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Original Article

Significance of Maternal Serum Pentraxin-3 Level in Assessment of Severity of Pre-eclampsia and Its Effect on Neonatal Outcome

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Abstract

Background: Preeclampsia is a multisystem, highly variable disorder specific to pregnancy. Pentraxin-3 (PTX3), a recently identified multimeric inflammatory mediator, it can be considered as a promising biomarker of preeclampsia and its severity. **Objective:** To determine the association between maternal serum PTX3 level and preeclampsia, its severity and its effect on the neonatal outcome. **Materials and Methods:** This case control study was carried-out at the Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Kirkuk City, Iraq from 1st of February, till 30th of November 2021. The study included 92 pregnant women at term who were divided into three groups (mild preeclampsia, severe preeclampsia, and pregnant without preeclampsia and regarded as control group). The neonatal outcomes were documented. PTX3 was measured in the serum using human PTX3 ELISA KIT. **Results:** PTX3 cutoff value of ≥120.8 pg/mL was associated with sensitivity of 100% and specificity of 96%. The correlation between PTX3 and urea, body mass index, birth weight, APGAR (A for neonatal appearance, P for heart rate, G for grimace, A for activity, R for respiration) score in 1 and 5 minutes showed that, there was significant positive weak correlation between PTX3 and urea, in which an increase in urea was associated with an increase in PTX3. Also, there was significant negative weak correlation between PTX3 with birth weight and APGAR 1, in which an increase in PTX3 was associated with a decrease in birth weight and APGAR in 1 min. **Conclusion:** PTX3 is one of the biochemical markers in diagnosing preeclampsia and distinguishing its severity and can be used as a marker for early neonatal outcome in preeclampsia.

Keywords: Neonatal outcome, pentraxin-3, preeclampsia, severity

Introduction

Preeclampsia is clinically defined by hypertension and proteinuria, with or without pathologic edema.[1] Preeclampsia complicates 2%–8% of all pregnancies.[2] It is a placental dysfunction characterized by an excess of antiangiogenic factors, this dysfunction passes in two phases: incorrect placentation in the first trimester followed by a maternal syndrome in the later second and third trimesters.[3] Preeclampsia sufferers are at increased risk of kidney, liver, and brain damage that can lead to organ failure or stroke. Placental abruption, preterm delivery, and pregnancy loss or stillbirth are also common in preeclampsia. Eclampsia can result from severe preeclampsia. Without delivery of the fetus, maternal and\or fetal death can occur.[4] Late preterm infants of preeclamptic women have higher risk of neonatal intensive care unit admission, longer neonatal hospitalization, and higher requirement of respiratory assistance.[5] These complications occur also in elective deliveries of late preterm infants born to mothers who have preeclampsia (PE), even if pulmonary maturity has been confirmed by lecithin/sphingomyelin ratios,

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because 10% develop respiratory distress syndrome.[6] Severe preeclampsia is a strong risk factor for intrauterine fetal death, with estimated stillbirth rate of 21 per 1000. However, in mild preeclampsia, the risk of fetal death is 50% less than pregnancies with severe preeclampsia.[1] Uteroplacental blood flow is decreased in pregnant with preeclampsia and is considered a significant risk factor for development of intrauterine growth restriction that is considered one of the most common causes of intrauterine growth restriction in the non-anomalous infant.[7] Low weight at birth is a significant public health problem and is frequently associated with neonatal morbidity and mortality. Reduced utero-placental perfusion also significantly increases the risk of preterm labor and other neonatal comorbidities.[8] The APGAR (A for neonatal appearance, P for heart rate, G for grimace, A for activity, R for respiration) score is recorded at 1 and 5 minutes after birth and can be repeated later if the result remains low. Preeclampsia has great implication on adverse neonatal outcome, which is associated with low APGAR score in comparison to normotensive pregnant.[9]

Pentraxin-3 (PTX3), a recently identified multimeric inflammatory mediator, has been reported as a promising biomarker of preeclampsia and its severity.[10] Studies confirmed that the PTX3 plays an important role in vascular inflammation and endothelial malfunction. PTX3 can reduce nitrous oxide synthesis, prevent cell proliferation,[11] block the effect of fibroblast growth factor 2. PTX3 also directly increases the synthesis of matrix metalloproteinases or can block the synthesis of nitrous oxide. PTX3 has a positive association with arterial hypertension. PTX3 is clearly involved in the pathogenesis of endothelial dysfunction, and it can be a biomarker in this direction, but further researches are needed to determine its reliability in this concept.[12]

Materials and Methods

Study design, setting, and data collection time

This study is a case control study that was carried out in the Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Kirkuk City, Iraq from the period of 1st of February, till 30th of November 2021. The protocol of this study was approved by Scientific Council of Obstetrics and Gynecology, Iraqi Board for Medical specialization. The study ethics were implemented in regard to Helsinki Declaration by oral informed consent of pregnant women.

