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Interleukin-6 Biomarker as Possible Predicator of Preeclampsia

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ABSTRACT

Preeclampsia (PE) is a serious illness that can harm both mothers and unborn children and may even be fatal. It contributes significantly to maternal fatalities in underdeveloped countries. PE, which affects 2%–3% of women who are pregnant after 20 weeks of pregnancy, is marked by proteinuria and hypertension. PE is a significant condition that plays a significant role in maternal fatalities in underdeveloped countries and is a significant cause of death for both mothers and newborns. Each year, around 60,000 maternal fatalities occur in the world. Serum interleukin-6 (IL-6) was measured in pregnant women during the first trimester and second trimesters. IL-6 was necessary to establish serum biomarkers that can accurately predict the onset of preeclampsia. In a prospective cohort study that was conducted in the Obstetrics and Gynecology Department and Antenatal Care Unit at Maternity and Pediatrics Teaching Hospital in AL-Diwaniyah – Iraq, 160 pregnant patients between the years of 20 and 40 who were normotensive and had gestational ages of 10 to 13 weeks were included in this research between August 2021 and May 2022. Bioassays for IL-6 were conducted after blood samples were obtained. At the end of the study, it was confirmed that for women with pre-eclampsia (n = 33, 22.0%) and those women with no pre-eclampsia (n = 117, 78.0 %), there was no significant difference in the level between the preeclampsia and no preeclampsia group ($p > 0.05$).

1. Introduction

Preeclampsia (PE) is a systemic syndrome that affects 2%–3% of pregnant females after 20 weeks of pregnancy and is marked by hypertension and proteinuria, PE is a serious cause of disease and death in both mothers and babies, PE is a causative agent of maternal death in poor nations. There are approximately 60,000 maternal deaths in the world each year (Sircar, Thadhani & Karumanchi, 2015). Multifetal gestations, previous preeclampsia, weight gain, vascular and connective tissue diseases such as systemic lupus erythematosus, and diabetes are all significant risk factors for preeclampsia (Ives, et al., 2020).

PE usually results in ischemic tissue, which produces extensive endothelial dysfunction. PE is also linked to circulatory system problems, abnormal liver function, renal failure, neuropathies, constriction, increased systemic vascular resistance, and hence diminished the passage of blood (Jasovic Siveska, 2013). The processes underlying preeclampsia's development of endothelial cell dysfunction remain unknown (Trivedi, Trivedi & Sagare, 2013). Preeclampsia is primarily caused by a failure of trophoblast invasion, which results in abnormal endothelial function and inflammation (Raymond & Peterson, 2011). Placental malfunction can be diagnosed early in the second trimester by abnormal levels of angiogenic factors in the mother's blood before preeclampsia symptoms appear (Levine, et al., 2004).

Cytokines are immune system intercellular mediators that play a key role in many aspects of pregnancy (Nair & Salomon, 2018). In fetal tissues, a wide range of cytokines

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are present, and research on cytokines demonstrate that some of them affect the development of pregnancy and the health of the children after delivery (Aggarwal, et al., 2019). Interleukin 6 (IL-6) is a soluble mediator that affects inflammation, immunological response, and hematopoiesis in a pleiotropic manner (Prairie, et al., 2021). It is a multifunctional cytokine initially discovered in 1986 that plays a key role in acute and chronic inflammation as well as autoimmune (Nawaz & Verma, 2020). IL6 is produced in response to infection, injury, and stress, and its increased expression has been linked to a number of chronic inflammatory and auto-immune illnesses (Cornelius, 2018).

Preeclampsia is marked by a lack of vascular remodeling, which causes diminished placental perfusion and a hypoxic environment for placental and embryonic tissues (Yagel, Cohen & Goldman-Wohl, 2020). When exposed to hypoxia, preeclamptic women's placental explants produce more IL-6 than normal pregnant women's explants. Increased IL-6 and CD4+ T cells are linked to pre-eclampsia (Nakashima, et al., 2021). T cells proliferate and release interleukins (ILs) and cytokines like IL-6 (Gronkowska, 2021).

According to a complete model of preeclampsia, immune maladaption at the implantation site leads to diminished trophoblast invasion and, as a result, poor transformation of the decidual spiral arteries and arterioles. Reduced utero-placental blood flow causes placental ischemia and hypoxia. In the maternal circulation, low levels of angiogenic factors are connected to high levels of anti-angiogenic factors, placental debris, reactive oxygen species, and proinflammatory cytokines. Proteinuria and hypertension, two of the most common symptoms of preeclampsia in women, are brought on by changes in the levels of these circulating chemicals, which increase endothelial cell activation and vascular damage (Stepan, Hund & Andraczek, 2020).

