the iron status parameters in preeclamptics and as compared to normotensive pregnancies in Palestine. Despite numerous studies that have been conducted around the world; the etiology of preeclampsia has been remaining unclear. There are many hypotheses has been suggested to explain its etiology. Many researchers reported that alteration of iron status is a risk factor for the pathogenesis of preeclampsia (Sultana, et al., 2012; Masti, & Pharm, 2014). Excess iron is postulated as causal factor in the oxidative stress in its radical form, which might be involved in the pathogenesis of preeclampsia (Masti, & Pharm, 2014). Elevated hemoglobin rather than anemia in pregnancy was linked to underlying Conditions like preeclampsia (Ugwuja, et al., 2010). The present study has shown that preeclamptic women have higher serum iron and ferritin levels as compared to normotensive women,

and these differences reached a statistically significant level. On the other hand, hemoglobin levels among cases not differ from those among controls. In addition, preeclamptic women have higher BMI in comparison to normotensive women. The findings of the current study were in the line with many recent studies conducted at preeclamptics women to determine iron status parameters and their comparison to normotensive pregnancies (Kanagal et al., 2014; Masti, & Pharm, 2014; Zafar, & Iqbal, 2008; Taheripanah, & Farkush, 2007; Rayman, et al., 2002; Lao, et al., 2000). Kanagal et al. conducted a case control study on 120 pregnant women (60 women with preeclampsia and 60 normotensives). This study reported the mean of serum iron and ferritin levels in preeclamptics were significantly higher compared to normotensives whereas hemoglobin levels did not show much difference. Also, preeclamptic women were older and higher BMI (Kanagal et al., 2014).



Likewise, another hospital-based study was carried out to in 30 preeclamptic cases and 30 age matched controls without having preeclampsia in the age group of 20-45years. Aimed to compare the serum levels of iron and TIBC in women with normal pregnancy and preeclampsia. This study showed that the mean of serum Iron levels was significantly higher in cases as compared to controls (Masti, & Pharm, 2014). Moreover, a case control study was performed on 33 preeclamptic patients and 33 normal pregnant women before parturition in Imam Hussein hospital. The results reported that the mean of serum ferritin was lower in the control group as compared in preeclampsics ( $P < 0.001$ ). On the other hand, the current study also reported that the ferritin levels have significant direct correlations with BMI and UA. Similar findings were found in the study done by Alam & Fatima. (2015) where they reported that individuals with high BMI had high levels of Serum Ferritin (Alam & Fatima et al., 2015). The present results also agree with the previous study done by Ghio et al. (2005) who suggested that serum concentrations of ferritin correlated positively with uric acid levels. This association was independent of an effect of gender, age, race/ethnic group, body mass, and alcohol consumption (Ghio et al., 2005). No meaningful relation was observed between hemoglobin and iron with BMI and UA. It seems that elevated serum ferritin can accelerate vascular damage (Taheripanah, & Farkush, 2007). The results of the current study confirm this phrase where it was found that ferritin concentration had significant direct correlations with systolic and diastolic BP.

## 5. Conclusions:

The gestational age, gestational number, BMI, systolic BP, diastolic BP, UA levels, iron levels, and ferritin levels were higher in the preeclampsics as compared to normotensives ( $P < 0.05$ ). These findings agree with most of the previous studies. The majority of cases had +2 proteinuria on dipstick testing. The ferritin levels had significant direct correlations with the gestational number, previous preeclampsia, BMI, systolic BP, diastolic BP, UA level, and proteinuria. In addition, Iron had a significant direct correlation with proteinuria.

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## الخلاص باللغة العربية:

### تقييم حالة الحديد عند الحوامل المصابات بتسمم الحمل، غزة، فلسطين

تسمم الحمل هو خلل لدى الحوامل يتميز بارتفاع تدريجي في ضغط الدم إضافة إلى ارتفاع تراكيز البروتين في البول في بعض الأحيان. زيادة تراكيز الحديد في الدم لدى الحوامل يُعتبر أحد العوامل المؤدية إلى اختلال التوازن بين الأيونات الحرة وموانع الأكسدة، واختلال التوازن هذا يُعتبر أحد العوامل المتعلقة بآلية حصول تسمم الحمل.

