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Biochemical Characteristics of Preeclampsia in Egyptian population

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Abstract

Currently, preeclampsia (PE) is one of the leading causes of death and severe maternal mortality. Although PE has multisystem complications, including cerebral haemorrhage, hepatic dysfunction, and renal dysfunction, the majority have successful pregnancy outcomes. Due to an incomplete understanding of the underlying pathogenesis, the prevention and treatment of PE have been challenging. Several factors and markers are used to predict and diagnose this disease. The goal of the current study was to investigate the role of the serum levels of vascular endothelial growth factor (VEGF), cancer antigen 125 (CA 125), and C reactive protein (CRP) in prediction and diagnosis of preeclampsia at Obstetrics and Gynaecology Department at Zagazig University Hospital. A case-control study targeted 30 women in the 3rd trimester of pregnancy, classified into 3 groups; Mild and severe preeclampsia and normal pregnancies as a control group. After complete routine assessment and detection the serum level of the following: VEGF levels, using enzyme-linked immunosorbent assays to measure CRP, and CA125 in the three groups. Among the three studied groups. There was a significant difference between the serum levels of CRP, CA125, and VEGF of preeclamptic women and those of control, where values of CRP were 4.2±1.1**,** 8±1.9 and 2±0.9 for mild, severe and control respectively. While values of median range of CA-125 were; 13.2, 15.3 and 11.7 for mild, severe and control respectively. However, values of median range of VEGF were; 581, 930 and 399.7 for mild, severe and control respectively. Therefore, serum values of CRP, CA125, and VEFG can play a pivotal role in the pathogenesis of preeclampsia and can be used as markers for the diagnosis and prediction of preeclampsia

Keywords: Preeclampsia, pregnancy, CA125, VEGF, CRP.

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1. Introduction

Preeclampsia is a complication of pregnancy associated with high maternal morbidity, mortality and intrauterine foetal growth restriction [1]. It is a specific human-pregnancy disease characterised by the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 5th month of gestation, occurs in about 2-8% of pregnancies [2]. More than 10% of women will develop preeclampsia on the 20th. Week of pregnancy and although the overwhelming majority of these will have successful pregnancy outcomes. The condition can give rise to severe multisystem complications including cerebral haemorrhage, hepatic and renal dysfunction and respiratory compromise. The diagnosis, prevention and treatment of this disorder has been challenging due to an incomplete understanding of the underlying pathogenesis [3]. A raising interest in the correlation between CRP and preeclampsia pathogenesis. C - reactive protein (CRP) is a plasma protein accompanied with acute inflammatory responses. An elevation in serum CRP have been associated with a possible predictive role for recurrent preeclampsia in women with a history of the disease in a prior pregnancy [4]. The CA-125 is a cell-surface antigen of high molecular weight. It is a mucin-like coelomic antigen, and it is available in 80% of non-mucus epithelial carcinomas of ovary [5]. This antigen is secreted from normal healthy tissue such as the coelomic epithelia [6]. It is a membrane-associated mucin that has a single transmembrane domain, it is characterized by being large in size and it contains about 22,000 amino acids [7]. Normally, the maternal serum levels of CA-125 are increased in pregnancy in two situations: at the beginning of pregnancy and postpartum period. The main cause of this elevation is the foetal chorionic, the amniotic fluid, and the maternal decidua [8]. The increase of the CA-125 in those situations indicates that the disintegration of the maternal decidua is a potential source and therefore the extension of the decidua and the separation of the trophoblasts from the decidua are introduced to be the mechanism by which the CA-125 is elevated [9]. Preeclampsia is related to reduction in trophoblasts migration into the maternal decidua, which will eventually lead to chronic inflammation within the placenta and this process, may result in increased levels of CA-125. When the condition of preeclampsia becomes more severe this makes the underlying inflammation much worse so it can be hypothesized that the maternal serum levels of CA-125 will be higher in females with severe preeclampsia than in other patients [10]. VEGF is produced by a variety of tissues and

cells and its release is generally increased by hypoxia. The properties of VEGF led to its study as a potential pathophysiological molecule in preeclampsia. However, there is a substantial, critical and serious discrepancy in the ongoing research's concerning the level of circulating VEGF in preeclampsia. Post-delivery VEGF concentrations fall in both preeclampsia and control groups suggesting that the placenta is the main source of VEGF production. Further evidence supporting the VEGF to have a pivotal role in pathogenesis of preeclampsia is provided by studies of the effect of VEGF on vascular function [11]. The aim of the current study is to assess the Biochemical criteria of Preeclampsia with special reference to the role of CRP, VEGF and CA 125 levels of serum in prediction of preeclampsia.