Study population

The study included initially 92 Rh +ve women with singleton viable pregnancy at a gestational age ≥37 weeks as assessed by menstrual dates and confirmed by first trimester ultrasounds scan who were admitted to the obstetric ward for assessment and management with no history of chronic hypertension; all patients were informed about nature of the study and their verbal consent was obtained.

Women participated in the study were divided into three groups:

Preeclampsia group: It included 60 women present with signs and symptoms of preeclampsia and were diagnosed as preeclampsia according to the American College of Obstetricians and Gynecologists (ACOG) definition and were subdivided into group A, which included 30 pregnant women diagnosed with mild preeclampsia, and group B included 30 pregnant women diagnosed with severe preeclampsia. Control group (group C): It included 32 normotensive pregnant women without known pregnancy complications and with matched gestational age.

The preeclampsia of pregnant women was defined according to ACOG by the presence of hypertension and proteinuria or no proteinuria, but with new incident hypertension with either thrombocytopenia (platelets $<100\times10^9$/L), or renal problem (serum creatinine > 1.1 mg/dL) or liver dysfunction (abnormal liver enzymes) or pulmonary edema or headache or visual symptoms. The PE is considered mild when blood pressure was less than 160/110 mmHg with proteinuria ≥300 mg in 24 hours, or in dipstick urine 1+ (which equal to 300 mg/L). Preeclampsia is considered to be severe if systolic blood pressure (SBP) was ≥160 mmHg or diastolic blood pressure (DBP) was ≥110 mmHg or both of them with proteinuria ≥500 mg in 24 hours, or dipstick urine 2+ or more (which equal to 1 g/L) or other signs of severity. The neonatal outcomes were documented including gestational age at delivery, birth weight, APGAR score in 1 minute and 5 minute and if needed for admission to neonatal intensive care unit, and the duration in days and indications. Low birth weight can be defined as birth of the baby at delivery 2500 g or less, and low APGAR score is defined as <7 at 1st 5 minute.

Inclusion criteria

Patients aged 16–45years, Rh +ve women, singleton viable pregnancy, gestational age ≥37 weeks.

Exclusion criteria

Multiple pregnancy, maternal autoimmune disease, maternal renal, cardiac, and hepatic disease, maternal malignancy, maternal infection, smoking, Rh –ve isoimmunization, preterm gestation, drug user (anti-inflammatory drugs).

Laboratory investigations

Pentraxin-3 assessment

It was measured in the serum using human PTX3 ELISA KIT (SunLong Biotech Co., LTD, China) following the manufacturer instructions using Biotek ELISA set (BioTek Instrument, USA).

Complete blood count

Was tested by Swelab™ Alfa Plus analyzer (Boule®, Sweden) using whole blood in ethylenediaminetetraacetic acid containing tubes.

Biochemical analysis

Serum liver function test (alanine aminotransferase, aspartate aminotransferase) and renal function tests (blood urea and serum creatinine) were conducted at Azadi teaching hospital laboratory by using the ARCHITECT c4000 clinical chemistry analyzer (Abbot, USA) using its costume kit, while urinary protein (dipstick testing) was tested by commercially available kit (MeriCheck 10, Merit pharmaceutical).

Statistical analysis

Descriptive and analytic statistics were performed using the Minitab version 19 software statistical program. The descriptive statistics include mean ± standard deviation (SD) of measurable variables and frequency of variables and percentages for categorical variables. Chi-square test and Fisher-Exact test for small frequency cells were used to compare between categorical variables. An independent *T*-test was used to compare between quantitative parameters. Scatter graph and Pearson's correlation coefficient (*r*) between the different parameters of each group (simple linear correlation) are estimated. Receiver operating characteristic curve is used to identify cut values, specificity, sensitivity, and area under the curve for tested marker. *P* values of ≤0.05 were considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 18 in 9/10/2022 to get this approval.

