Research Article

First-trimester uterine artery Doppler and PAPP-A levels as predictors of pre-eclampsia in a South Asian population; Mardan city, Pakistan

Dr. Zulfiqar Ali Khan[1*], Shumaila Khawaja Khail[1], Faryal Jahan[2], Abubakar Amin[3]

[1]Swat Medical College & Allied Teaching Hospitals Saidu Sharif swat
[2]Shifa Tameer e Millat University, Islamabad
[3]International Institute of Technology Culture and Health Sciences, Gujranwala.

***Corresponding author's email:** womenhospitalmardan@gmail.com

Abstract

One of the most common causes of maternity and neonatal fatalities and mortality is Pre-eclampsia (PE) which is responsible for 14% of global maternal deaths. The condition is primarily attributed to impaired trophoblastic invasion, which increases uterine artery pulsatility index (PI). A predictive analysis was done at Swat Medical College and Women's Hospital in Mardan, Pakistan from June 2022 to June 2023, including 218 pregnant women aged 11-13+6 weeks. Females with multifetal pregnancies, congenital fetal anomalies, and pre-existing medical conditions were excluded from this research. Uterine artery the Doppler and the PAPP-A testing were done to screen the conditions. Of 624 screened women, 218 were included in the final analysis using SPSS. The study population's mean age was 28 years, with 59% primiparous and 41% multiparous women. The incidence of PE was 35.5%, and gestational hypertension was 22.5%. Women developing hypertensive disorders had significantly higher mean uterine artery PI (2.11) compared to normotensive women (1.21, $p=0.01$), and significantly lower mean PAPP-A MoM levels (0.78 vs. 1.42, $p<0.001$). Coupled aberrant uterine blood vessels PI and PAPP-A predicted PE with high significance ($p<0.001$). Uterine artery in the first trimester Doppler and PAPP-A levels are effective in predicting pre-eclampsia in a South Asian population. Implementing these screenings could enhance early detection and management of PE, potentially reducing associated morbidity and mortality.

Keywords: Pre-eclampsia (PE), Pulsatility index (PI), Uterine artery Doppler, Maternal mortality, Gestational hypertension, Pregnancy-associated plasma protein-A (PAPP-A).

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Introduction

Pre-eclampsia (PE) is among the most prevalent indicators of complications during pregnancy that results in mortality and is a condition peculiar to pregnancy. It is responsible for 14% of maternal deaths globally [1-3]. It is devasting and potentially fatal for both the mother and the unborn child, and it contributes to perinatal and maternal morbidity [4]. During their pregnancy, 10% of women

suffer high blood pressure, and 2-8 percent suffer complications associated with high blood pressure which become a responsible cause for the worsening of pregnancy and post-natal abnormalities. Pre-eclampsia is a diversified complication that affects the neurological, hematological, renal, and hepatobiliary systems [5].

Pre-eclampsia is caused by decreased trophoblastic cell invasion into the myometrial parts of the arteries and capillaries, which causes greater flow resistance in the uteroplacental unit and transmission to the uterine arteries [6] Consequently, the pulsatility index (PI) rises. Therefore, before clinical symptoms appear, Uterine arteries' Doppler spectral interpretation may be able to detect maternal complications linked to uteroplacental insufficiency [7].

As the placenta forms, placental products are discharged into the circulation. All of these are the biological signs which demonstrate the disease progression of malfunctioning placenta formation. Pregnancy-associated plasma protein-A (PAPP-A) is a syncytiotrophoblast-derived protease enzyme focusing on insulin-like growth factor binding protein-4 (IGFBP-4). Low levels of PAPP-A quantities lead to shortened quantities of free insulin-like growth factor (IGF) in the bloodstream, which may trigger pre-eclampsia and hinder embryonic growth.

Recent research indicates that in chromosomally normal pregnancies, reduced mother's serum PAPP-A concentrations throughout the preliminary trimester are linked to a higher chance of pre-eclampsia development later [8-10].

It is still difficult to predict pre-eclampsia in advance. Researchers have previously investigated several markers. PAPP-A, and artery Doppler after throughout the first trimester of pregnancy, the uterus positively predicted pre-eclampsia according to the published data in the literature. Nonetheless, most of the research that is now accessible was done on African American and Caucasian populations. There is still a lack of South Asian population data [11]. Our goal is to determine if pre-eclampsia may be predicted by seeing abnormalities in both screening and diagnostic tests at 11 to 13^{+6} weeks of gestation during pregnancy [12].

