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Uterine Artery Doppler and Serum Pentraxin-3 Level in Preeclampsia and Its Correlation to Intrauterine Growth Restriction

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ABSTRACT

Background: Preeclampsia (PE) is a pregnancy-specific condition associated with hypertension and proteinuria, often leading to intrauterine growth restriction (IUGR). Pentraxin 3 (PTX-3), an inflammatory molecule, has been linked to the pathophysiology of PE, with increased levels in women with established PE.

Objective: This study aimed to evaluate the utility of PTX-3 as a biomarker in pregnancies with abnormal uterine artery Doppler and its correlation with IUGR.

Patients and Methods: A retrospective cohort study was conducted at Banha University Hospital on 80 women in their third trimester. Participants were categorized into four groups: control (normotensive), mild PE, severe PE, and severe PE with IUGR. Serum PTX-3 levels, uterine artery Doppler indices, blood pressure, and proteinuria were assessed.

Results: Serum PTX-3 levels significantly increased across the groups, with levels of 2.83±1.38 ng/ml in controls, 9.34±1.48 ng/ml in mild PE, 25.19±2.87 ng/ml in severe PE, and 31.78±1.66 ng/ml in severe PE with IUGR ($p<0.0001$). Doppler indices, including systolic ($p<0.0001$) and diastolic blood pressure ($p<0.0001$), also showed significant differences. PTX-3 correlated positively with systolic blood pressure ($r=0.84$, $p<0.0001$), diastolic blood pressure ($r=0.71$, $p<0.0001$), proteinuria ($r=0.68$, $p<0.0001$), and Doppler indices ($r=0.86$, $p<0.0001$).

Conclusion: PTX-3 levels are significantly elevated in women with PE and IUGR, correlating strongly with clinical parameters such as blood pressure, proteinuria, and Doppler indices. PTX-3 may serve as a valuable biomarker for assessing the severity of PE and predicting IUGR.

Keywords: Preeclampsia, Pentraxin 3, Intrauterine Growth Restriction, Doppler Indices.

INTRODUCTION

Preeclampsia (PE) is a pregnancy-related disorder marked by high blood pressure and protein in the urine after 20 weeks of gestation, typically resolving within 6-12 weeks postpartum in women with normal blood pressure before pregnancy [1].

Intrauterine growth restriction (IUGR) refers to when fetal growth falls short of its expected potential, often due to abnormal placental development, resulting in inadequate oxygen and nutrient supply to the fetus [2]. Approximately one-third of PE cases are linked with IUGR, contributing to significant maternal and fetal/neonatal morbidity and mortality [3]. Growing evidence suggests that placental abnormalities may negatively influence pregnancy outcomes in both IUGR and PE [4].

The onset of PE is believed to be caused by reduced uteroplacental perfusion due to improper cytotrophoblast invasion of spiral arterioles, leading to the hypothesis that an ischemic placenta releases soluble factors into the maternal circulation, causing endothelial dysfunction and the clinical signs of PE [5]. There is increasing evidence suggesting that an abnormal immune or inflammatory response between the developing trophoblast and maternal decidua plays a crucial role in the development of PE[6].

Pentraxin-3 (PTX-3), an inflammatory molecule from the same family as C-reactive protein (CRP), is produced in response to inflammatory triggers by several cell types, including endothelial cells, monocytes, macrophages, and fibroblasts [7]. PTX-3 is found in the receptive endometrium, with abnormal expression linked to pregnancy loss [8]. Maternal PTX-3 levels are significantly elevated in women with established PE in the third trimester compared to those with normal pregnancies [9]. In normal pregnancies, PTX-3 levels in the first trimester range from 1.4-4.6 ng/ml, with high levels being indicative of PE, while normal levels are not [10].

Uterine artery Doppler is a non-invasive technique used to evaluate uteroplacental circulation and has shown clinical potential in high-risk pregnancies [11]. Pregnancies in the second trimester with abnormal uterine perfusion caused by impaired trophoblast invasion are at a high risk of developing PE and IUGR [12]. However, Doppler measurements alone can overestimate the likelihood of later complications, as only around 30% of these women actually develop the condition [13].

This study assessed the value of serum PTX-3 measurement in patients with PE after 34 weeks gestation with abnormal uterine artery Doppler and its correlation to IUGR.

PATIENTS AND METHOD

Study design

This retrospective cohort study involved 80 pregnant women in their third trimester, who were selected from those attending the antenatal care clinic at Banha University Hospitals.

