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THE ROLE OF SOLUBLE ENDOGLIN IN ESTIMATION OF PREECLAMPSIA SEVERITY: A CASE CONTROL STUDY CONDUCTED IN MOSUL CITY-IRAQ

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ABSTRACT

Background: The pathophysiology of preeclampsia has been extensively studied, yet significant problems remain unanswered. The diagnostic tools that are currently available for early detecting preeclampsia are few therefore it is essential and crucial to investigate the possibility of developing a diagnostic technique that might detect preeclampsia in pregnant before clinical symptoms appear. **Objectives:** Is to identify patients who are prone to develop severe preeclampsia using soluble Endoglin, allowing for early intervention and better disease outcomes in Mosul City. **Methods:** This study is a prospective case-control study. Conducted at Mosul General Hospital between January 2021 to December 2023. The questionnaire was divided into three main sections. The first section provides demographic information about the study participants. The second section covers laboratory findings of the study participants. And section three for soluble endoglin level. **Results**: The study includes 150 pregnant ladies, who were split into 100 preeclampsia groups, 50 severe PE versus 50 non-severe PE, and 50 normotensive women. Furthermore; the mean age of the study participants are 25.53 ± 5.26 years, while; the mean of gestational ages of the study participants are 34.72 ± 4.37 weeks. Moreover; statistically significant difference between the study groups found regarding gestational age (P value <0.001) and abortion (P value=0.032). Additionally; statistically significant difference between the study groups found regarding gravity (more gravity found among cases group), parity (more parity among cases group), abortion (more abortion among cases group). It's evident that the soluble endoglin levels increased as the severity of preeclampsia increased. In other word; the mean levels were 1.72 ± 0.52 for non-severe and 4.13 ± 2.34 for severe and 0.33 ± 0.13 for controls. Lastly; the study found that the optimum cut off points of endoglin for detecting non-severe and severe preeclampsia were 0.86 ng/mL and 1.13 ng/mL. **Conclusion:** Soluble endoglin may be a new biomarker for determining the severity of preeclampsia, and greater research involving numerous centers and larger population is required for accurately detect the cut off value of soluble endoglin after which non-severe and severe preeclampsia definitively occurred.

KEYWORDS: Soluble Endoglin, Diagnosis, Prediction, Preeclampsia.

1- INTRODUCTION

Preeclampsia is a prevalent obstetric condition that affects roughly 2-15 percent of pregnancies globally.[1] It is a pregnancy-specific multisystem disorder that is a major cause of maternal and newborn morbidity and mortality.[2] Unexpectedly, its prevalence is gradually rising in both high and low-income countries.[3]

The pathophysiology of preeclampsia has been extensively studied, yet significant problems remain unanswered. Although it is commonly known that preeclampsia is caused by the placenta, the precise etiopathogenetic process is still unclear. As a result, the only effective treatment for preeclampsia is delivery of the pregnancy and placenta removal.[4-6] The diagnostic tools that are currently available are few and only confirm the diagnosis after signs and symptoms have appeared. It is therefore essential and crucial to investigate the possibility of developing a diagnostic technique that might detect preeclampsia in pregnant women before clinical symptoms appear.[7-8]

The fundamental cause of preeclampsia is an imbalance of angiogenic and antiangiogenic elements in maternal

circulation, which results from abnormal remodeling of spiral uterine arteries and subsequent placental ischemia.[9] These factors have been thoroughly investigated as potential sources of biomarkers with significant diagnostic value.[10] Soluble endoglin, the extracellular domain of the homodimeric transmembrane glycoprotein endoglin, is an antiangiogenic factor produced in greater quantities by the hypoxic preeclamptic placenta.[11] Endoglin has an antiangiogenic effect in preeclampsia by binding to transforming growth factor (TGF-β1) in maternal circulation and inhibiting it signaling in endothelial cells.[11-12] The concentration of soluble endoglin may rise before symptoms appear, and its levels are also linked to the severity of preeclampsia. Endoglin may therefore make it possible to identify and diagnose pregnant women who are at a high risk of developing preeclampsia and other serious problems early.[13] The study aims to identify patients who are prone to develop severe preeclampsia using soluble Endoglin, allowing for early intervention and better disease outcomes.