2. Materials and Methods

2.1. Technical design

A study included 30 women classified into three groups; mild preeclampsia, severe preeclampsia and normal pregnancy as a control group. They were recruited in the 3rd trimester pregnancy from Obstetrics and Gynaecology Department of Zagazig University Hospital. This study carried out at Zoology Department Faculty of Science, Zagazig University, and Obstatric and Gynaecology Department of Zagazig University.

- **Group I:** 10 pregnant females suffering from mild preeclampsia in the third trimester of pregnancy.
- **Group II:** 10 pregnant females suffering from severe preeclampsia in the third trimester of pregnancy.
- **Group III:** 10 females with normal pregnancy as control group in the third trimester.

2.2. Inclusion criteria

2.2.1. Cases of preeclampsia

Cases of preeclampsia are diagnosed by systolic blood pressure ≥140 mmHg, ddiastolic blood pressure ≥90 mm and Proteinuria >150 mg/24h urine collection.

2.2.2. Cases of Mild preeclampsia

Mild preeclampsia is diagnosed by systolic blood pressure ≥140 mmHg, while diastolic blood pressure ≥ 90 mmHg, proteinuria in 24h collected urine is > 0.3 gm/day and gestational age is more than 20 weeks. There are no other signs of problems with either the mother or the foetus.

2.2.3. Cases of Severe preeclampsia

Severe preeclampsia is diagnosed by systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥110 mmHg, and proteinuria >2g/24h urine collection, Symptoms as headache, blurring of vision, epigastric pain and other complications.

2.2.4. Duration of the study

The experimental period of the current study started from March 2019 until completing the sample size.

2.3. Operational design Methods

2.3.1. Detailed history

Detailed history (personal, obstetric, menstrual, past and family history) will be obtained from the recorded data in patient's official files

2.3.2. Complete general examination

- BL.P. -Pulse. -Temp. – L.L: for edema. -Chest and heart
- Maternal body weight and body mass index (BMI).
- Laboratory investigations including CBC, urine analysis including proteinuria, liver function, kidney function and bleeding profile.

2.4. Assessment of serum C - reactive protein by Enzyme Linked Immunosorbent Assay (hs CRP ELISA)

Quantitative determination of C-reactive protein (CRP) in serum of patients and controls by hs CRP ELISA (DRG, EIA-3954,USA) [12].

2.5. Assessment of serum cancer associated antigen CA125 by ELISA

Quantitative determination of the cancer associated antigen CA125 in serum of patients and controls by Can Ag CA125 ELISA (Fujirebio Diagnostics, cat no 400-10) [13].

3. Results and discussion

3.1. Detection of VEGF levels in the serum of experimental groups

3.1.1. C Reactive Protein (CRP) level

In mild preeclampsia group was (4.2±1.1), in severe cases was (8.0±1.9) and in control group (2.0±0.9) [14].

3.1.2. Cancer Antigen125 (CA 125)

In mild preeclampsia group CA125 ranged from 10.1 to 20.6, in severe cases was ranged from11.9-23.1 and in control group ranged from 6 to 14.

The results of the current study highlight the importance of the studied three markers; CRP, CA-125 and VEGF in the pathogenesis, diagnosis and prediction of preeclampsia. Concerning CRP, in the present study, there was a significant difference between the studied groups in comparison to control as regard CRP levels. These results are in agreement with other investigators.

Table 1. C-reactive protein (CRP) levels in the studied groups

Character	Mild preeclampsia 10	Severe preeclampsia 10	Control 10	*P*-value
CRP Mean + SD	4.2 ± 1.1	8. ± 1.9	2. ± 0.9	0.01*

**P*-value <0.001 highly statistically significant difference. This table shows that there is significant difference between the studied groups as regard the CRP.

Table 2. CA 125 (Cancer Antigen 125) in the studied groups

z	Mild preeclampsia 10	Severe preeclampsia 10	Control 10	*P*-value
CA 125 Median Range	13.2 10.1-20.6	15.3 11.9-23.1	11.7 (6-14)	0.04*

**P*-value < 0.05 statistically significant difference. This table shows that there is significant difference between the studied groups as regard d CA125.

Table 3: Serum VEGF in preeclampsia and control groups.

Character	Preeclampsia (N=20)	Control (N=10)	*P-* value
*** serum VEGF (pg/ml) Range Median**	791 278.7-1266.9	399.7 279.3-564.2	<0.001*

**P*-value <0.001 highly statistically significant difference. This table shows that there is a significant difference between the diseased and control group as regard serum VEGF.

Table 4. Serum VEGF in the studied groups.

Character	Mild pre-eclampsia	Severe Preeclampsia	Control	*P*-value
*** Serum VEGF(pg/ml) Median Range**	(581)a 278.7-790	(930)b 490 -1266.9	(399.7) 279.3-564.2	<0.001*

*P-value <0.001 highly statistically significant difference.

TVEGF= vascular endothelial growth factor. This table shows that there is a significant difference between the three groups as regard serum VEGF.

