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Significance of Interleukin-6 as Early Biochemical Marker in Rural Pre-Eclamptic Pregnant Women

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Abstract

Introduction: *Preeclampsia is one of the medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. There is limited invasion of the spiral arteries that supply superficial layers of the decidua which results in reduced uterine perfusion pressure and placental ischaemia . This ischemic placenta may induce the release of pro inflammatory cytokines like IL6 that may contribute to wide spread endothelial damage, pathognonomic of preeclampsia. Hence we would to like analyse the serum IL-6 in preeclamptic pregnant women.*

Materials and methods: *This is an Observational study. 30 rural preeclamptic pregnant women and 30 normal rural pregnant women in third trimester, irrespective of gravida and age were included in this study. 3ml of venous blood was collected under aseptic conditions and analysed for IL6 and routine biochemical investigations. The levels of IL-6 were measured by DIAsource IL-6 ELISA kit supplied by Rue du Bosquet, Beligium. Statistical analysis was done by student "t" test.*

Results: *The levels of IL-6 in serum of preeclamptic pregnant women were found to be significantly increased when compared with normal pregnant women (p <0.001).*

Conclusion: *Significant elevation of IL-6 suggests that there is an increased maternal inflammatory response and endothelial dysfunction in preeclamptic pregnant women. Early identification of placental ischaemia and endothelial dysfunction using biochemical marker IL-6, will help to prevent multiorgan damage and impending complications in pre-eclamptic pregnant women as early as possible.*

Keywords: *Interleukin-6, Preeclampsia, Endothelial dysfunction, Cytokines, Biochemical marker.*

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I. Introduction

Preeclampsia is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality . The incidence of preeclampsia in hospital practice varies widely from 5% to 15%. The incidence in primigravidae is about 10% and in multigravidae is 5%.[1]

Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after the 20th week in a previously normotensive and nonproteinuric woman. Increased maternal deaths are mainly related to Eclampsia, accidental hemorrhage, acute renal failure, pulmonary edema, disseminated intravascular coagulopathy and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. Though mortality has been reduced significantly in the advanced countries, it still remains high in the developing world. [1]

In preeclampsia, there is failure of the second wave of endovascular trophoblast migration and there is reduction of blood supply to the fetoplacental unit. The failure of trophoblast invasion results in reduced uterine perfusion pressure and placental ischaemia . The ischemic placenta may induce the release of bioactive circulating factors including pro inflammatory cytokines like IL6 that may contribute to mediate the wide spread endothelial damage pathognonomic of preeclampsia.[2]

Preeclampsia is a multisystem disorder with greatest effects on the central nervous system, the liver, the kidney and the coagulation system, with resultant organ damage. The increased plasma levels of these markers above the reference limits in the healthy pregnant population is indicative of some degree of organ dysfunction.[2]

Many maternal and fetal complications (Maternal-eclampsia, oliguria and anuria, preterm labor, HELLP syndrome, ARDS and Fetal – Intrauterine death, asphyxia, prematurity and intrauterine growth restriction) are likely to appear in pre-eclampsia patients due to multiorgan damage. The early identification of

placental ischemia and endothelial injury to organs using biochemical marker IL-6 will help to prevent multiorgan damage and complications in pregnant women as early as possible.

II. Methodology

This observational study was done with 30 rural preeclamptic pregnant women and 30 normal rural pregnant women in Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Rajah Muthaiah Medical College. The study population and controls are from third trimester presented with absence of labour and absence of premature rupture of membranes. Multiple gestation, diabetes mellitus, gestational diabetes mellitus, chronic hypertension, pyrexia of unknown origin, pelvic inflammatory diseases, and with other endocrinal disorders were excluded from the study.

Study was approved by our Institutional Human ethics committee (IHEC/757/2021). A written informed consent was obtained from all subjects after clearly explaining them about the nature, purpose and duration of the study in the vernacular language.

3ml of venous blood samples were collected under aseptic conditions and analysed for fasting blood glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phophatase, serum electrolytes and IL-6.

The collected data was tabulated and analysed using statistical softwares. Statistical analysis was performed using student "t" test and results were compared with controls.