While inflammatory cytokines like IL-6 have been found to be higher in preeclamptic women, it is unclear if modest and long-term increases in cytokines during pregnancy might cause blood pressure to rise (Mauro, et al., 2021). Reduced uterine perfusion pressure (RUPP) raises arterial pressure and impairs endothelial function in pregnant women (Bakrania, et al., 2019). In pregnant women, the RUPP generates a persistent inflammatory response marked by increased circulating TNF-, IL-6, and immunological infiltrates in the placenta (Bakrania, et al., 2019; Granger, Spradley & Bakrania, 2018). Furthermore, in pregnant women, a decrease in RUPP is a significant stimulant for AT1-AA synthesis (Cunningham, et al., 2021). However, it's probable that the enhanced maternal inflammatory response associated with placental ischemia in pregnancy contributes to the formation of AT1-AA in response to RUPP (Gumusoglu, et al., 2020). The blood levels of IL-6 in RUPP were recently revealed to be increased (Issotina Zibrila, et al., 2021). The infusion of IL-6 into pregnant women, both acute and chronic, raised arterial pressure and lowered renal plasma flow and glomerular filtration rate (Bakrania, et al., 2020; Sani, Vahed & Ardalan, 2019). The stimulation of the renin-angiotensin system and AT1-AAs by IL-6 might result in increased vasoconstriction, decreased sodium excretory function, and hypertension (Dechend, Lamarca & Davidge, 2022).

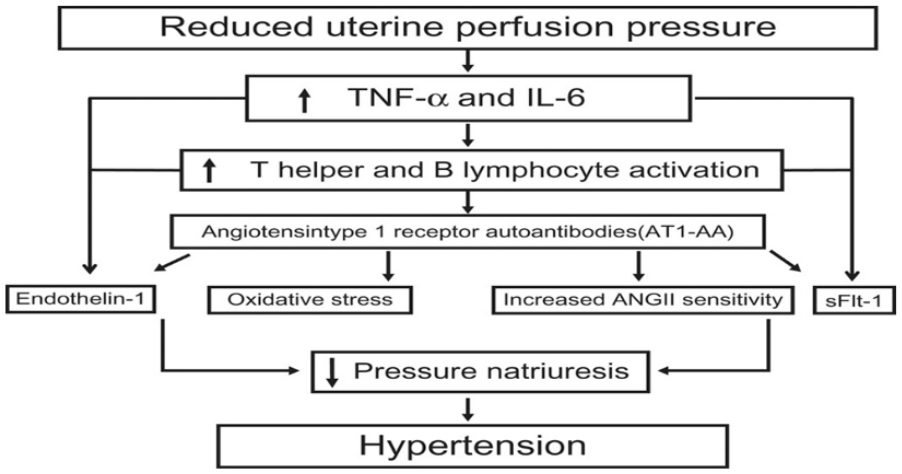

Fig. 1. Inflammatory cytokines, TNF-α and IL-6 function in immune activation in the pathogenesis of pre-eclampsia hypertension (Lamarca, Brewer, & Wallace, 2011)

2. Materials and Methods

The study was a prospective cohort study that was conducted in the Obstetrics and Gynecology Department and Antenatal Care Unit at Maternity and Pediatrics Teaching Hospital in AL- Diwaniyah – Iraq, from the period of August 2021 May 2022, in which 160 pregnant patients aged 20-40 years normotensive were enrolled in this study with gestational age 10-13 weeks. Blood samples were collected and bioassays for IL-6 were performed. Then, at 24-28 weeks, blood samples were collected again to assess IL-6 and follow-up of the patients for the development of any evidence of any adverse pregnancy outcome.

The IL-6 assay was performed using an IL-6 kit from MyBioSource, USA.

2.1. Inclusion Criteria

Pregnant singleton, normotensive, gestational age of 10-13 weeks based on an accurate last menstrual period date, in the first trimester.

2.2. Exclusion Criteria

Women were not included if they had fetal structural or chromosomal abnormalities or pregnancy with medical disorders such as heart disease, diabetes mellitus, chronic

hypertension, thyroid disorders, liver disorders, autoimmune disorders, and maternal renal disease.

