RESEARCH ARTICLE

The role of arginase estimation to predict hypertensive disorder of pregnancy at an earlier stage

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Abstract

Objective: To determine the significance of serum arginase estimation as a predictor of pregnancy-induced hypertension and preeclampsia at an early stage.

Method: The observational, cross-sectional study was conducted from October 15, 2021, to October 15, 2022, at the Department of Chemical Pathology, in collaboration with the Department of Obstetrics and Gynaecology, Pakistan Railway Hospital, Islamic International Medical College Trust, Rawalpindi, Pakistan, and comprised pregnant women with 20-25 weeks of gestation who were divided into three groups. Those having no complications were placed in control group A, those with pregnancy-induced hypertension in group B, and those with preeclampsia in group C. Serum arginase, uric acid, alanine transaminase, platelet count and spot urinary protein levels were measured for each subject. Data was analysed using SPSS 26.

Results: Of the 90 women, 30(33.3%) were in group A with mean age 27.27±2.90 years, 30(33.3%) were in group B with mean age 30.17±2.48 years, and 30(33.3%) were in group C with mean age 29.33±3.11 years. There were significant intergroup differences in the mean levels of serum arginase, serum uric acid, alanine transaminase, platelet count and spot urinary protein ($p<0.05$).

Conclusion: A moderate to marked increase in serum arginase levels in pregnancy-induced hypertension and preeclampsia cases, combined with abnormal serum uric acid and alanine transaminase levels along with low platelet count suggested that serum arginase estimation could be used to predict hypertensive disorders of pregnancy at an early stage.

Key Words: Arginase, Preeclampsia, Pregnancy-induced hypertension.

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Introduction

Hypertensive disorders of pregnancy are the leading causes of maternal and perinatal morbidity and mortality.[1] Pregnancy-induced hypertension (PIH) and preeclampsia (PE) are the two main categories of hypertensive disorders of pregnancy that are responsible for more than 50,000 maternal deaths per year, and complicate approximately 10% of total pregnancies.[2]

Hypertension developed during pregnancy after 20 weeks of gestation is called PIH.[3] Proteinuria of 300mg/24 hours and systolic blood pressure (SBP) 140mmHg or diastolic blood pressure (DBP) 90mmHg are diagnostic of preeclampsia in a pregnant woman.[4] More complications are observed in patients with early onset of PIH before 32 weeks of gestation.[2,5] Inadequate placentation of spiral arterioles and aberrant trophoblastic invasion result in ischaemic placental tissue, which is the fundamental pathophysiological mechanism behind PIH. Complications of preeclampsia include stroke, eclampsia, abruptio placentae, disseminated intravascular coagulation (DIC), haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, liver haemorrhage, pulmonary oedema, respiratory distress syndrome (RDS), acute renal failure and death.[6] Preeclampsia also limits the intrauterine growth of foetus, leading to miscarriage and premature birth resulting into increased perinatal morbidity and mortality.[7]

During normal pregnancy, significant physiological changes occur, including 40% to 50% increase in blood volume and cardiac output, and decrease in total peripheral resistance due to vasodilation, resulting in decreased arterial BP. Endothelial factors, such as plasma nitric oxide (NO), play a vital role in controlling BP during pregnancy.[6,8]

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Throughout a normal pregnancy, endogenous NO is one of the main vasodilators responsible for maintaining and regulating the cardiovascular system.[9] The levorotatory arginine (L-arginine), an amino acid, is used as substrate in the formation of NO in endothelial cells by endothelial NO synthase (eNOS) enzyme.[10] The L-arginine is also utilised by arginase enzyme, resulting in the formation of L-ornithine and urea in the liver, endothelial cells, and placenta.[11] Increased expression of arginase activity, reducing the bioavailability of the L-arginine to eNOS, can decrease NO production and uncouple the NOS to produce more superoxide. The superoxide immediately reacts with endogenous NO to produce another toxic oxidant peroxynitrite (ONOO-). These oxidants further decrease the levels of tetrahydrobiopterin (BH4), which is essential for normal eNOS coupling. These changes lead to vascular endothelial cells dysfunction.[12] Due to decreased levels of NO, vasoconstriction of blood vessels and abnormal natriuresis lead to increased BP, which causes PIH and PE.[10,11,13]

Limited literature is available with conflicting results on the utility of serum arginase estimation as a predictor of hypertensive disorders of pregnancy. The current study was planned to determine the significance of serum arginase estimation as a predictor of PIH and PE at an early stage.