Results

Study subjects' demographics and pathological characteristics

Table 1 shows that the mean age and mean body mass index (BMI) did not significantly differ among the participants groups (P = 0.94) and (P = 0.89), respectively. SBP and DBP in group B were significantly higher than those in

Table 1: The demographic characteristics of the studied groups

	Cases	*N*	Mean	Std. deviation	*P* value*
Age	Group A	30	30.57	5.83	0.94
	Group B	30	31.1	6.4	
	Group C	32	30.75	6.79	
BP (mmHg)	Group A	30	140.83	10.67	**0.0001**
	Group B	30	160.7	10.6	
	Group C	32	110.98	10.08	
DBP (mmHg)	Group A	30	90.8	7.2	**0.001**
	Group B	30	110.3	6.1	
	Group C	32	70.53	10.06	
BMI (kg/m²)	Group A	30	23.78	3.2	0.89
	Group B	30	22.29	3.1	
	Group C	32	22.25	3.3	

BMI = body mass index

*ANOVA test

Table 2: Comparison in biochemical data across participants groups

	Group A		Group B		Group C		*P* value*
	Mean	SD	Mean	SD	Mean	SD	
Pentraxin3 (pg mL)	194.1	29.6	290.8	50.7	84.0	19.5	**0.0001**
Hb (mg/dL)	12.99	0.70	11.69	1.54	12.63	1.09	0.15
AST (IU/L)	38.13	6.61	31.28	8.45	32.41	6.09	0.12
ALT (IU/L)	37.82	5.46	33.60	7.03	33.78	5.33	0.081
Uric (mg/dL)	6	1	7	1	6	5	0.14
Urea (mg/dL)	34	5	38	23	26	9	**0.005**
Creatinine (mg/dL)	0.60	0.17	0.63	0.18	0.56	0.18	0.35
RBS (mg/dL)	85	15	84	15	85	14	0.96

ALT = alanine aminotransferase, AST = aspartate aminotransferase, *Independent sample *t* test

group A and C. In addition, group A was higher than group C ($P < 0.05$).

Comparisons in biochemical data across participants groups

PTX3 level was significantly higher in group B (severe preeclampsia) when compared to group A and C. The same pattern is seen in group A (mild preeclampsia) relative to group C (control group) ($P = 0.0001$). Apart from all other biochemical laboratory results, only urea showed significant higher level across group A and B compared to group C ($P = 0.005$) [Table 2].

The diagnostic and prognostic accuracy of pentraxin 3

The PTX3 cutoff value ≥120.8 pg/mL was associated with sensitivity of 100% and specificity of 96% to distinguish between group B (severe preeclampsia group) from group A (mild preeclampsia) and C the control group [Figure 1A].

The mean distribution of PTX3 showed significant higher level of PTX3 among severe preeclampsia (group B) compared to mild preeclampsia (group A) ($P = 0.0001$). The PTX3 cutoff value ≥ 232.2 pg/mL was associated with sensitivity of 90% and specificity of 86% to distinguish between severe and mild cases of preeclampsia [Figure 1B].

Neonatal outcomes across participant groups

Regarding gender among the participants of the study, it was almost equally distributed between the two genders among all the studied groups. Preeclampsia showed no effect on the meconium-stained liquor among the participant. Regarding birth asphyxia among the