Numerous research studies in the past have employed after 15 weeks means at the start of the second trimester of pregnancy the uterine artery Doppler screening is a pre-eclampsia diagnostic method. However, in the first trimester, trophoblast invasion is most active and helpful for screening. As a result, examining uterine artery Doppler in the initial stages of gestation is justified. The institute's conduct recommends a timely anomalous examination and multiple indicators, PAPP-A together with free beta human chorionic gonadotrophin (βhCG), are used for routine screening for aneuploidy at 11–13 weeks. There will be no extra expenses for the patient's treatment undergoing therapy. This needs to be remembered, particularly in emerging nations like Pakistan [13].

Methodology

After receiving clearance from the Institute Ethics Committee, a prospective analytical investigation was conducted at the Swat Medical College and Women's Hospital Mardan, Pakistan throughout a year, from June 2022 to June 2023. The Cochran formula [14] was used to determine the sample size. Based on a 10% prevalence of pre-eclampsia, a sample size of 218 was determined. All pregnant women who visited the Outpatient Clinics at or before 11-13 weeks during pregnancy, were eligible to participate in the study, provided their consent, and volunteered to be followed up with. All the women were

residents of the Mardan city. Women who were multifetal gestating had congenital abnormalities in the fetus, were on antihypertensive medication, or had concurrent medical Diseases including excessive arterial pressure, elevated glucose phases, heart, liver, and kidney-related abnormalities, and brain and blood-related diseases were not included in the research. At the initial appointment, a thorough history was taken, an overall and complete examination was performed, and informed consent was obtained for research participation. Specific characteristics were documented, particularly their ages, equality, and body-mass index, education, employment, religion, domicile, occupation, and socioeconomic level (as measured by the modified BG Prasad Scale 2018 [15] and past family history of high blood pressure women were encouraged to have uterine artery Doppler performed at 11-13 weeks in conjunction with a regular nuchal translucency, nasal bone scan when dates and fetal heart activity were confirmed. To mitigate inter-observer differences, radiologists performed all of the scans at the Department of Radiodiagnosis at Swat Hospital Mardan. It was noted that the uterine artery pulsatility index existed. Multiples of the median (MoM) were used to signify the PAPP-A values in the dual markers report. The Swat Medical College and Women's Hospital in Mardan, Pakistan's Department of Biochemistry conducted the dual markers test.

Four groups comprised the study population: patients with a normal PAPP-A and an abnormal uterine artery Doppler; patients with a normal first-trimester uterine artery Doppler and an abnormal PAPP-A; patients with both abnormal and normal investigation results; and finally, patients with both abnormal and normal investigation results. The schedule for follow-up appointments was as follows: weekly until week 40 or until birth, once bi-weekly until week 28, and once every four weeks until week 36. The participant's blood pressure and urine probing were recorded at every follow-up appointment. Pre-eclampsia and gestational hyper-tension were diagnosed and defined following the 2013 criteria of the American College of Obstetricians and Gynecologists (ACOG) & Task Force on Hypertension in Pregnancy, 2013).

The statistical evaluation

The statistical evaluations were performed using edition 16 of the Statistical Package for Social Sciences (SPSS) (IBM, Armonk, New York). The PAPP-A MoM and UtA-PI were compared among people with normal hypertension compared to those who acquired hypotension problems utilizing the student t-test (independent t-test). The relationship between the result and the demographic parameters was examined employing the Chi-square test. The PAPP-A MoM and UtA-PI values were utilized to generate the Receiver Operating Curve (ROC). $P < 0.05$ was deemed significant for entirely statistical investigations, while $P < 0.001$ remained deemed very important.

Results

During the study period, 624 prenatal women who were 11 or less weeks along made an appointment with the outpatient department. 269 of them were eliminated because they didn't meet one or more of the requirements. Of the remaining women, 80 did not accept to follow-up and were therefore omitted, and 355 obtained early anomaly scans without a uterine artery Doppler from outside reports. A final analysis of data from 218 women was produced from the 275 women who gave their consent to participate in the trial since 57 of them were misplaced to complement besides remained not included in the data investigation.

Table 1 shows that 12% of the women were in the 18–20 stage variety, 29% in the 26–30 age range, and 48% in the 36–40 age range. At 18.3 years old was the youngest contestant and 40 years old was the oldest. Of the women in the Mardan study population, 41% were multiparous and 59% were primiparous.

74% of the women graduated from middle and intermediate education, whereas 27% completed elementary school. Most of them were housewives (55%), with 45% being employed. Among all participants, 71% were from the Class I socioeconomic scale, with none from Class IV or Class V. Most women were urban residents (61%), while 39% lived in rural areas. The religious composition was predominantly Muslim (87%), followed by Christians (23%), Hindus (2%), and Sikhs (0.5%). Additionally, 64% of the females had high blood pressure in their families, whereas 36% did not have it.

