

PREDICTIVE MARKERS FOR ADVERSE PREGNANCY OUTCOMES: INSIGHTS FROM A PROSPECTIVE COHORT STUDY ON MATERNAL FACTORS, BIOMARKERS, AND UTERINE ARTERY DOPPLER RESULTS

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Abstract

Background: Complications in pregnancy, such as preterm delivery, pregnancy-induced hypertension (PIH), and intrauterine growth restriction (IUGR), demand effective predictive strategies for improved outcomes. This study explores associations between maternal factors, first-trimester biomarkers, and second-trimester uterine artery Doppler results to enhance early risk detection and treatment.

Methods: A prospective cohort study of 500 antenatal women investigated correlations between demographic variables, maternal dual test markers (serum beta-HCG, serum PAPP-A), and uterine artery Doppler studies. Statistical analyses assessed associations with preterm birth, PIH, and IUGR.

Results: Serum beta-HCG levels below the 5th percentile correlated significantly with preterm birth (RR 2.3131, $p = 0.0288$). Low serum PAPP-A levels (<5th percentile) associated with PIH (RR 2.1447, $p = 0.0204$) and IUGR (RR 2.0953, $p = 0.0002$). Uterine artery Doppler indices (>0.58 RI) demonstrated associations with PIH (RR 2.2448) and IUGR (RR 1.6293). Diastolic notching correlated with preterm birth, PIH, and IUGR.

Conclusions: This study identifies serum beta-HCG, PAPP-A, and uterine artery Doppler indices as valuable predictors for adverse pregnancy outcomes, emphasizing their potential in early risk detection.

Keyword: Pregnancy complications, Predictive markers, Uterine artery Doppler, Maternal biomarkers, Preterm birth, Pregnancy-induced hypertension, Intrauterine growth restriction.

INTRODUCTION

Natural biological processes, pregnancy, labor, and delivery usually result in positive results for moms and babies. On the other hand, departures from the standard may result in severe morbidity or maternal and neonatal death. Predicting conditions including preeclampsia, preterm delivery, early rupture of membranes, and fetal growth restriction can be difficult, especially in nulliparous women, for whom traditional risk factors and maternal history are sometimes insufficient.¹

Modern prenatal care is moving toward a risk-based strategy due to the necessity of anticipating unfavorable obstetric outcomes early in pregnancy. Determining risk factors—like reduced fertility, advanced maternal age, and increased BMI—is now essential to starting preventive care plans to reduce possible problems. The changing nature of society and the impact of late marriages and lifestyle modifications on reproductive patterns make it critical to comprehend the complex interactions between biochemical results, biophysical factors, and less than ideal pregnancy outcomes.²

There is no denying the placenta's critical function in the course of pregnancy. Pregnancy-induced hypertension (PIH) and intrauterine growth restriction (IUGR) are two disorders linked

to early disruption in placental activity, especially in the first trimester. The intricacy of fetal growth regulation is further highlighted by knowledge of the molecular mechanisms involving insulin and insulin-like growth factors, as well as PAPP-A's function in controlling free IGF levels.³

Pregnancy problems have been associated with low levels of maternal serum PAPP-A and free β -HCG, according to recent retrospective investigations. This emphasizes the necessity of precise and sensitive prediction testing to pinpoint groups that are at-risk and enable prompt treatment. The necessity of early identification is highlighted by the complex link between poor placentation and unfavorable outcomes such pre-eclampsia, fetal growth restriction, fetal mortality, and abruptio placenta.⁴

Increased blood flow impedance in uterine arteries is a consequence of impaired placentation, which is defined by insufficient trophoblastic invasion of spiral arteries. One potentially useful method for identifying women who are at-risk throughout the first and second trimesters is the use of Doppler ultrasonography investigations that incorporate waveform indices or notching. Prompt actions, directed by these evaluations, have the capacity to reduce morbidity and death among mothers and fetuses.⁵

With an emphasis on their predictive usefulness for third-trimester obstetric problems, this research attempts to investigate the associations between maternal factors, first-trimester blood biomarkers, and second-trimester uterine artery Doppler results. Our goal is to improve overall pregnancy outcomes by deciphering the complex web of pregnancy and aiding in the development of more efficient methods for early risk detection and treatment.

MATERIALS AND METHODS

Study Site: This prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at Holy Family Hospital, New Delhi.

Study Population: The study included 500 booked antenatal patients attending the Outpatient Department (OPD) of Holy Family Hospital during the first trimester of pregnancy, regardless of parity.