Table 5. The cut off value of serum and placental VEGF

Character	Pre-eclampsia N=20 No (%)	Control N=10 No (%)	*P*- value
***Serum VEGF** pg/ml. **>370 (T=19)** **<370 (T=11)**	17 (85.0) 3 (15.0)	2 (20.0) 8(80.0)	0.00*

*$p <$ *There was a statistical significant difference*

This table shows that the cut off values of serum VEGF is 370 pg/ml.

Table 6: The diagnostic value of serum VEGF

Character	Sensitivity %	Specificity %	PPV %	NPV %
Serum VGPF	85	80	89.5	72.7

This table shows the diagnostic value of VEGF in diagnosis of preeclampsia where the sensitivity was 85% and specificity was 80%, positive predictive value was 89.5% and negative predictive value was 72.7%.

Bargale who reported that hs-CRP levels were higher in preeclamptic women when compared to normotensive women and also the hs-CRP appeared to be of higher level in severe preeclampsia women than in the mild Preeclampsia women [15]. Therefore, it could be used as tool to determine severity of disease progression. In addition, Flafil and Maysoon recorded higher levels of CRP in women with preeclampsia indicating the presence of correlation with the severity of the disease. They suggested that the cause of elevated serum CRP in preeclamptic patients might be a result of reduced plasma volume in these patients [16]. In addition, Picklesimer reported that endothelial dysfunction leads to elevated serum CRP in inflammation [4]. Since early identification of patients with increased risk of preeclampsia is one of the important goals in obstetrics, it has been attempted to elaborate on the correlation between such inflammatory markers and presence of preeclampsia. The relationship between the high levels of CRP and preeclampsia had been reported, which is in agreement with our results [17]. As regards CA-125, in our study there was a significant difference between the studied groups as compared to control. This could be explained by the reduced trophoblastic migration into the maternal decidua, which leads to chronic inflammation within the placenta in case of pre-eclampsia. This process may lead to increased expression of CA-125. The underlying inflammatory process worsens when pre-eclampsia becomes severe in a patient. Thus, it can be hypothesized that maternal serum CA-125 levels will be higher in females with severe pre-eclampsia than in mild or normal cases. In accordance with the current study, Cebesoy *et al*. investigated serum levels of CRP and CA-125, which were significantly higher in women with preeclampsia / eclampsia when compared to healthy pregnant women. Therefore, the authors concluded that CRP and CA- 125 are elevating markers in preeclampsia [10]. Other researchers reported that there was a trend toward an elevation in CA-125 concentrations for pregnancies that are destined to develop preeclampsia. Fahim *et al*. reported that the mean serum concentration of CA125 was (32.59±1.63), (39.7±1.19), (52.92±2.88 in control mild and severe preeclampsia respectively which indicates that serum CA125 level increase with the severity of preeclampsia [18]. This may be explained as serum CA125 level related to impaired placentation, which causes intermittent disruption of placental perfusion ischemia-reperfusion type injury, oxidative stress and systemic inflammatory response.

Concerning VEGF, the present study recorded marked significant difference in VEGF levels between the preeclamptic groups and the control one being higher in the former two than the latter one. Other investigators are in agreement with these results. Several groups have demonstrated that circulating VEGF concentrations are significantly altered in preeclampsia. In addition, in agreement with our study, El-Salahy *et al*. reported that women with preeclampsia (mild or severe) had a significantly higher values of VEGF compared to controls [19]. VEGF is thought to lead to increased endothelial cell permeability, which is a pathologic abnormality in women with preeclampsia. Findings demonstrate that women with a definite increase in endothelial permeability (those with HELLP syndrome and preeclampsia) indeed had non-detectable concentrations of VEGF. The findings of an association of decreased VEGF concentrations with a disease of increased VEGF concentrations with a disease of increased endothelial permeability (leakage) is perplexing, and we cannot explain it [20]. On contrary to our study and from another side observed that, the sera from preeclamptic women had lower concentration of VEGF compared to controls. VEGF has also been shown to participate in the regulation of trophoblast cell survival, proliferation, migration and endovascular differentiation [21]. It was demonstrated that maternal serum VEGF level in this preeclampsia group was higher than the control group; the difference was statistically significant 20 [22]. Celik *et al*. explained the increase of VEGF in the preeclampsia group by endothelial cell damage that occurs in preeclampsia increases VEGF production during endothelial repair [23]. Increased concentration of circulating VEGF may cause extravasation of plasma proteins and proteinuria, which is the main symptom of preeclampsia [24]. The other possibility is that VEGF is secreted from the placenta and its production is increased in response to local ischemia in the placental infarction areas as a result VEGF increases in response to placental hypoxia [25].

4. Conclusions

CRP, CA125 and VEFG play a role in the pathogenesis of preeclampsia and can be used as markers for the diagnosis during the first and second trimester of pregnancy.

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