Table 2 presents the study data, which reveals that the incidence of hypertensive disorders was 22.5%, gestational hypertension was 22.5%, and pre-eclampsia was 35.5% of the study participants.

Table 1: Demographic features of the study participant

Demographic features		Number of participants (n=218) and percentage
Maternal age	18-20	12 (5.5%)
	21-25	55 (25.2%)
	26-30	63 (29%)
	31-35	40 (18.3%)
	36-40	48 (22%)
Parity	Primiparous	129 (59%)
	Multiparous	89 (41%)
BMI	<18.5	9 (4%)
	18.5-24.9	78 (36%)
	25-29.9	62 (28%)
	≥30	69 (32%)
Education	Postgraduate	18 (8%)
	Graduate	69 (32%)
	Higher Secondary	74 (34%)
	Secondary	30 (14%)
	Primary	27 (12%)
Socioeconomic class	I	155 (71%)
	II	50 (23%)
	III	13 (6%)
Occupation	Housewife	119 (55%)
	Working	99 (45%)
Religion	Muslim	189 (87%)
	Christian	23 (10.5%)
	Hindu	5 (2%)
	Sikh	1 (0.5%)
Residential area	Rural	85 (39%)
	Urban	133 (61%)
Hypertension in family	Present	139 (64%)
	Absent	79 (36%)

Table 2: Outcome associated with pregnancy

Outcome	Number of participants (n=218) and percentage
Normotensive	92 (42%)
Pre-eclampsia	77 (35.5 %)
Gestational Hypertension	49 (22.5 %)

As demonstrated in Table 3, the study findings indicated that the mean uterine artery pulsatility index (2.11) of those experiencing hypertension problems during pregnancy is substantially greater (p=0.01) than the average endometrial PI of individuals who did not (1.21).

Table 3: A comparison of the average intrauterine artery pulsation index throughout the initial month of hypertension diseases of pregnancies and normally hypertensive.

Normo-tensive		Hypertensive disorders of pregnancy		t-value	p-value
Mean uterine artery PI	SD	Mean uterine artery PI	SD		
1.21	0.69	2.11	0.71	-2.53	0.01

Table 4 shows that the mean first-trimester PAPP-A MoM values (0.78) for pregnant women with hypertensive disorders were considerably lesser than the mean PAPP-A MoM values (1.42, p<0.001) for those without these illnesses.

Table 4: Comparison of mean PAPP-A MoM levels among women with hypertensive disorders of pregnancy and normotensive women

Normo-tensive		Hypertensive disorders of pregnancy		t-value	p-value
*Mean PAPP-A MoM	SD	Mean PAPP-A MoM	SD		
1.42	0.54	0.78	0.27	-2.79	<0.001

*MoM: Multiples of Median, SD: Standard Deviation, PAPP-A: pregnancy-associated plasma protein-A.

When two testing values were unacceptable the prevalence of pre-eclampsia was 11.6%; when both measures were regular, the frequency was 28.5%. These features' overall correlation to pre-eclampsia was extremely meaningful (p<0.001), as seen in Table 5.

Table 5: Comparison of hypertensive disorders of pregnancy among the study groups

Screen characteristic	Hypertensive disorders of pregnancy		Normotensive n (%)	Total	χ2	Degree of freedom	p-value
	Pre-eclampsia n (%)	Gestational hypertension n n (%)					
Both abnormal	9 (11.6%)	5 (10%)	17 (19%)	31	35.4	5	<0.001
*UtA-PI abnormal, PAPP-A normal	19 (24.6%)	15 (30.6%)	26 (28%)	60			
UtA-PI normal, PAPP-A abnormal	27 (35.3%)	21 (43%)	14 (15%)	62			
Both Normal	22 (28.5%)	8 (16.4%)	35 (38%)	65			
Total	77	49	92	218			

* UtA-PI: uterine artery pulsatility index, PAPP-A: pregnancy-associated plasma protein-A.

Discussion

An important strategy to reduce illness and death in the mother and the fetus associated with inadequate therapy and delayed diagnosis is to predict pre-eclampsia. Several papers are available in which researchers have predicted pre-eclampsia using various techniques. Only in the 1980s were serum biological markers tested to indicate pre-eclampsia. The present learning determined to regulate if maternal blood PAPP-A and uterine artery Doppler remained effective pre-eclampsia screening tools in the first trimester. Together, these two causes resulted in the 49 percent occurrence of hypertension in maternity, with pre-eclampsia prevalence reported to be 35 percent and pregnant women with hypertension prevalence at 22 percent (Table 2). Pre-eclampsia prevalence in the previously indicated study groups was 11.6% in the primary group, 24.6% in the other, 35% in the tertiary, and 28.5% in the quarter (Table 5). Consequently, when together study findings were incorrect, the chance of pre-eclampsia was much advanced ($p<0.001$).