Eligibility criteria

Cases were included if participants had a known last menstrual period (LMP), a gestational age (GA) between 34 to 40 weeks, a singleton pregnancy,

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and were aged between 18 and 35 years. Exclusion criteria were pregnant women with previous medical disorders such as chronic hypertension, diabetes mellitus, renal, cardiac, endocrine, or autoimmune diseases, multiple pregnancies, and those with a forgotten or uncertain date of LMP.

The study included four groups:

Group I (control, 20 cases), consisted of normotensive women with systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DPB) <90 mmHg on two separate occasions, no significant proteinuria, no history of chronic hypertension or renal disease, no diabetes or autoimmune conditions, and no use of medications apart from tonics and iron, with no warning symptoms.

- **Group II** (mild PE, 20 cases) had elevated diastolic blood pressure (90-110 mmHg), minimal proteinuria, no severe symptoms like oliguria or visual disturbances, and normal laboratory investigations.
- **Group III** (severe PE, 20 cases) included women with blood pressure ≥160/110 mmHg, proteinuria ≥0.5 gm/24 h, oliguria, visual/cerebral disturbances, and abnormal laboratory results.
- **Group IV** (severe PE with IUGR, 20 cases) included those with severe PE plus IUGR, defined by birth weight below the 5th percentile with abnormal uteroplacental perfusion.

Assessments

All cases underwent a full history taking, general and abdominal examination, and ultrasonography to determine GA, fetal life, and identify IUGR (defined as a birth weight below the 5th percentile of a reference group, with a symmetric growth profile and abnormal uteroplacental perfusion), congenital malformations, or oligohydramnios. Doppler imaging was also performed, and blood samples were collected to measure serum PTX-3 levels. Additionally, midstream urinary protein was measured using a dipstick test, and liver and kidney function, CBC, and coagulation profile were assessed.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Benha University. All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring they were fully informed about the study's purpose, procedures, and potential risks as well as ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were coded, entered, and analyzed using SPSS (Statistical Package for the Social Sciences) on an IBM-PC compatible computer. Quantitative variables were described using the mean, standard deviation (SD), and range, while qualitative variables were expressed in terms of frequency and percentage. The Chi-square test (X^2) was used to compare qualitative variables between groups, and correlation analysis was conducted to evaluate the strength of the relationship between two variables, with the correlation coefficient (r) indicating the strength and direction of the association. One-way ANOVA (Analysis of Variance) was used to assess the differences in means across multiple groups. P-values were interpreted as follows: $P > 0.05$ (non-significant) and $P < 0.05$ (significant).

RESULTS

The mean age was similar across groups, ranging from 24.41 to 25.15 years. GA at the time of assessment also showed no significant difference. No significant differences were observed in terms of gravidity and parity. However, SBP and DBP increased significantly with disease severity. Additionally, PTX-3 levels, SD, and RI showed significant increases in the preeclamptic groups compared to controls **(Table 1)**.

Table 1: Demographic characteristics, mean of systolic, diastolic blood pressure, serum pentraxin-3, and Doppler indices of the studied groups

Variable	Control (n=20)	Mild preeclampsia (n=20)	Severe preeclampsia (n=20)	Severe preeclampsia with IUGR (n=20)	Test of significance	P-value
Age/years	24.82±6.22	24.41±5.19	25.12±5.22	25.15±4.6	F=0.36	0.77
Gestational age /weeks	38.75±1.17	37.85±0.99	37.3±1.62	37.1±1.6	F=1.81	0.15
Gravidity No.%						
1-2	10 (50.0%)	15 (75.0%)	16 (80.0%)	13 (65.0%)	X^2=4.79	0.19
3-4	6 (30.0%)	3 (15.0%)	2 (10.0%)	5 (25.0%)	X^2=3.13	0.37
> 4	4 (20.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)	X^2= 1.37	0.71
Parity No. %						
Primipara	8 (40.0%)	14 (70.0%)	12 (60.0%)	11 (55.0%)	X^2=3.81	0.28
1-3	9 (45.0%)	4 (20.0%)	6 (30.0%)	7 (35.0%)	X^2=2.96	0.40
> 3	3 (15.0%)	2 (10.0%)	2 (10.0%)	2 (10%)	X^2=0.38	0.95
SBP Mean ± SD	113.0 ± 5.7 @	145.2±4.9 @	173.5±12.5 #	170.5±10.5 #	F=198.1	<0.001*
DBP Mean ± SD	72.0±7.67 @	92.9±4.07 @	104.5±6.86 #	103.5±5.87 #	F=115.9	<0.001*
Pentraxin-3 mean ± SD	2.83±1.38 @	9.34±1.48 @	25.19±2.87 @	31.78±1.66 @	F=878.7	<0.001*
Doppler SD Mean ± SD	2.27±0.27 @	2.68±0.15 @	3.41±0.21 @	4.37±0.8 @	F=184.1	<0.001*
Doppler RI Mean ± SD	0.57±0.05 @	0.63±0.03 @	0.71±0.12 @	0.85±0.11 @	F=157.239.24	<0.001*