Study Design: A prospective cohort study design was employed.

Sample Size Calculation: Based on a previous study indicating significant differences in maternal serum PAPP-A and free beta-hCG among groups with adverse outcomes, a minimum sample.

n ≥ (Zα + Zβ)² / (ES)²

where Zα is the Z-value at a two-sided alpha error of 5%, Zβ is the Z-value at a power of 90%, SD is the standard deviation, and ES is the effect size.

Study Period: The study was conducted from November 2014 to June 2016.

Inclusion Criteria:

- Pregnant women in the first trimester of pregnancy
- Singleton pregnancy

Exclusion Criteria:

- Multiple pregnancy
- Essential hypertension
- Pregestational diabetes
- Severe anemia
- Systemic lupus erythematosus (SLE)
- Renal and heart disease
- Fetal congenital malformations

Methodology: An informed written consent was obtained from all participants. Detailed information, including age, parity, maternal education, race, socio-economic status, obstetric history, family history, past medical history, smoking habits, and physical activity, was collected during the first antenatal visit. Body mass index (BMI) and mean arterial pressure (MAP) were recorded at this visit. General and systemic examinations, along with routine antenatal investigations, were performed.

Laboratory Tests:

- Maternal serum PAPP-A and free beta-hCG were measured between 11 to 14 weeks using the ELISA method.

- Results were converted into multiples of the median (M.O.M) using expected median marker levels in normal pregnancies.
- Abnormal values were defined as < 5th percentile or > 95th percentile.

Ultrasonography:

- Doppler ultrasound of uterine artery velocity waveform was performed at 20-22 weeks.
- Resistance index (RI) was calculated, and a value of > 0.58 was considered elevated.
- Persistent early diastolic notching or elevated RI was considered abnormal.
- Regular follow-up through the third trimester was conducted to note the development of complications.

Definitions:

1. Pregnancy-Induced Hypertension (PIH):
 - Hypertension diagnosed after 20 weeks of gestation.
 - Proteinuria and other criteria as defined in the study.
2. Intrauterine Fetal Growth Restriction (IUGR) or Fetal Growth Restriction (FGR):
 - Failure of the fetus to reach its genetic growth potential.
 - Small for gestation age (SGA) defined as estimated fetal weight or abdominal circumference < 10th percentile.
3. Preterm Delivery:
 - Delivery before 37 completed weeks of gestation after viability.

Statistical Methods:

- Data presentation: Categorical variables as number and percentage, continuous variables as mean ± SD and median.
- Normality of data tested using Kolmogorov-Smirnov test.
- Statistical tests: Unpaired t-test/Mann-Whitney Test, Chi-Square test/Fisher's exact test.
- Diagnostic tests for sensitivity, specificity, NPV, and PPV.
- Relative risk calculation.
- Statistical significance considered at p < 0.05.
- Data entry in MS EXCEL spreadsheet; analysis conducted using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

The results reveal significant associations between maternal serum markers, uterine artery Doppler indices, and adverse pregnancy outcomes. Table 1 indicates a notable relationship between serum beta-HCG levels below the 5th percentile and preterm birth (RR 2.3131, p = 0.0288). Conversely, higher levels (>95th percentile) show no association. Table 2 demonstrates a significant correlation between low serum PAPP-A levels (<5th percentile) and the development of PIH (RR 2.1447, p = 0.0204), while Table 3 shows a similar association with IUGR (RR 2.0953, p = 0.0002). Uterine artery Doppler findings in Table 4 reveal a significant association between resistance index (RI) >0.58 and both PIH (RR 2.2448) and IUGR (RR 1.6293). Diastolic notching in Table 5 is associated with preterm birth, PIH, and IUGR, emphasizing its potential as a comprehensive predictive marker. These findings underscore the utility of these markers in anticipating adverse pregnancy outcomes.

TABLE 1 : RELATION OF ABNORMAL SERUM B-HCG LEVELS WITH PRETERM BIRTH

Percentile	MOM	Preterm	Normal	Sensitivity	Specificity	PPV	NPV	Relative Risk	P value
<5 th percentile	<0.47	7(16.67%)	35(83.33%)	17.50%	92.39%	16.67%	92.79%	2.3131	0.0288
>95 th percentile	>2.38	0(0.00%)	4(100.00%)	0.00%	99.13%	0.00%	91.94%	1.2272	0.8795