Pre-eclampsia and pregnant hypertension patients had a mean uterine artery PI value of 2.11, which was considerably greater than that of the untreated group ($p=0.01$) (Table 3). Satish et al. [15], Gomez with coworkers, and Narang with coworkers [6, 9] found comparable mean PI values across the afflicted groups: 2.34, 2.04, and 1.94, respectively [15-18]. According to Goetzinger et al., [5] there was no discernible change in the uterine artery PI standards among the afflicted and modest groups. [19].

With a degree of sensitivity of 68% and precision of 52.99% at a cut-off of 1.48, uterine blood vessel PI at $11\text{-}13^{+6}$ workweeks was thought to be an effective marker for disorders of hypertension of gestation. In a different investigation, Staboulidou et al. [19] similarly originate a cut-off of 1.52. In Uttar Pradesh, India, Narang et al.'s [9] study revealed comparable sensitivity (75.9%) and specificity (79.6%). Odibo et al., [10] reported a warmth of 64 percent as well [19-21]. At the 95%th centile of uterine artery PI, Martin et al., [8] and Gomez et al., [6] had reduced compassion (27% and 23.9%, respectively). A lower sensitivity of 52% was also demonstrated by Goetzinger et al. [22-25].

This study found that for uterine artery PI in the examination for prenatal pregnancy, the PPV was 23.61% and the NPV was 88.57%. Similar research was done in India by Singh et al. [26], and although the NPV was identical (97.33%), the PPV was significantly higher (92%).

The mean PAPP-A MoM of 0.78 (Table 4) for the group in our study that had both gestational hypertension and pre-eclampsia was comparable to the mean PAPP-A MoM of 0.88 and 0.772 reported in the training by Goetzinger et al., [5] and Spencer et al. [17-19]. In this study, the threshold worth for PAPP-A MoM at 11-13 weeks was 0.41, with a sensitivity of 28% and specificity of 90.6 %. Comparable results were obtained, with sensitivity and specificity of 16 percent and 93 percent, respectively [21]. Odibo et al., [10] found that PAPP-A sensitivity was 58% higher than that of Staboulidou et al., [19] who also found that PAPP-A MoM was 0.58 as the threshold value for pre-eclampsia [12-14]. At a cutoff point of 0.5, Patil et al. [11] was 52%, while our study's PPV was 38.89%.

While both screening values are abnormal, the prevalence of pre-eclampsia is almost 12%, as Table 5 illustrates. When both indicators are normal, the overall prevalence of pre-eclampsia in the afflicted group is 28%. Their combined relationship to pre-eclampsia is quite strong ($p<0.001$). Satish et al. [15] and

Staboulidou et al. [19] also made the same findings. Odibo et al., [10] found that although the group with early pre-eclampsia had a higher median uterine artery MoM, this alteration was not statistically important. There was a considerable reduction in the PAPP-A MoM in the affected group. Therefore, integrating all the variables to increase the screening capability did not assist [16-18].

PAPP-A was shown to be a reliable indicator of early-onset pre-eclampsia [25]. In predicting the incidence of late PE and hypertension during pregnancy, including PAPP-A in the grouping of motherly variables, mean arterial pressure (MAP), and uterine artery did not significantly enhance the results. According to Goetzinger et al., [5] uterine artery Doppler, ADAM12, PAPP-A, and maternal features together indicated 50%, 48%, and 52% of patients who had pre-eclampsia at 11-14 weeks of pregnancy. Therefore, increasing the predictability by combining all the factors did not help [14, 19].

Tan et al. [20] reported that while PAPP-A did not enhance testing efficiency, UtA-PI, MAP, and placental mammal growth factor (PlGF) predicted 90 percent of early-PE, 75 percent of preterm-PE, and 41 percent of term-PE. In a similar vein, PAPP-A was not shown to aid in prediction [23-25].

One of the research's limitations was the unbalanced demographic makeup of the study sample. This resulted presumably from the study's setting at a tertiary care facility. Better outcomes may have been obtained with a longer research period, a larger sample size, and two or more sites spread throughout various regions.

Conclusion

First-trimester uterine artery Doppler and PAPP-A levels are significant predictors of pre-eclampsia in pregnant women. This study demonstrates that elevated uterine artery pulsatility index and low PAPP-A levels can effectively classify females at higher hazard for developing pre-eclampsia. Implementing these screenings in clinical practice could enhance early detection and management of pre-eclampsia, potentially improving maternal and fetal health outcomes. However, further research with a more diverse and larger sample size is recommended to confirm these findings and improve generalizability.

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