Data are presented as n (%) or mean ± SD, IUGR: Intrauterine Growth Restriction, F: ANOVA test, X^2: Chi-Square test, SBP: Systolic Blood Pressure, SD: Standard Deviation, DBP: Diastolic Blood Pressure, Doppler SD: Doppler Systolic/Diastolic Ratio, RI: Resistance Index, *: Significant p-value <0.5, @: This group significantly differ from other groups, #: This group significantly differ from other groups except with this symbol.

In the mild PE group, 45.0% had mild proteinuria (+), whereas 55.0% had moderate (++) and none with severe (+++) proteinuria. In the severe PE group, 60.0% exhibited severe proteinuria (+++), and in the severe PE with IUGR group, 65.0% had severe proteinuria (+++). Moderate proteinuria (++) was observed in 40.0% of severe PE and 30.0% of severe PE with IUGR, with no significant difference **(Table 2)**.

Table 2: Frequency of proteinuria among patients

	Preeclampsia				
	Mild preeclampsia	**Severe preeclampsia**	**Severe preeclampsia with IUGR**	**(X^2)**	**P**
Proteinuria					
1 Mild (+)	9 (45.0%) @	0 (00%)	1 (5.0%)	17.52	<0.001*
2 Moderate (++)	11 (55.0%)	8 (40.0%)	6 (30.0%)	2.61	0.27
3 Severe (+++)	0 (00%) @	12 (60.0%)	13 (65.0%)	21.53	<0.001*

Data are presented as n (%), IUGR: Intrauterine Growth Restriction, X^2: Chi-Square test, *: Significant p-value <0.5, @: This group significantly differ from other groups.

Age showed little to no significant correlation with any group. GA exhibited weak correlations across all groups. Gravidity and parity also did not show significant correlations. Proteinuria was positively significantly correlated with Severe PE (r = 0.44) but not with other groups. SBP had a strong positive correlation with Severe PE (r = 0.70) and Severe PE with IUGR (r = 0.76). DBP was significantly correlated with both Mild PE (r = 0.44) and Severe PE (r = 0.62). Doppler SD showed a significant correlation with Severe PE with IUGR (r = 0.68), while Doppler RI did not show significant correlations in any group **(Table 3)**.

Table 3: Correlation coefficient between pentraxin-3 and laboratory results, blood pressure and Doppler indices

Variable	Control		Mild Preeclampsia		Severe Preeclampsia		Severe Preeclampsia with IUGR	
	(r)	p	(r)	p	(r)	p	(r)	p
Age	0.09	0.71	0.003	0.98	-0.27	0.23	-0.12	0.60
Gestational Age (GA)	-0.18	0.43	0.25	0.27	0.35	0.12	0.02	0.90
Gravidity	-0.03	0.87	0.07	0.76	-0.09	0.69	-0.03	0.84
Parity	-0.03	0.87	0.03	0.89	-0.09	0.69	0.06	0.79
Proteinuria	-	-	0.09	0.70	0.44	0.04*	0.28	0.22
SBP	-0.02	0.91	0.26	0.25	0.70	<0.001*	0.76	<0.001*
DBP	0.44	0.04*	-0.11	0.64	0.62	<0.001*	0.36	0.11
Doppler SD	0.18	0.43	-0.09	0.68	-0.25	0.28	0.68	0.001*
Doppler RI	0.09	0.67	-0.24	0.30	-0.28	0.22	0.22	0.34

GA: Gestational Age, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SD: Systolic/Diastolic Ratio, RI: Resistance Index, *: Significant p-value <0.5.

