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Association of First-Trimester Maternal Serum PAPP-A, Free β-hCG, and Placental Growth Factor with Adverse Pregnancy Outcomes: A Prospective Observational Study

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Abstract
Background
Adverse pregnancy outcomes such as preeclampsia, fetal growth restriction, preterm delivery, and oligohydramnios contribute significantly to maternal and perinatal morbidity and mortality. Early identification of women at risk allows timely preventive interventions. Maternal serum biomarkers including pregnancy-associated plasma protein-A (PAPP-A), free beta-human chorionic gonadotropin (β-hCG), and placental growth factor (PlGF) have been proposed as early predictors of placental dysfunction and adverse pregnancy outcomes.
Objective
To evaluate the association of first-trimester maternal serum PAPP-A, free β-hCG, and PlGF levels with adverse pregnancy outcomes.
Methods
A prospective observational study was conducted among antenatal women between 9 weeks and 13 weeks + 6 days of gestation attending a tertiary care teaching hospital. Maternal serum PAPP-A, free β-hCG, and PlGF were measured during the first trimester using time-resolved fluoroimmunoassay. Participants were followed until delivery, and pregnancy outcomes were recorded. Statistical analysis was performed using Mann–Whitney U tests and multivariate logistic regression.
Results
A total of 123 women were enrolled, and 119 completed follow-up. Preeclampsia occurred in 6.72% of pregnancies, while preterm delivery and oligohydramnios occurred in 4.24% each. Gestational diabetes mellitus was observed in 2.52%, PROM in 3.36%, and fetal growth restriction in 3.40% of pregnancies. Multivariate analysis demonstrated significant associations between serum analytes and preeclampsia prediction (p=0.01). PlGF and PAPP-A showed the strongest relationship with preeclampsia risk. No significant associations were observed for most other adverse pregnancy outcomes.
Conclusion
First-trimester PlGF and PAPP-A are promising biomarkers for the prediction of preeclampsia. Incorporating PlGF into routine first-trimester screening may improve early identification of women at risk, allowing implementation of preventive measures such as low-dose aspirin therapy and enhanced antenatal surveillance.
Keywords: *PAPP-A, Placental Growth Factor, β-hCG, Preeclampsia, Adverse Pregnancy Outcomes, First-Trimester Screening*

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I. Introduction

Adverse pregnancy outcomes remain a major public health concern worldwide. Conditions such as preeclampsia, fetal growth restriction (FGR), preterm birth, gestational diabetes mellitus (GDM), and placental insufficiency are associated with substantial maternal and neonatal morbidity. Increasing evidence suggests that the pathophysiological processes underlying these complications originate early in pregnancy, particularly during placentation.

Maternal serum biomarkers measured during the first trimester have emerged as potential tools for early risk stratification. PAPP-A and free β-hCG are routinely used in aneuploidy screening, whereas PlGF has gained increasing attention as a marker of placental angiogenesis and dysfunction. Abnormal levels of these analytes have been associated with impaired placentation and subsequent pregnancy complications.

This study aimed to evaluate the association between first-trimester maternal serum PAPP-A, free β-hCG, and PlGF concentrations and adverse pregnancy outcomes in a prospective cohort of pregnant women.

II. Materials and Methods

Study Design

Prospective observational study.

Study Setting

Department of Obstetrics and Gynecology, KAHER's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, India.

Study Population

Pregnant women between 9 weeks and 13 weeks + 6 days gestation attending the antenatal clinic were recruited after informed consent.

Inclusion Criteria

- Singleton pregnancies
- Gestational age between 9 and 13+6 weeks

Exclusion Criteria

- Pre-existing diabetes mellitus
- Chronic hypertension
- Cardiac disease
- Renal disease
- Multiple gestation

Biomarker Assessment

Maternal venous blood samples were collected during the first trimester. Serum PAPP-A, free β-hCG, and PlGF levels were analyzed using AutoDELFIA time-resolved fluoroimmunoassay.