2-PATIENT AND METHODS

This study is a prospective case-control study. It was approved by the Nineveh Directorate of Health. It was conducted on 150 pregnant women between "January 2021 to December 2023," who were split into 100 preeclampsia groups, 50 severe PE versus 50 non-severe PE, and 50 normotensive women. Participants were collected from Mosul General Hospital and signed informed consent forms. The study included singleton pregnancies diagnosed with preeclampsia who were admitted to the hospital or attended an outpatient clinic. The mothers were under 40 years old, had a gestational age of ≥ 32 weeks, and met the diagnostic criteria for severe and non-severe PE. A control group was matched for age and gestational age.

The following criteria were used to diagnose preeclampsia.

(a) Preeclampsia types are classified as either non-severe if the systolic or diastolic blood pressure is ≥140 or ≥90 mm Hg, respectively, measured twice at least 6 hours apart, or severe if the systolic or diastolic blood pressure is ≥160 or ≥110 mm Hg, respectively, in a single measurement; (b) if the protein in the urine dipstick in both groups is greater than +2; further characteristics for the severe type include: Maternal end organ damage, fetal growth restriction or death, and persistent headache or other brain or vision problems.

Five milliliters of venous blood were drawn from each patient on an empty stomach the morning before the treatment. The blood was allowed to coagulate at 37°C for 10-15 minutes before being centrifuged at 4000 rpm/min. The serum was then stored in a refrigerator at −80°C. Pregnant women's blood pressure was measured using a mercury sphygmomanometer in a sitting posture. Protein in urine was analyzed using the Sulfosalicylic acid test and quantitative measurement. Serum soluble endoglin levels were measured twice using enzyme-linked immunosorbent assay (ELISA).

Statistically analysis done by using the SPSS (scientific package for social sciences) version 30.0 software. In order to compare between the study groups, the ANOVA test was used. The ROC curve demonstrates more sensitive and specific cutoff points. P-values less than 0.05 were regarded as statistically significant.

3-RESULTS

The study includes 150 pregnant ladies, the mean age of the study participants are 25.53 ± 5.26 years, while; the mean of gestational ages of the study participants are 34.72 ± 4.37 weeks. Moreover; statistically significant difference between the study groups found regarding gestational age (P value <0.001) and abortion (P value=0.032). As shown in table 3.1.

Table 3.1: Basic information of the study participants.

Variable	Non severe Preeclampsia = 50	Severe Preeclampsia = 50	Controls = 50	P-value
Maternal age (year), mean ± Standard deviation	25.39 ± 5.49	25.72 ± 5.34	24.89 ± 6.23	0.820
Gestational age (weeks)	35.48 ± 1.34	33.39 ± 0.49	36 ± 2.29	**<0.001**
Gravidity: -Less than five -More than five	 42 (84%) 8 (16%)	 48 (96%) 2 (4%)	 45 (90%) 5 (10%)	0.392
Parity: 0 1-3 More than 3	 21 (42%) 17 (34%) 12 (24%)	 23 (46%) 21 (42%) 6 (12%)	 26 (52%) 11 (22%) 13 (26%)	0.249
Abortion: -Yes -No	 11 (22%) 39 (78%)	 8 (16%) 42 (84%)	 2 (4%) 48 (96%)	**0.032**

Table 3.2 shows comparison between the study groups regarding mean ± Standard deviation of endoglin level (ng/ml), which was statistically significant (P value <0.001).

Table 3.2: Comparison between the study groups regarding soluble endoglin levels.