TABLE 2: RELATION OF SERUM PAPP-A WITH PIH

Percentile	MOM	PIH	Normal	Sensitivity	Specificity	PPV	NPV	Relative Risk	P value
<5 th percentile	<0.46	11(15.07%)	62(84.93%)	26.83%	86.49%	15.07%	92.97%	2.1447	0.0204
>95 th percentile	>2.83	0(0.00%)	3(100.00%)	0.00%	99.35%	0.00%	91.75%	1.5000	0.7607

TABLE 3: RELATION OF SERUM PAPP-A WITH IUGR

Percentile	MOM	IUGR	Normal	Sensitivity	Specificity	PPV	NPV	RR	P value
<5 th percentile	<0.46	24 (32.88%)	49 (67.12%)	26.37%	88.02%	32.88%	84.31%	2.0953	0.0002
>95 th percentile	>2.83	0(0.00%)	3(100.00%)	0.00%	99.27%	0.00%	81.69%	0.6803	0.7715

TABLE 4: RELATION OF RI WITH PRETERM

		Preterm Birth		Total
		N	Y	
RI	<0.58	196(93.33%)	14(6.67%)	210 (100.00%)
	>0.58	264(91.03%)	26(8.97%)	290 (100.00%)
Total		460(92.00%)	40 (8.00%)	500 (100.00%)

TABLE 5: DISTRIBUTION OF PATIENTS ACCORDING TO DIASTOLIC NOTCH

	Frequency	Percentage
A	475	95.00%
P	25	5.00%
Total	500	100.00%

DISCUSSION

This study delves into the intricate landscape of complications during the third trimester of pregnancy, a critical period marked by increased vulnerability to adverse outcomes. With shifting lifestyles, obstetricians worldwide grapple with the escalating challenges posed by complications such as preterm birth, pregnancy-induced hypertension (PIH), and intrauterine growth restriction (IUGR). Recognizing the imperative need for efficient predictors, this investigation focused on maternal dual test markers, uterine artery Doppler studies, and demographic variables to unravel their potential roles in anticipating these complications and, consequently, improving pregnancy outcomes.⁷

In the exploration of 500 antenatal pregnant women, the study sought to identify correlations between various factors and the occurrence of preterm birth, PIH, and IUGR in the third trimester. The demographic variables under scrutiny included age, parity, body mass index (BMI), and mean arterial pressure (MAP). Maternal dual test markers, specifically serum beta-HCG and serum PAPP-A, were assessed alongside uterine artery

Doppler studies, including resistance index and diastolic notching.⁸

The study uncovered that out of the total cohort, 8.00% experienced preterm delivery, 8.20% developed PIH, and 18.20% had babies affected by IUGR. The subsequent exploration into maternal serum beta-HCG levels revealed a significant association with preterm birth, with a relative risk of 2.3131 in patients with levels below the 5th percentile. However, no such association was identified with PIH or IUGR, echoing findings from previous studies.⁹

Turning attention to serum PAPP-A, the study illuminated a significant connection between low PAPP-A levels in the first trimester and the subsequent development of PIH and IUGR. The relative risks underscored the predictive potential, with a 2.1447-fold increase for PIH and a 2.0953-fold increase for IUGR. Nonetheless, no significant association emerged between low PAPP-A levels and preterm birth, a contrast to findings in some previous studies.¹⁰

Uterine artery Doppler studies were integral to this investigation, unveiling a notable association between resistance index (RI) greater than 0.58 and the development of both PIH and IUGR. The study illuminated a relative risk of 2.2448 for PIH and 1.6293 for IUGR in patients with elevated RI. Intriguingly, diastolic notching in uterine artery Doppler exhibited significant associations with preterm birth, PIH, and IUGR, revealing its potential as a comprehensive predictive marker.¹¹

While demographic variables such as age, parity, BMI, and MAP were considered, the study found no significant associations between maternal age or parity and the development of complications. BMI demonstrated a notable connection with PIH, aligning with certain studies but diverging from others, emphasizing the intricate interplay of factors in predicting outcomes.¹²

Despite these insightful findings, the study candidly acknowledges its limitations, including a confined time frame, a relatively modest sample size, and potential demographic gaps in the study population. Inter-observer errors in uterine artery Doppler studies also introduce a layer of complexity.¹³

CONCLUSION

In conclusion, this study delves into third-trimester complications in 500 pregnant women, unveiling serum beta-HCG and PAPP-A as predictive markers for preterm birth, PIH, and IUGR. Uterine artery Doppler, particularly resistance index and diastolic notching, emerges as a valuable screening tool. Despite limitations, the study lays the groundwork for refined predictive models.

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