Patients and Methods

The observational, cross-sectional study was conducted from October 15, 2021, to October 15, 2022, at the Department of Chemical Pathology, in collaboration with the Department of Obstetrics and Gynaecology (OB-GYN), Pakistan Railway Hospital (PRH), Islamic International Medical College Trust (IIMCT), Rawalpindi, Pakistan. After approval from the institutional ethics review committee of Riphah, the sample size was estimated using Cochran's formula,[14] with 95% confidence interval (CI) and 5% margin of error, based on PIH prevalence 6.7% in the Pakistani population.[15] The sample was raised using non-probability convenience sampling technique from among those visiting the antenatal clinic and OB-GYN ward inpatients. Those included were pregnant women with 20-25 weeks of gestation. Pregnant women with chronic hypertension, systemic and chronic illness, known cardiovascular disease and diabetes mellitus were excluded.

After taking informed consent from the subjects, they were divided into three groups. Those having no complications were placed in control group A, those with PIH having BP ≥140/90mmHg on two separate occasions without proteinuria were placed in group B, and those with PE having BP ≥140/90mmHg on two separate occasions with proteinuria >0.3g protein/24 hours in urine were placed in group C.

Demographic and clinical data was collected, including age, parity, height, weight, BP and body mass index (BMI). Maternal venous blood samples were collected from the antecubital vein for the estimation of plasma arginase, serum bilirubin, alanine transaminase (ALT), alkaline phosphatase (ALP), urea, creatinine and uric acid. The samples were centrifuged at 1,000rpm for 5 minutes to prepare serum collectively, then stored at temperatures ranging 2-8oC. The serum arginase samples were kept chilled at -20°C. Serum bilirubin, ALT, ALP, urea, creatinine and uric acid tests were performed on an automated Chemistry Analyzer Selectra Pro M Series by ELITech Group, Netherland using reagents by Merck &Co (Innoline) MSD, USA. For platelet count, venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, and platelet count was done using automated Haematological Analyzer XP-100 by SYSMEX CORPORATION, JAPAN. Serum arginase estimation was done with Sandwich enzyme immunoassay method-based Arginase ELISA kit, manufactured by BioAssay Systemson ELISA Reader: HumaReader, Manufactured by HUMAN Diagnostics Worldwide. Urine sample was collected for the estimation of spot urine proteins on an automated chemistry analyser Selectra Pro M Series by ELITech Group, Netherland using reagents by Merck &Co (Innoline) MSD, USA.

Data was analysed using SPSS 26. Kolmogorov-Smirnov test was applied to test data normality. Frequencies and percentages were computed for categorical data, such as age and gender, and chi-square test was used for comparisons. Quantitative data was presented as mean ± standard deviation (SD). Since the data had normal distribution, therefore, one-way analysis of variance (ANOVA) and post-hoc Turkey analysis were applied to compare the results of serum arginase levels among the study groups. Pearson Product Moment correlation was used to determine the correlation of serum arginase with BP, spot urinary protein, serum creatinine, ALT and platelet count. Cross-tabulation analysis across the groups was done to investigate the association between normal and raised categories of serum arginase and normal and overweight categories of BMI, serum uric acid and ALT. P≤0.05 was considered significant.

Results

Of the 90 women, 30(33.3%) were in group A with mean age 27.27±2.90 years, 30(33.3%) were in group B with mean age 30.17±2.48 years, and 30(33.3%) were in group

Table-1: Demographics characteristics (n = 90)

Parameters/ Variables	HC (Mean ±SD)	PIH (Mean ±SD)	PE (Mean ±SD)	P value
Women Age(years)	27.27±2.90	30.17±2.48[a]	29.33±3.11[a]	0.65
Gestational age (Weeks)	22.13±1.4	22.77±1.57	22.93±1.6	0.75
BMI (kg/m2)	22.48±1.71	24.25±1.52[a]	26.25±1.78[ab]	0.00
Systolic BP (mm of Hg)	120.07±7.43	145.00±5.09[a]	151.33±7.76[ab]	0.00
Diastolic BP (mm of Hg)	72.90±13.41	100.33±8.09[a]	117.70±20.78[ab]	0.00
Primigravida	3 (10.0%)	2 (6.7%)	0 (0.0%)	
Multigravida	27 (90.0%)	23 (76.7%)	24 (80.0%)	
Grand Multi gravida	0 (0.0%)	5 (16.7%)	6 (20.0%)	

[a]p<0.05 vs HC, [b]p<0.05 vs PIH. PE: Preeclampsia, PIH: Pregnancy-induced hypertension, HC: Healthy control, BMI: Body mass index, BP: Blood pressure.