2.3. Statistical Analysis

The statistical package for social sciences (SPSS) version 25 and Microsoft Office Excel 2013 were used to gather, summarize, analyze, and present data. Number and percentage were used to express qualitative (categorical) variables, whereas, numerical variables were first tested for normality using the Kolmogorov-Smirnov test, and then normally distributed numeric variables were expressed as mean (an index of central tendency) and standard deviation (an index of dispersion), while non-normally distributed numeric variables were expressed as median (an index of central tendency) and inter-quartile range (an index of dispersion). P-values equal to or less than 0.05 were used to indicate significance. P-values equal to or less than 0.01 were considered high significance.

3. Results and Discussion

160 patients were enrolled in the study, but only 150 patients were followed up as 10 patients were lost from the study. At the end of the study and based on blood pressure measurements and urine examination for protein, women were classified into two major subgroups, those women with pre-eclampsia (n = 33, 22.0 %) and those women with no pre-eclampsia (n = 117, 78.0 %).

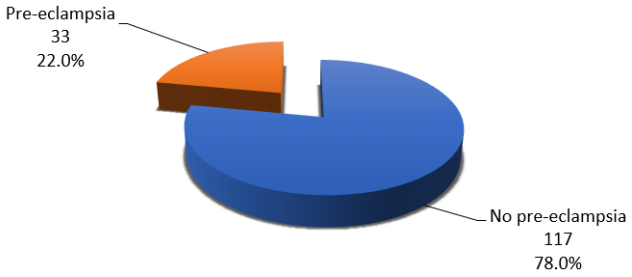

Fig. 2. Pie chart showing the frequency distribution of women enrolled in the current study according to occurrence of pre-eclampsia

Regarding serum IL-6, there was no significant difference in its level at baseline visit or at follow up (p > 0.05), figures 3 and 4; however, its level at baseline was substantially higher in preeclampsia group in comparison with no preeclampsia group, 20.68 (18.73) pg/ml versus 17.35 (10.61) pg/ml, respectively and the p-value was very close to the significance level of 0.05 as it was 0.084.

Table 1
Comparison of IL-6 levels at baseline and at follow up

Characteristic	Total	Pre-eclampsia	No pre-eclampsia	P
	n = 150	n = 33	n = 117	
Baseline IL-6 (pg/ml)				
Median (IQR)	17.86 (12.20)	20.68 (18.73)	17.35 (10.61)	0.084 M
Range	7.02 -73.12	8.40 -73.12	7.02 -53.26	NS
Follow up IL-6 (pg/ml)				
Median (IQR)	12.75 (11.62)	13.68 (10.00)	12.00 (12.83)	0.401 M
Range	2.37 -94.78	8.59 -94.70	2.37 -94.78	NS

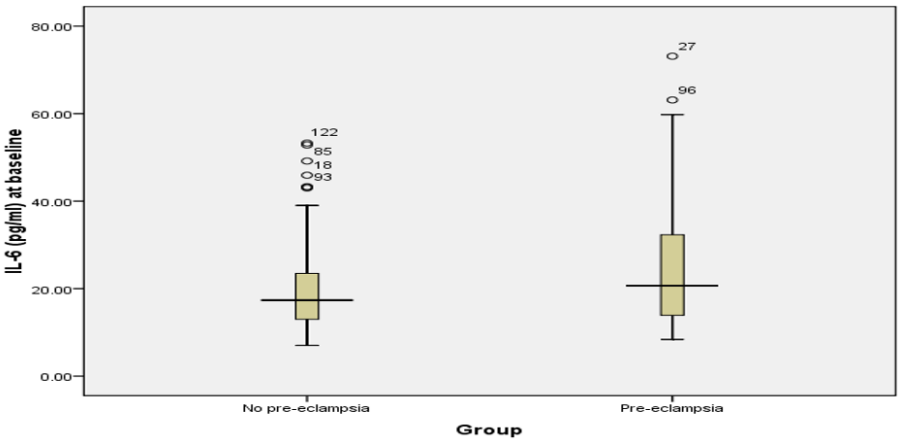

Fig. 3. Box plot showing comparison of serum interleukin-6 (IL-6) at baseline between preeclampsia group and no preeclampsia group