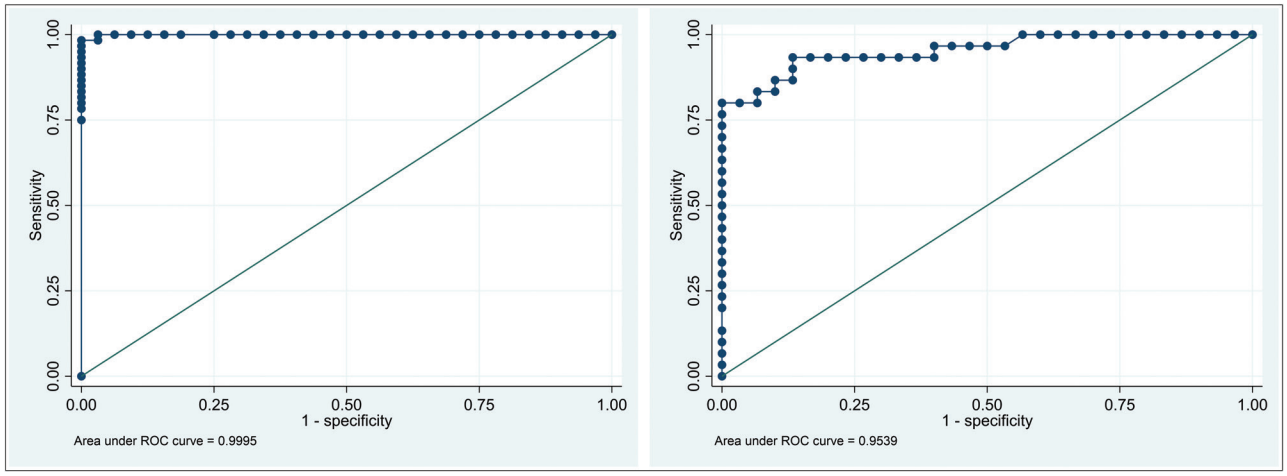

Figure 1: (a) Receiver–operating characteristic curve analysis of pentraxin-3 which distinguishes severe preeclampsia from control and mild cases at ≥120.8 pg/mL. (b) Receiver–operating characteristic curve analysis of pentraxin-3 and severity of preeclampsia (severe cases) at ≥232.2 pg/mL

Table 3: Neonatal outcomes across participants groups

		Group A		Group B		Group C	
		Count	Row N %	Count	Row N %	Count	Row N %
Neonatal gender*	Female	17	56.6%	14	46.6%	16	50%
	Male	13	43.4%	16	53.4%	16	50%
Meconium**	No	24	80%	27	90%	26	81.2%
	Yes	6	20%	3	10%	6	18.8%
Asphyxia***	No	30	100%	28	93.3%	32	100%
	Yes	0	0.0%	2	6.7%	0	0.0%

*$P = 0.73$, **$P = 0.51$, ***$P = 0.12$

Table 4: Group statistics of birth weight and APGAR1 and 5 minutes across participant groups

	Group A		Group B		Group C		*P* value
	Mean	SD	Mean	SD	Mean	SD	
Birth weight	3.11	0.47	3.09	0.48	3.40	0.44	**0.01**
APGAR1 (min)	6.67	0.92	5.30	1.02	6.63	0.98	**0.001**
APGAR5 (min)	8.30	0.70	8.30	0.75	8.41	0.91	0.83

APGAR = A for neonatal appearance, P for heart rate, G for grimace, A for activity, R for respiration

Table 5: Correlation between Pentraxin-3 and urea, body mass index, birth weight, APGAR 1&5 minute

		Urea	BMI	Birth weight	APGAR1	APGAR5
Pentraxin3	Pearson correlation	0.240	–0.001	–0.243	–0.439	–0.040
	P value	0.021	0.989	0.019	0.001	0.705
	N	92	92	92	92	92

participant, the statistical analysis showed no significant difference across all groups [Table 3].

Statistics of birth weight and APGAR 1 and 5 minutes across participant groups

Regarding birth weight the values reflects statistically significant difference among the groups ($P < 0.01$) as shown in Table 4. APGAR score at 1 minute was significantly higher among control and group A (mild preeclampsia) compared to severe preeclampsia group (group B) ($P = 0.001$), while APGAR score in 5 minutes among group A (mild preeclampsia) participants was 8.3. The mean APGAR score at 5 minutes did not show significant difference among the three groups [Table 4].

Pentraxin-3 and other parameters

There was significant positive weak correlation between PTX3 and urea, in which an increase in urea was associated with an increase in PTX3 ($P = 0.02$, $r = 0.24$). Also, there was significant negative weak correlation between PTX3 with birth weight ($P = 0.01$, $r = –0.24$) and APGAR 1 ($P = 0.001$, $r = –0.43$), in which an increase in PTX3 was associated with a decrease in birth weight and APGAR at 1 minute [Table 5].

Discussion

Increasing evidence suggests that preeclampsia is resulted from exaggerated inflammatory reactions, which can cause endothelial dysfunction.[13] In severe preeclampsia, PTX3 can be a promising biomarker but, the studies that are available are of small sample sizes, and analyses are not always adjusted for confounders.

In this study, there was no significant difference in age among groups, and this was similar to study done by Wenas and Al Massawi in Iraq, in which they found no significant difference in the age of participants between pregnant with preeclampsia and normotensive pregnants,[14] and this was against different studies that are conducted in Iraq by Majeed *et al*.,[15] by Sheen *et al*.,[16] by Lamminpää *et al*.[17], and by Ogawa *et al*.[18] The discrepancy in the results might be attributed to the difference in the study design, population size, and possible effect of genetic factors.