Variable	Non severe Preeclampsia = 50	Severe Preeclampsia = 50	Controls = 50	P-value
Endoglin level (ng/ml), mean ± Standard deviation	1.72 ± 0.52	4.13 ± 2.34	0.33 ± 0.13	**<0.001**

Table 3.3 illustrates comparison and correlation between patients with non-severe preeclampsia and those with severe preeclampsia regarding; biochemical variable (ALT, AST, and serum uric acid) levels. No statistically significant difference and mild positive correlation with endoglin concentration found patient with non-severe preeclampsia and those with severe preeclampsia regarding ALT and AST levels. Lastly; no statistically significant difference and mild negative correlation with endoglin concentration were found between the two groups regarding uric acid level.

Table 3.3: Comparison and correlation with endoglin concentration between patients with non-severe preeclampsia and those with severe preeclampsia regarding biochemical parameters.

Variable	Non severe Preeclampsia = 50	Severe Preeclampsia = 50	P-value	Correlation coefficient with Endoglin Concentration
Alanine amino transferase (IU/L), mean ± Standard deviation	29.22 ± 7.73	31.02 ± 5.31	0.203	0.210
Aspartate amino transferase (IU/L), mean ± Standard deviation	28.78 ± 6.35	29.304	0.639	0.123
Uric acid (mg/dL), mean ± Standard deviation	6.49 ± 1.49	6.32 ± 1.44	0.681	-0.130

The serum soluble endoglin levels in non-severe and severe preeclampsia were analyzed, using ROC-curves as a diagnostic biomarker. The findings demonstrated that, when compared to control, the area-under-the-curve (AUC = 1) for both severe and non-severe preeclampsia patients. The accuracy measures for detecting non-severe and severe preeclampsia groups at cutoff point value of 0.86 ng/ ml and 1.13 ng/ml respectively were shown in table 3.4.

Study group	Cutoff point value (ng/mL)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Non-severe preeclampsia	0.86	96.4 %	91.1%	93.3%	95.6%
Severe preeclampsia	1.13	97.1%	90.7%	94.2%	96.8%

4- DISCUSSION

The shallow migration of cytotrophoblasts to the uterine spiral arterioles leads to poor vascular remodeling and a hypo-perfused placenta. When the placenta becomes ischemic, it releases angiogenic substances that might cause maternal vascular endothelial dysfunction.[14-15]

The current study found that patients with non-sever and sever preeclampsia had a significant lesser gestational age than control group in contrast to the maternal ages, which runs with Naglaa Mohamed Moharram et al.[16] In the same way of Asma Mehmood et al[17] and Ahmed Mohamedain et al[18] the study that the parity and gravidity of patients with non-severe and severe preeclampsia were comparable to control group. From the other hand; preeclampsia found to be more prevalent among patients with previous abortion which is goes with Abiyot Wolie Asres et al study result.[19]

Regarding soluble endoglin levels; this study showed that the level increased as the severity of preeclampsia increased. Moreover; the study found that the ALT and AST levels were mild positively correlated with soluble endoglin and serum uric acid was mild negative correlated with soluble endoglin level. These results are parallel to Naglaa Mohamed Moharram et al.[16] and Yuganti C Sawarkar Lamyaa[20] study results.

From the other hand; this study found that the optimum cut off points of endoglin for detecting non-severe and severe preeclampsia were 0.86 ng/mL and 1.13 ng/mL which is closed to what was found by Lamyaa Taha Muhammed et al.[21]

The study's findings are limited by a small sample size of women from only one hospital, which may not be representative of all of Mosul hospitals. However; larger sample from different districts may provide a more comprehensive view of the role of endoglin in detection

of preeclampsia. Additionally; this study did not include cases of gestational or persistent hypertension. And due to limited resources, a Doppler study was not conducted for both the study participants. Lastly; cases were enrolled at induction of labor rather than early gestation which make prediction of preeclampsia useless.

5- CONCLUSION AND RECOMMENDATION

Soluble endoglin may be a new biomarker for determining the severity of preeclampsia, and greater research involving numerous centers and larger population is required for accurately detect the cut off value of soluble endoglin after which non-severe and severe preeclampsia definitively occurred.

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Conflict of intertest

About this study, the authors disclose no conflicts of interest.

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