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# Serum IL 6 and umbilical artery Doppler indices in pre-eclamptic patients☆

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**KEYWORDS**

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**Abstract** *Objectives:* To study the changes in serum IL 6 levels in pre-eclamptic patients and to detect any correlation between these changes and changes in the umbilical artery Doppler velocimetry.

*Methods:* In Shatby Hospital, 100 pregnant women, at or beyond 32 weeks were selected and divided into three groups: group A with severe pre-eclampsia, group B with mild pre-eclampsia, and group C with normal pregnancy as control. Measurement of maternal serum IL 6 using ELISA and umbilical artery Doppler velocimetry was done. Kruskal–Wallis, Mann–Whitney U tests, and Spearman's rank correlation tests were used.

*Results:* A statistical significant difference ($p < 0.001$) was found regarding serum IL-6 level. Using ROC curve for IL 6 levels, it is suggested that IL 6 of 0.82 ng/dl is a cutoff level to early diagnose mild pre-eclampsia (with sensitivity 87.5% and specificity 100%). A statistical significant correlation was found between maternal serum IL 6 levels and S/D ratio and RI in severe pre-eclamptic group ($p < 0.05$).

*Conclusion:* Maternal serum IL 6 > 0.82 ng/dl can be implicated as an early laboratory diagnosis of mild pre-eclampsia. The significant correlation between maternal serum IL 6 levels and Doppler velocimetry supports both the immunologic and the systemic endothelial dysfunction theories of pre-eclampsia.



## 1. Introduction

Pre-eclampsia is a systemic disorder unique to pregnancy occurring in 4–8% of pregnant women. It is characterized by new onset of hypertension and proteinuria after 20 weeks of gestation.[1] There is widespread belief that reduced uteroplacental perfusion is the central pathophysiologic process

☆ The research protocol was approved by our institutional Ethics Committee before the study began. A Written informed consent for participation in the study was taken from all recruited women.

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involved in the development of preeclampsia. This reduced perfusion results from shallow trophoblast invasion with incomplete endovascular alteration, thereby inhibiting essential morphological changes of the maternal uterine vasculature needed to reform the spiral arterioles into low-resistance vessels.[2,3] This inadequate trophoblast invasion may result from decreased expression of human leukocyte antigen-G (HLA-G) leading to an abnormal interaction with decidual natural killer (NK) cells, which are believed to play a major role in these processes through the production of immunoregulatory cytokines and angiogenic factors. More recently, the theory of deficient trophoblastic invasion has been disputed on the basis of evidence that failure to remodel the uterine arteries is also associated with intra-uterine growth restriction, where no signs of hypertension and proteinuria are observed.[4] Two theories have highlighted the "excessive inflammation" and the angiogenic imbalance" theories as the cause of pre-eclampsia.[5] Evidence of inflammation theory includes elevated inflammatory cytokines and uncontrolled increased activation of the complement system.[6] Macrophages, neutrophils, and T lymphocytes of the T helper (Th-1) subset are the predominant cell types mediating the inflammatory cascade in pre-eclamptic women. Pro-inflammatory cytokines such as IL-6 and TNF alpha interact with important blood pressure regulatory systems such as the renin–angiotensin system, sympathetic nervous system and endothelial factors.[7] IL-6 is a pro-inflammatory cytokine produced by mononuclear phagocytes, endothelial cells, fibroblasts and T cells, expressed in the reproductive tract and gestational tissues and exerts regulatory functions in embryo implantation and placental development, as well as the immune adaptations required to tolerate pregnancy.[8,9]

IL-6 may increase the permeability of endothelial cells by changing the cell shape and rearrangement of intracellular actin fibers.[10] The quantitative importance of the renin-angiotensin system in mediating the effects of IL-6 during pregnancy is unknown and remains to be an important area of investigation.

Doppler velocimetric parameters have become established as the cornerstone mechanism to examine RI, PI, and S/D ratio of the maternal-fetal circulation. Women developing pre-eclampsia have significantly altered velocimetric parameters, indicative of high vascular RI, compared with women with normal uterine perfusion.[11]

### 1.1. Objectives

The objectives were to study the changes in serum IL 6 levels in pre-eclamptic patients of different severity and to detect any correlation between the changes in the maternal serum IL 6 levels and changes in the umbilical artery Doppler velocimetry in pre-eclamptic patients.

### 1.2. Methods

100 pregnant women, at or beyond 32 weeks of gestation (32–40 weeks) were selected from the out-patient ante-natal clinic and from the inpatient pre-eclamptic unit in Shatby Maternity University Hospital. Pre-eclampsia was diagnosed according to the American college of Obstetricians and Gynecologists in its last version, de novo arterial hypertension, after 20th week of gestation, with systolic blood pressure $>140$ mmHg or diastolic blood pressure $>90$ mmHg, in two separate measurements, at least 4 h apart. Blood pressure was measured with the pressure cuff placed on the left arm at the heart level in sitting position. In addition, the presence of proteinuria of more than 300 mg/L in a random sample is the other essential finding to fulfill the diagnosis.

### 1.3. Exclusion criteria

Multiple pregnancy, pregnancy complicated with diabetes mellitus or thyrotoxicosis or pyelonephritis, hypertension diagnosed before 20th week of gestation have been excluded. Patients with chronic inflammatory diseases (e.g. systemic lupus erythromatosis, rheumatoid arthritis, inflammatory bowel disease) or with acute inflammatory diseases (e.g. tonsillitis, urinary tract infections) and pregnancy before 32 weeks of gestation, have been excluded.

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Patients were divided into three groups: group A (40 patients) with severe pre-eclampsia, group B (40 patients) with mild pre-eclampsia, and group C (20 pregnant women) with normal pregnancy as control.

Blood samples were taken from all included women for testing serum IL-6 levels. Umbilical artery Doppler velocimetry was done to all cases to measure S/D ratio, Pulsatility index PI, and Resistance index RI.

### 1.4. Sample collection and biochemical analysis

Blood samples were drawn from an ante-cubital vein into EDTA tubes in all patients. All collected blood samples were immediately centrifuged at 4000 rpm and $+4$ °C for 10 min and then the collected sera were transferred to Eppendorf tubes and kept at $-70$ °C until they were analyzed. IL-6 levels were determined using Enzyme-linked immunosorbent Assay ELISA according to the manufacturer's instructions. Intra and inter assay coefficients of variation ranged from 3% to 7%.

### 1.5. Statistical analysis

Mean and standard deviation were used to describe numerical variables. Kolmogorov–Smirnov test was used to evaluate the distribution pattern of the data. Kruskal–Wallis test was used for comparison between 3 groups. Mann–Whitney U test was used for comparison between two groups.

The ability of IL-6 concentrations to discriminate between pre-eclamptic and non-pre-eclamptic pregnancies was quantified by using the area under the receiver operating characteristic (ROC) curve. This area is a suitable measure to summarize the discriminative power of a value and can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). A value of 0.7–0.8 is considered to represent reasonable discrimination, and a value of $>0.8$ is good discrimination. When the ROC curve is plotted with 1-specificity on the abscissa and the corresponding values for sensitivity on the ordinate the point of the ROC curve closest to the upper left corner of the coordinate system

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