Regarding BMI, there was no difference in BMI among the studied groups in our study. This was against Poorolajal and Jenabi meta-analysis results.[19] Also, it is against study by Bondar *et al*.[20] who showed that obesity increases the overall risk of preeclampsia by approximately two- to three-fold. In our study, the mean BMI was within normal range and further studies are needed to evaluate the risk of obesity on preeclampsia. A study done by Al yasiry, Jwad, Hasan, and Alsayigh showed the importance of losing weight before pregnancy in overweight and obese women.[21]

Pentraxin-3 and severity of preeclampsia

There was significantly higher level of PTX3 in group B (severe) participants when compared to group A (mild) and C (control). Also, in group A to group C, the PTX3 level was higher in preeclampsia pregnant women and it increases significantly with severity of preeclampsia. This was in line with Hamad *et al*. study[22] and with study by Boij *et al*.[23]

Moreover, Cozzi *et al*.[24] study showed that the maternal increase of PTX3 correlates with the severity of disease with higher PTX3 concentrations in severe PE. Another study by Cetin *et al*.[25] showed that higher level of PTX3 among preeclampsia women compared to normal pregnant women; however, no significant difference of PTX3 levels was found between mild and severe preeclampsia. This difference might be related to difference in the study setting, method of measurement, and study subjects' inclusion criteria and size.

Also, a study by Cakmak *et al*.[12] concluded that additional information can be provided by PTX3 beyond that provided by conventional procedures that can predict the presence of preeclampsia and assess its severity.

The PTX3 cutoff value ≥120.8 pg/mL was associated with sensitivity of 100% and specificity of 96% to distinguish between group B (severe preeclampsia group) from group A and C. Also, The PTX3 cutoff value ≥232.2 pg/mL was associated with sensitivity of 90% and specificity of 86% to distinguish between severe and mild cases of preeclampsia which had given a higher sensitivity and specificity for PTX3 for detecting preeclampsia and its severity.

Garg *et al*.[26] studied the role of PTX3 in pregnant with preeclampsia as compared to normal pregnancy and to assess the predictive value of pentraxin for the development of PE, and they found that abnormally high level of PTX 3 can precede the occurrence of preeclampsia that indicates the role of endothelial dysfunction and inflammatory response in preeclampsia. PTX 3 can be used to identify women at high risk for the development of preeclampsia.

Pentraxin-3 and neonatal outcomes

The correlation of PTX3 with asphyxia and meconium did not demonstrate significant correlation. There was significant weak negative correlation between PTX3 level with mean birth weight ($P = 0.01$, $r = –0.24$) and APGAR score in 1 minute ($P = 0.001$, $r = –0.43$). This came from the fact that an increase pentaxin-3 is associated with severity of preeclampsia which is associated with more adverse neonatal outcomes. A lower APGAR score, at 1 minute, was significantly associated with severe preeclampsia when compared to both mild and control groups. This result is in line with a study conducted Susilo *et al*.[27] that showed that severe preeclampsia is associated with lower APGAR score. Also, a study done by Sirenden *et al*.[28] revealed that the APGAR score was low among severe preeclampsia group. In a meta-analysis study by Abate *et al*.,[29] it showed that the first minute APGAR score was lower in preeclampsia as compared to normotensive women. However, the study showed that there was no significant difference between pregnant with preeclampsia and normotensive pregnant on the fifth minute APGAR score. This demonstrated that the neonatal outcome is affected significantly by severity of preeclampsia and special attention to babies born for pregnant women with severe preeclampsia.

In this study, the mean of birth weight was significantly less among severe preeclampsia group in comparison to control group. This was in line a study conducted by Getaneh *et al*.[30]

The correlation between PTX3 and urea in our study showed significant positive weak correlation between PTX3 and urea. This result is against results by Turkmen *et al*.[31] study that showed no correlation between PTX3 and urea, and no significant correlation was found between serum PTX 3 level and creatinine, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, lactate dehydrogenase, platelet. Another study by Manjareeka *et al*.[32] showed that a small increase in urea level of pre-eclamptic women; however, no correlation was found with levels of PTX3 in pre-eclamptic subjects. This strengthens the role of PTX3 in evaluation of preeclampsia as independent factor.

In conclusion, PTX3 level was significantly higher in pregnant women with preeclampsia. Also, the PTX3 level was significantly higher in pregnant women with severe preeclampsia when compared to mild preeclampsia. PTX3 is one of the biochemical markers in diagnosing preeclampsia and distinguishing its severity. This study recommends PTX3 might be utilized as prognostic marker for the severity of preeclampsia and adverse neonatal outcome. This study encourages health authorities to provide patients with high PTX3 level with the adequate facilities to manage high risk patients and their neonates.

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Conflicts of interest

There are no conflicts of interest.

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