C with mean age 29.33±3.11 years. BMI, SBP and DBP values were significantly higher in group C than group A and B, and in group B compared to group A (Table 1).

Mean serum arginase and serum uric acid levels were significantly higher in group C than group A and B, and in group B compared to group A (p<0.05) ALT and ALP levels, platelet counts and spot urinary protein values were significantly higher in group C patients compared to those in groups A and B (Table 2).

Serum arginase and had a positive correlation with SBP and spot urinary protein in group B and C patients (p<0.05). Other associations were also noted (Table 3).

There were 12(40%) patients in group B and 24(80%) in group C with raised arginase levels who were overweight. Also, 6(20%) patients in group B and 16(53.3%) in group C with raised serum arginase levels who had high serum uric acid levels. There were 6(20%) patients in group B and 25(83.3%) in group C with raised serum arginase levels who had raised serum ALT levels (Table 4).

Table-3: Correlation of serum arginase with other study variables.

Parameters	HC		PIH		PE	
	r value	P value	r value	P value	r value	P value
Systolic/Diastolic BP (mm Hg)	-0.03/0.14	0.81/0.88	0.16*/0.28*	0.05/0.05	0.21*/0.33*	0.05/0.05
Spot Urinary Proteins (RR <30 mg/dl)	0.1	0.61	0.24*	0.03	0.53*	0.01
ALT(U/L)	-0.10	0.15	0.16	0.01*	0.22*	0.03
Platelets Count (150 – 400 x 109/L)	0.16	0.40	0.20	0.30	-0.79*	0.05

HC: Healthy control, PIH: Pregnancy-induced hypertension, PE: Preeclampsia, BP: Blood pressure, ALT: Alanine transaminase.
* Correlation is significant at the 0.05 level (2-tailed)

Table-2: Intergroup comparison of biochemical parameters.

Biochemical Parameters	HC (Mean ±SD)	PIH (Mean ±SD)	PE (Mean ±SD)	P value
Serum Arginase (ng/ml)	32.25±4.75	49.84±4.92a	75.11±5.18ab	<0.001
Serum uric acid(mg/dl)	5.53±0.83	7.12±0.51a	8.53±0.58ab	<0.001
ALT(IU/L)	27.00±3.29	38.77±2.80	62.93±16.62ab	<0.001
Platelets 109/L (Normal 150 to 400)	195.13±38.84	140.63±15.32	90.15±10.87ab	<0.001
Spot Urinary proteins (mg/ dl) (Normal 0 to 30 mg/dl)	18.27±2.19	27.45±3.15	42.69±6.7ab	<0.001
Serum bilirubin (mg/dl)	0.60±0.14	0.65±0.14	0.67±0.12a	0.08
Serum creatinine (mg/dl)	0.64±0.14	0.64±0.14	1.69±0.10	0.26
Serum urea(mg/dl)	32.80±4.66	43.47±3.54	51.93±4.68	<0.001
ALP(IU/L)	89.10±46.57	140±35.21	194.80±45.72ab	<0.001
AST(IU/L)	27.87±3.66	27.33±4.04	28.80±3.84	0.33

[a]p<0.05 vs HC, [b]p<0.05 vs PIH. PE: Preeclampsia, PIH: Pregnancy-induced hypertension, HC: Healthy control, ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase.

Discussion

The current study was planned to determine the significance of serum arginase estimation as a predictor of PIH and PE at an early stage. To make the results more reliable, efforts were made to ensure that there was minimal variation in age across the groups. As the vast difference in the ages of the study participants may involve other physiological and pathological factors affecting the results, extreme margins of ages were not included.

Pregnant women with 20-25 weeks of gestation with an average gestational age of 22.94±1.86 weeks were included. An earlier study elucidated pregnant woman

Table-4: Cross-tabulation analysis.

Study Groups	Serum Arginase (ng/ml)	BMI Categories		Serum Uric Acid (2.6-6.0 mg/dl)		Serum ALT (upto 32 u/l)	
	Normal/ Raised	Normal (18.5 -24.9)	Overweight (25.0-29.9)	Normal	Raised	Normal	Raised
HC (n=30)	Normal (32.25±4.75)	26 (86.7%)	4(13.3%)	29 (96.6%)	1(0.4%)	30 (100%)	0 (0.0)
PIH (n=30)	Raised (49.84±4.92)	18 (60.0%)	12 (40.0%)	24 (80%)	6 (20%)	24(80%)	6(20%)
PE (n=30)	Raised (75.11±5.18)	6 (20.0%)	24 (80.0%)	14 (47%)	16 (53%)	5(16.7%)	25(83.3%)