هدفت هذه الدراسة إلى تقييم حالة الحديد عند الحوامل المصابات بتسمم الحمل مقارنة بمجموعة ضابطة من نفس العمر ونفس عمر الحمل، غزة، فلسطين.

منهجية هذه الدراسة مقارنة مجموعة تجريبية بمجموعة ضابطة، نُفذت في الفترة الزمنية (مايو - سبتمبر 2018) على ما مجموعه 100 من السيدات الحوامل (50 لديهن ضغط حمل و 50 حملهن طبيعي) كلا المجموعتين كانت أعمارهم بين 18-35 عام وعمر الحمل ما بين 26 إلى 36 أسبوع، أُستخدمت الاستبانات لجمع البيانات الشخصية والاجتماعية والصحية لكلا المجموعتين، كلا المجموعتين خضعوا لتقييم القياسات الجسمية ولتقدير التراكيز البيوكيميائية للحديد والفرتين واليوريك أسيد والهيموجلوبين، تم استخدام برنامج الحزمة الإحصائية للعلوم الإنسانية النسخة العشرون في تحليل بيانات الاستبانات ونتائج التحاليل البيوكيميائية.

لاحظت الدراسة أن عُمر الحمل وعدد مرات الحمل السابق كان أعلى لدى المجموعة التجريبية مقارنة بالمجموعة الضابطة، إلا أن هذا الاختلاف لم يكن ذو دلالة احصائية. إضافة إلى ذلك، سجلت الدراسة ارتفاع ذو دلالة احصائية في كل من مؤشر كتلة الجسم وضغط الدم الانبساطي وضغط الدم الانقباضي ومستويات اليوريك أسيد لدى المجموعة التجريبية مقارنة بالمجموعة الضابطة ( $P < 0.01$ ). كما وجدت الدراسة أن معظم النساء المصابات بضغط الحمل كان لديهن بروتين في البول بتركيز (++) . من جهة أخرى، لم تسجل الدراسة فروقات ذات دلالة احصائية بين كلا المجموعتين فيما يتعلق بتركيز هيموجلوبين الدم. في حين لوحظ ارتفاع ذو دلالة احصائية في مستويات كل من الحديد والفرتين في الدم لدى المجموعة التجريبية مقارنة بالمجموعة الضابطة. إضافة إلى ذلك، لوحظ وجود علاقة طردية وذات دلالة احصائية بين تركيز الفرتين مع كل من عدد مرات الحمل و الإصابة السابقة بالحمل الخطر ومؤشر كتلة الجسم وضغط الدم الانبساطي والانقباضي وتراكيز كل من اليوريك أسيد في السيرم والبروتين في البول لدى المجموعة التجريبية ( $P < 0.01$ ). وبالمثل كانت العلاقة طردية وذات دلالة احصائية بين كل من مستويات الحديد في السيرم وتراكيز البروتين في البول لدى المجموعة التجريبية ( $P < 0.01$ ). بينما لم تجد الدراسة علاقة بين تراكيز الهيموجلوبين في الدم مع كل المؤشرات السريرية والبيوكيميائية السابقة.

**استنتجت الدراسة أن السيدات المصابات بالحمل الخطر لديهن مستويات أعلى من الحديد والفرتين مقارنة بالسيدات ذوات الحمل الطبيعي، لذلك يجب قياس مستويات الحديد للسيدات المصابات بضغط الحمل قبل اعطائهن مكملات الحديد، لأن ذلك قد يعود على صحتهن بالضرر أكثر من النفع.**

**الكلمات المفتاحية:** الحمل الخطر، الحديد، الفرتين، قطاع غزة، فلسطين