Inclusion criteria:

1. third trimester pregnancy
2. with absence of labour
3. with absence of premature rupture of membranes

Exclusion criteria:

1.multiple gestation,
2.diabetes mellitus,
3.gestational diabetes mellitus
4.chronic hypetension,
5.Pyrexia of unknown origin
6.pelvic inflammatory disease and
7.any other endocrinal disorders.

Procedure methodology

Study was approved by our Institutional Human ethics committee (IHEC/757/2021). A written informed consent was obtained from all subjects after clearly explaining them about the nature, purpose and duration of the study in the vernacular language.

3ml of venous blood sample was collected under aseptic conditions and analysed for fasting blood glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phophatase, serum electrolytes and IL-6. Measurement of serum IL-6 was done using DIAsource IL-6 ELISA kit (Rue du Bosquet, Beligium).

Statistical analysis

The data collected were entered into microsoft excel, master chart was created. Compilation of data and analysis was done using SPSS (statistical package for social sciences) version 26. In order to find out the difference between the groups, Student "t" test was applied. "P" value of less than 0.05 was considered to be statistically significant.

III. Results

The mean age for study population was 25.87±5.78 and for controls was 25.77±4.55. Table-1 shows mean and standard deviation of gestational age, weight, height, random blood glucose, urea, creatinine, Na and K electrolytes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and IL-6, Student "t" test was applied. "P" value of less than 0.05 was considered to be statistically significant.

Table-1

Parameter	Preeclamptic pregnant women n=30	Normal pregnant women n=30	P-value
Gestational age(weeks)	34.90±3.25	35.10±3.76	0.382
Weight (Kg)	75.86±17.06	68.40±13.91	0.069
Height (cm)	149.03±5.93	148.50±5.13	0.711
Fasting blood glucose (mg/dl)	88.20±16.44	91.53±11.45	0.366

Urea(mg/dl)	21.73±5.55	21.77±3.95	0.979
Creatinine(mg/dl)	0.760±0.10	0.737±0.08	0.335
Sodium(mEq/L)	138.73±3.27	138.63±2.69	0.898
Potassium(mEq/L)	4.112±0.33	4.003±0.22	0.684
ALT(mg/dl)	25.23±3.75	23.1±5.92	0.106
AST(mg/dl)	33.6±3.71	20.9±4.94	0.001**
ALP(mg/dl)	163.33±12.5	86.9±9.04	0.001**
IL-6(pg/ml)	140.83±12.68	19.36±5.84	0.001**

** P value less than 0.05 is significant

Table-1 shows the values of gestational age, weight, height, random blood sugar, urea, creatinine, sodium, potassium, ALT, AST, ALP and interleukin-6 in preeclamptic pregnant women and normal pregnant women. The values of aspartate aminotransferase, alkaline phosphatase and interleukin-6 where significantly increased in preeclamptic pregnant women when compared with normal pregnant women.

Table-2 shows the correlation of Interleukin-6 with other parameters

Variable		**Interleukin-6**
Fasting blood glucose(mg/dl)	Pearson Correlation	-0.041
	Sig. (2-tailed)	0.756
Aspartate aminotransferase(mg/dl)	Pearson Correlation	0.177
	Sig. (2-tailed)	0.180
Alanine aminotransferase(mg/dl)	Pearson Correlation	0.063
	Sig. (2-tailed)	0.634
Alkaline phosphatase(mg/dl)	Pearson Correlation	0.444**
	Sig. (2-tailed)	0.001**
Urea (mg/dl)	Pearson Correlation	0.080
	Sig. (2-tailed)	0.549
Creatinine (mg/dl)	Pearson Correlation	0.157
	Sig. (2-tailed)	0.237
Sodium (mEq/L)	Pearson Correlation	-0.075
	Sig. (2-tailed)	0.572
Potassium (mEq/L)	Pearson Correlation	-0.016
	Sig. (2-tailed)	0.905

**Statistically significant at $p \leq 0.05$

Table-2 shows that IL-6 shows significant correlation with Alkaline phosphatase (ALP).