HC: Healthy control, PIH: Pregnancy-induced hypertension, PE: Preeclampsia, BMI: Body mass index, ALT: Alanine transaminase.

with gestational age 20-25 weeks were more at a risk of developing hypertension and preeclampsia.[14]

The current study found that majority of PE and PIH patients were multigravida, followed by grand multigravida, and 30-50% of women who had PIH in their first pregnancy developed PIH in their second pregnancy. In a series of studies conducted from 1985 to 2010, it was noted that around 10% of the women who had experienced eclampsia in a previous pregnancy subsequently developed the condition in the next pregnancy. Additionally, it was found that one-third of women who had gestational hypertension or PE in a previous pregnancy experienced at least one more episode of the same condition in a subsequent pregnancy.[15]

There was an increasing trend of BMI among controls (22.48±1.71), PIH patients (24.25±1.52) and PE patients (26.25±1.78) In the current study, which was in line with earlier findings.[16]

The current results revealed that pregnant women with hypertension had varying levels of serum arginase, depending on the severity of their condition. The levels were found to be significantly higher in PE patients (75.11±5.18) compared to PIH patients (49.84±4.92) and controls (32.25±4.75). Other studies showed similar results along with other PE parameters, including ALT activity and serum uric acid levels.[17,18]

Additionally, in patients with PIH and PE, the current study found a positive correlation between serum arginase levels and SBP and DBP. In the past decade, several studies have been conducted on various biomarkers to predict PIH and PE, and to thereby reduce their associated complications. According to a 2018 study, biomarkers were increasingly important in predicting PE.[19] However, a literature review showed that there was a limited range of biomarkers that had a positive correlation with PE, but further research was needed to determine their specificity, sensitivity and cost-effectiveness. An ideal biomarker for predicting PE would be able to identify pregnant women at an early stage of the disease. Many studies have investigated multiple-marker algorithms to predict PE and reduce its complications.[20]

In PIH cases, the platelet count was found to be marginally low or at the lower end of the normal range. However, in PE patients, the platelet count was found to be considerably low in the current study. This trend was consistent with earlier findings.[21] A study examined similar trends, and concluded that deranged arginase raises the likelihood of PE and may impact the levels of circulating nitrite in healthy pregnant women, as well as low platelet counts in pregnant women with PE.[19]

Correlation analysis between arginase levels and platelet counts in PIH and PE women showed an inverse correlation in PE women in the current study. This implied that when arginase levels rise in pregnant women with PE, their platelet count decreased. Van der Tuuk et. al. found that severe cases of gestational hypertension could result in haemolysis, leading to a decreased platelet count and elevated liver enzymes, ultimately resulting in HELLP syndrome or eclampsia[22].

In the current study, ALT levels of PE women were significantly high compared to PIH patients and controls. Correlation analysis between ALT and serum arginase levels revealed a strong positive correlation both in PE and PIH patients, but arginase levels were not high enough to cause raised levels of ALT in PIH patients. Another study showed the same pattern of raised ALT in PE patients.[23]

The current study found that only 20% of PIH patients with high arginase levels had high serum uric acid levels, while 53.3% of pregnant women with PE and high arginase levels had raised serum uric acid levels. The results indicated a consistent pattern of increasing serum uric acid levels in both PIH and PE groups, which was consistent with a previous research.[24]

PE patients had a notable increase in spot urinary protein in the current study, while in PIH women, the levels were within the normal range, but close to the cut-off level of <30mg/dl. A significant positive correlation was found between serum arginase levels and spot urine proteins. Hence, when PE patients had high levels of arginase, their urinary protein levels also increased. Proteinuria has been reported by numerous studies related to PE patients.[25]

The current study has limitations as it had a comparatively small sample size. Additionally, a comprehensive understanding of the predictive significance of the arginase estimate might not have been fully achieved due to the lack of extensive long-term follow-up data. It is crucial to conduct more extensive long-term studies with larger sample sizes and continued follow-ups to validate the current findings.

Conclusion

A moderate to markedly raised levels of serum arginase in PIH and PE pregnant women, respectively, along with deranged levels of serum urea, creatinine, uric acid and ALT, along with platelet count and spot urine protein values encouraged the use of serum arginase estimation

as an early predictor of hypertensive disorders of pregnancy, like PIH and PE.

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Authors' Contribution:
SS: Conceived, design, biochemical analysis and statistical analysis.
MNA: Conceived, design, review and final approval.
SQ: Statistical analysis, data interpretation, reference management and proof reading.
SS: Gynaecology examination of study participant and data interpretation.