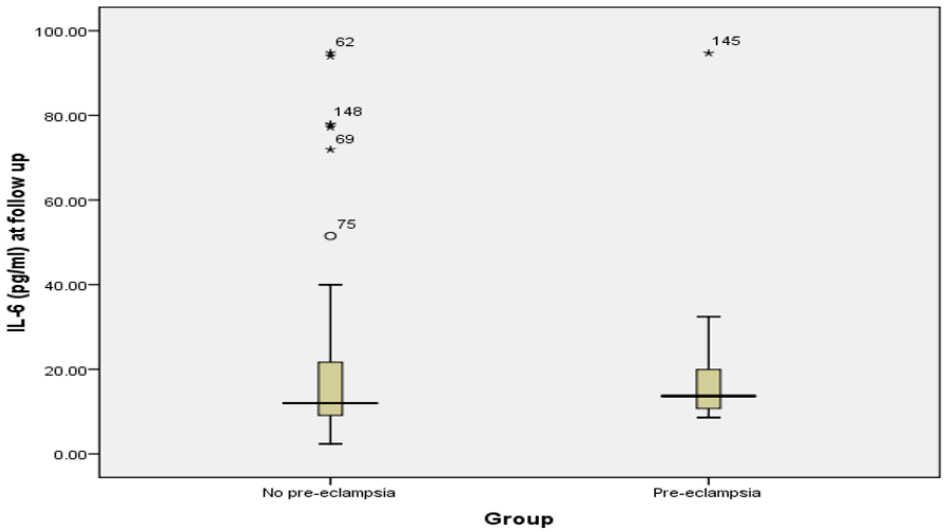

Fig. 4. Box plot showing comparison of serum interleukin-6 (IL-6) at follow up between preeclampsia group and no preeclampsia group

The ROC analysis revealed that serum IL-6 was a poor predictive marker for preeclampsia because the area under the curve (AUC) was < 0.7 and subsequently the sensitivity was low (42.4 %) in spite of an acceptable specificity level of 42.4 %, as shown in figure 5.

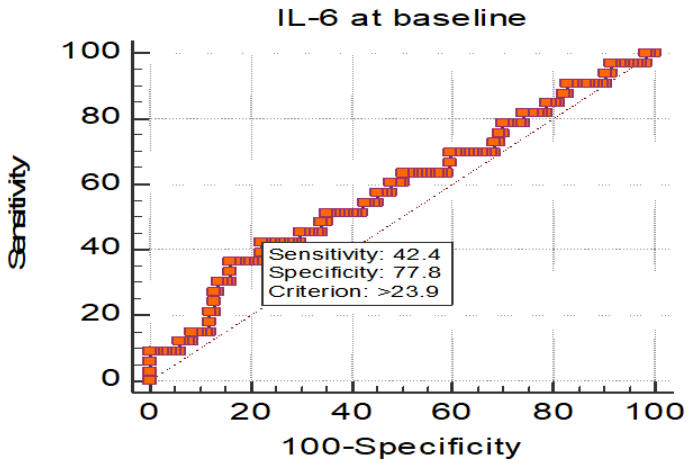

Fig. 5. Receiver operator characteristic (ROC) curve analysis to find the cutoff value of serum interleukin-6 (IL-6) that can predict a diagnosis of preeclampsia

Table 2
The characteristic of the ROC analysis for serum IL-6

Characteristic	IL-6
Cutoff	>23.9
AUC	0.587
95% CI	0.503 to 0.666
p-value	0.154 NS
Sensitivity %	42.4
Specificity %	77.8
Accuracy %	58.7

IL-6: interleukin-6; **AUC**: area under curve; **: significant at $p \leq 0.01$; **NS**: not significant

There was no significant difference in serum IL-6 levels at baseline or at follow-up ($p > 0.05$), as shown in figures 3 and 4; however, its level at baseline was significantly higher in the preeclampsia group compared to the control group, with a p-value of 0.084, which was very close to the significance level of 0.05. Negi, Rahul, et al. (2022), it was found that the IL-6 levels were not found to be significantly different between normotensive women and preeclamptic women (Negi, et al., 2022). Gencheva, et al., (2022) showed no

significantly different levels of serum interleukin-6(27). Setiawati, (2020) showed that there was no significant difference between normotensive women and preeclamptic women.

4. Conclusion

In conclusion, Proinflammatory cytokines may have a role in the development and pathophysiology of preeclampsia. The inflammatory cytokines IL6 were found to be elevated in severe preeclampsia in this study. The study revealed that serum IL-6 was a poor predictive marker for preeclampsia.Elevated maternal serum IL-6 levels are not useful as a specific marker for the prediction of preeclampsia. It was No significant difference was observed in maternal serum IL-6 levels between the preeclampsia and no preeclampsia groups.

Competing Interests

The authors have declared that no competing interests exist.

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