IV. Discussion

Interleukin-6 is increased seven times in preeclamptic pregnant women when compared with normal pregnant women in our study, because in preeclampsia, there is failure of the second wave of endovascular trophoblast migration and there is reduction of blood supply to the fetoplacental unit[1]. The failure of trophoblast invasion results in reduced uterine perfusion pressure and placental ischaemia . The ischemic placenta may induce the release of bioactive circulating factors including pro inflammatory cytokines like IL6 that may contribute to mediate the wide spread endothelial damage pathognonomic of preeclampsia[1].

Alkaline phosphatase (ALP) is an enzyme produced primarily by cells of liver, bone, kidney, small intestine and placenta. It appears in maternal serum in the second trimester and increases progressively with gestational age. During pregnancy serum ALP levels increase progressively with a maximum value in third trimester. Review of the literature has linked markedly elevated serum ALP levels is seen in obstetric and perinatal conditions, including preterm labor, hypertensive disorders of pregnancy and low birth weight. The exact mechanism of this association is unknown, but an overwhelming majority of literature suggests placental dysfunction as the primary cause[3].

Elevated circulating ALP may be a marker of placental injury. The elevated levels of serum PLAP and ALP in a pregnant, hypertensive woman may be attributed to placental dysfunction, resulting in an increased serum concentration of the enzyme. The mechanism of increase seen in hypertensive disorders of pregnancy is thought to be due to overactive shedding of syncytiotrophoblasts with subsequent necrosis and apo necrosis of the syncytiotrophoblast particles. This damage may be seen microscopically, with placental pathology demonstrating placental infarction and damage to villous syncytiotrophoblasts[3].

This study also reports significant differences in the serum levels of liver enzymes, Aspartate Amino Transferase (AST), and Alkaline phosphatase (ALP), between pre-eclamptic subjects and control group. The increased plasma levels of these markers above the reference range in the healthy pregnant population is indicative of some degree of organ dysfunction[4,5].

Pre-eclampsia causes hepatocellular dysfunction reflected by elevation of serum alanine transaminase, aspartate transaminase and alkaline phosphatase[12]. Grossly, the liver shows diffuse, fine or blotchy haemorrhages on cut surface, while histologically, fibrin thrombi are found in portal vessels and hepatocellular necrosis[6].

This finding is consistent with reports by *Ifeoma udenze et al*;[2] 2015 reported that increase in pro inflammatory cytokines, IL-6 levels in the women with severe preeclampsia (95.21pg/ml) when compared with normal pregnant women(12.92pg/ml) and also by *Dan mihu et al*;[11] in 2016 reported that IL-6 had two-fold increase in preeclamptic pregnant women.

Ayse ekin kara et al;[7], 2019 reported that the serum levels of hs-CRP, and IL-6 were not elevated in pregnancies complicated with preeclampsia compared with normal pregnancies and also *Norma C Serrano et al*;[8] in 2020 reported that there is not a causal association between elevated levels of CRP and IL-6 in the presence of pre-eclampsia. The disparity in the reports from these studies may be from differences in time of sampling, studies not distinguishing between mild or severe forms of preeclampsia and differences in study design; prospective or cross sectional as opposed to case control studies, amongst others.

Our study shows a significant relationship between IL-6 with ALP (Alkaline phosphatase) suggesting that inflammation is high and leads to the tissue damage in preeclampsia.

The reduced uterine perfusion pressure and resultant placental ischemia in preeclampsia induces the release of cytokines that mediate immunologic, inflammatory and reparative host responses that contribute to the widespread endothelial damage and resultant hypertension and organ dysfunction in preeclampsia[9,10].

V. Conclusion

Our study has shown a statistically significant increase in the levels of the pro inflammatory cytokine, IL 6 in rural pregnant women with preeclampsia when compared with women with normal pregnancy and a significant corelationship between inflammatory markers IL-6 with alkaline phosphatase suggesting that multiple factors are involved in the tissue inflammation that result in tissue damage, which is the hallmark of preeclampsia.

Limitations

Only 30 pre-eclamptic pregnant women were selected for our study, A long term study with 1000 or more pre-eclamptic pregnant women will give us a better picture.

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