The correlation analysis revealed that Age, GA, Gravidity, and Parity did not have significant correlations. However, SBP (r = 0.84), DBP (r = 0.71), Proteinuria (r = 0.68), Doppler SD (r = 0.86), and Doppler RI (r = 0.87) all showed strong and statistically significant positive correlations **(Table 4)**.

Table 4: Correlation of serum pentraxin-3 with laboratory results, blood pressure and Doppler indices among patients (n=60)

	r	p
Age	-0.01	0.89
Gestational age	-0.16	0.21
Gravidity	0.07	0.55
Parity	0.07	0.59
SBP	0.84	0.000*
DBP	0.71	0.000*
Proteinuria	0.68	0.000*
Doppler (SD)	0.86	0.000*
Doppler (RI)	0.87	0.000*

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SD: Systolic/Diastolic Ratio, RI: Resistance Index, *: Significant p-value <0.5.

DISCUSSION

PE significantly contributes to maternal and perinatal morbidity and mortality [14]. Impaired spiral artery remodeling leads to ROS-induced endothelial dysfunction, causing complications like PE and IUGR [15]. Elevated PTX-3, an inflammatory marker, is linked to adverse perinatal outcomes [9]. Doppler ultrasound aids in detecting uteroplacental abnormalities in PE [16]. The study evaluated serum PTX-3 levels in PE patients after 34 weeks of gestation with abnormal uterine artery Doppler findings and their correlation with IUGR.

In this study, demographic data, including age, gestational age, gravidity, and parity, showed no significant differences between control and PE groups, aligning with findings by some investigators, who reported comparable maternal and gestational ages between normal and PE groups [17].

In this study, SBP and DBP increased with the severity of PE, with significant differences between control, mild, and severe groups, though severe cases with and without IUGR showed no difference. These findings align with previous studies which reported significantly higher SBP and DBP in preeclamptic pregnancies and associated these elevations with increased risks of complications [18,19].

This study found that PTX-3 levels increased progressively from controls to mild and severe PE, with the highest levels observed in severe PE with IUGR, with significant differences between groups. Similar findings were reported by some authors, who observed significantly elevated PTX-3 levels in preeclamptic pregnancies compared to normal pregnancies, with even higher levels in cases of PE with IUGR [20].

In the PE group, uterine artery PI and PTX-3 levels were elevated early in gestation [21]. First-trimester abnormal uterine Dopplers are sensitive in identifying PE cases associated with severe growth restriction and early-onset disease but are less predictive in high-risk cases without significant placental defects, suggesting that maternal circulation may play a more crucial role in such cases [22].

The present study found that Doppler measurements, including RI and SD, progressively increased from controls to severe PE with IUGR, with statistically significant differences between groups. Consistently, previous study reported higher uterine artery Doppler indices, such as PI and RI, in preeclamptic pregnancies compared to normotensive controls, highlighting their association with PE severity and complications [23].

In the current study, proteinuria was more commonly observed in severe PE and severe PE with IUGR, with mild proteinuria being more prevalent in mild PE. Severe proteinuria was significantly higher in severe PE and severe PE with IUGR compared to mild PE. These findings align with some authors indicating that severe PE is associated with higher blood pressure and proteinuria levels [24].

In the current study, significant correlations were observed between PTX-3 and various variables. In the control group, PTX-3 was correlated with DBP only. In mild PE, no significant correlations were found. In severe PE, PTX-3 showed significant correlations with proteinuria, SBP, and DBP. In severe PE with IUGR, PTX-3 was significantly correlated with SBP and Doppler (SD). A strong positive correlation was found between PTX-3 and Doppler (SD) in severe PE with IUGR. Overall, in the entire patient group, PTX-3 was significantly correlated with SBP, DBP, proteinuria, and Doppler indices (SD, RI). Strong positive correlations were noted between PTX-3 and SBP, DBP, Doppler (SD, RI), and proteinuria.

Abnormal uterine Dopplers in the first trimester are effective in detecting PE cases linked to severe growth restriction and early-onset disease. However, they are less reliable in high-risk cases without significant placental abnormalities, implying that maternal circulation could be a more critical factor in these situations

The limitations of this study include its single-center design and small sample size, which may limit the generalizability of the findings, as well as the lack of follow-up data.

CONCLUSION

Elevated serum PTX-3 levels in women with late-onset PE (>34 weeks) were associated with abnormal uterine artery Doppler findings and showed a positive correlation with disease severity, being most pronounced in cases of PE with IUGR.

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Conflict of Interest: Nil.

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