Outcomes

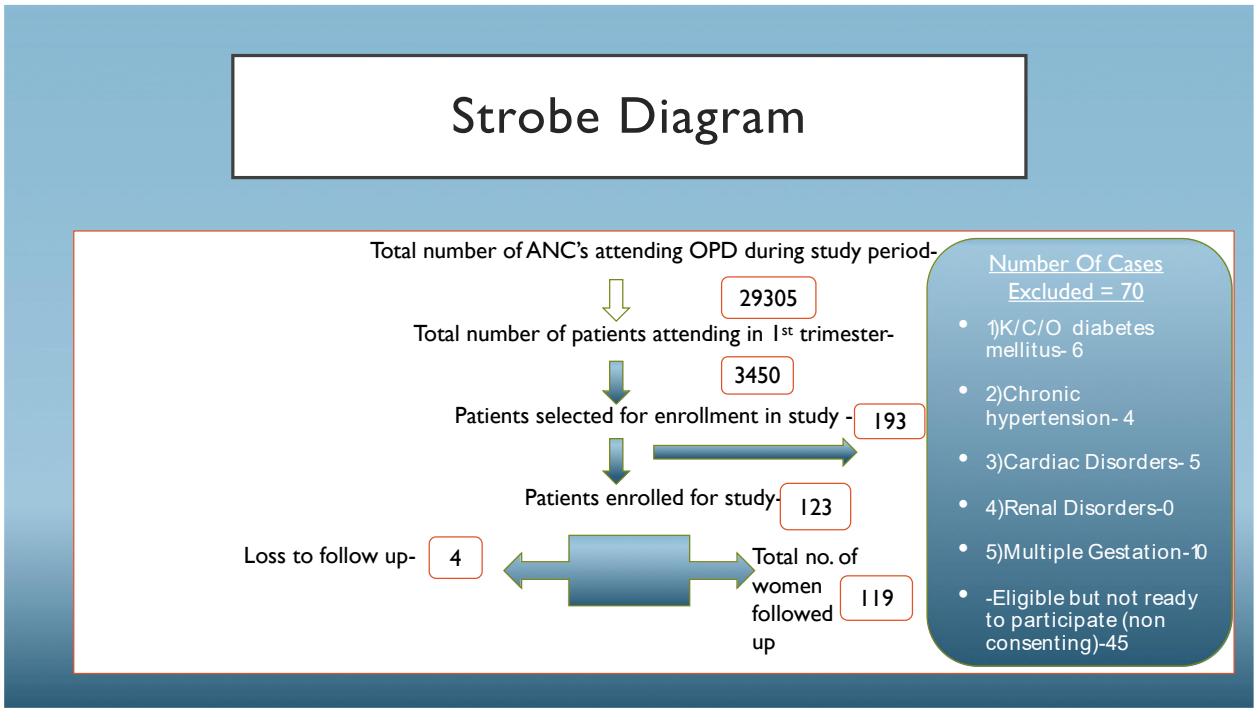
Primary adverse pregnancy outcomes included:

- Preeclampsia
- Gestational hypertension
- Fetal growth restriction
- Preterm delivery
- Oligohydramnios
- PROM
- Gestational diabetes mellitus
- Chromosomal abnormalities

Statistical Analysis

Data were analyzed using R software version 4.2.1. Continuous variables were expressed as mean ± SD. Associations between serum analytes and outcomes were evaluated using Mann–Whitney U tests and multivariate logistic regression. Statistical significance was defined as $p < 0.05$.

Results



A total of 123 women were enrolled, with 119 completing follow-up. The mean maternal age was 27.8 ± 4.55 years. Most participants were primigravidae (60.5%) and conceived spontaneously (97.5%).

The incidence of adverse pregnancy outcomes included:

- Preeclampsia: 6.72%
- Preterm delivery: 4.24%
- Oligohydramnios: 4.24%
- Gestational diabetes mellitus: 2.52%
- PROM: 3.36%
- Fetal growth restriction: 3.40%

Multivariate analysis demonstrated a statistically significant association between first-trimester serum analytes and preeclampsia prediction (p=0.01). PlGF and PAPP-A contributed meaningfully to risk assessment, while β-hCG showed a weaker predictive role.

PROM showed a significant association with elevated PlGF levels. However, no significant associations were found between serum analytes and preterm labor, oligohydramnios, gestational diabetes mellitus, or fetal growth restriction.

Only one participant demonstrated increased risk for Down syndrome, while all others screened negative for trisomy 18 and trisomy 13.

Discussion

This study supports the growing evidence that first-trimester biomarkers reflect placental function and may identify women at increased risk of preeclampsia. PlGF, a proangiogenic factor essential for placental vascular development, showed particular promise when combined with traditional dual-marker screening.

The findings align with previous studies demonstrating improved predictive performance when PlGF is incorporated into first-trimester screening models. Early identification of high-risk pregnancies provides an opportunity for preventive interventions, including low-dose aspirin therapy and intensified antenatal surveillance.

The absence of significant associations with other adverse outcomes may be attributed to the relatively small sample size and widespread aspirin use among high-risk participants, which may have modified disease occurrence.

Strengths and Limitations

Strengths

- Prospective study design
- First-trimester biomarker assessment
- Follow-up until delivery

Limitations

- Single-center study
- Modest sample size
- Potential confounding effect of aspirin prophylaxis
- Limited number of adverse outcome events

III. Conclusion

First-trimester maternal serum PlGF and PAPP-A demonstrate potential utility in predicting preeclampsia. Incorporation of PlGF into routine first-trimester screening may improve identification of women at risk for placental dysfunction and hypertensive disorders of pregnancy. Larger multicenter studies are needed to validate these findings and determine the clinical value of integrating PlGF into universal antenatal screening programs.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

No external funding was received for this study.

Ethical Approval

The study was conducted following institutional ethical approval and informed consent from all participants.

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