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ORIGINAL ARTICLE

Long-Term Predictors of Gestational Hypertension: Placental Growth Factor, Pregnancy-Associated Plasma Protein-A and Free Beta-Hcg Versus Mean Arterial Pressure and Uterine Artery Doppler Versus a Combination of Both: A Comparative Study

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Abstract

Background According to WHO, hypertensive disease is the leading cause of direct maternal mortality accounting for 10–25% in developing countries (James in Heart, 90(12):1499–504). This study compares the combinations of mean arterial pressure (MAP) and uterine artery doppler (UAD) versus serum-free β HCG, pregnancy-associated plasma protein-A, and placental growth factor (PlGF) versus a combination of all variables at 11 to 13^{+6} as long-term predictors of pregnancy-induced hypertension (PIH).

Materials and Methods A prospective, observational cohort study recruited 97 primigravidae at 11 to 13^{+6} weeks gestation at GMCH. Follow-up was done at 32–34 weeks and before delivery. Development of PIH, mode of delivery, birthweight, maternal and fetal adverse outcomes were documented, analyzed and compared among three groups. In Group A-biophysical markers, Group B-biochemical markers and in Group C all variables were used.

Results The mean age, maternal weight, height and BMI of patients developing gestational hypertension were 30 ± 5 years, 64.3 ± 12.5 kg, 155.8 ± 5.5 cm and 26.4 ± 4.1, respectively. Out of the 3, Group C is the best screening test for predicting the overall chance of development of gestational hypertension with a sensitivity of 97.37% and specificity of 38.98% ($p < 0.0001$). A mild negative correlation is seen between PlGF levels and severity of PIH (p-0.0382).

Conclusion MAP and UAD can be easily incorporated into the infrastructure of most hospitals. If the biochemical test kits are made available at a low cost through available programs such as JSSK, it can bring down the MMR by preventing gestational hypertension.

Keywords Gestational hypertension · Free β HCG · PAPP-A · PlGF · Uterine artery doppler · Mean arterial pressure

Introduction

Hypertension is a leading cause of maternal and perinatal mortality in India. In Assam, gestational hypertension is the 2nd most common cause of maternal mortality following hemorrhage [2]. Hypertension is diagnosed when blood pressure exceeds 140 mmHg systolic or 90 mmHg diastolic or both on two occasions at least 4–6 h apart and develops after 20 weeks gestation in a woman with previously normal blood pressure [3].

Human chorionic gonadotropin is a glycoprotein synthesized from syncytiotrophoblast. It peaks in maternal serum by 8–10 weeks and then slowly decreases to reach a plateau at 18–20 weeks of gestation [4]. It regulates placental development, angiogenesis, and vasculogenesis. Several studies

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indicate that high and/or low HCG level is a marker of subsequent clinical manifestation of pre-eclampsia. *Pregnancy-associated plasma protein-A* (PAPP-A) is a glycoprotein that acts on insulin-like growth factor protein secreted by syncytiotrophoblast. Placental pathology can lower its levels. Decreased serum PAPP-A during 11–13 weeks of gestation is associated with adverse outcomes of pregnancy such as stillbirth, preterm birth, intrauterine growth retardation (IUGR), and preeclampsia in chromosomally normal fetuses [5]. *Placental growth factor* (PlGF) belongs to the vascular endothelial growth factor (VEGF) family and is predominantly expressed in the placenta. The serum level of PlGF is low in the first trimester of uncomplicated pregnancies and increases from 11 to 12 weeks onwards. It peaks at 30 weeks and thereafter decreases. Low PlGF is a marker of abnormal placentation [6]. *Uterine Artery Doppler* (UAD) reflects the faulty trophoblastic invasion of spiral arteries, resulting in diminished placental perfusion and greater upstream uterine artery resistance. *Mean arterial pressure* (MAP) is influenced by cardiac output and systemic vascular resistance [7].

The idea behind this study is to identify high-risk pregnancies and to pinpoint patients who are likely to develop gestational hypertension along the course of their pregnancy. In 2013, Akolekar R et al. in their study based on maternal characteristics, biophysical and biochemical markers at $11–13^{+6}$ weeks gestation found that the combination of the three detected 96% of cases of preeclampsia requiring delivery before 34 weeks and 54% of all cases of preeclampsia at a fixed false positive rate of 10% [8].

Early prediction will help us initiate timely interventions to prevent gestational hypertension in high-risk women. One of the most promising treatment options is low-dose aspirin. FIGO recommends all high-risk women identified by first-trimester screening should receive low-dose aspirin prophylaxis at a dose of 150 mg to be taken every night commencing at 11–14 + 6 weeks gestation until either 36-week gestation, when delivery occurs, or when pre-eclampsia is diagnosed. [9] Combined screening tests, if made accessible to society at a low cost, will decrease maternal morbidity and mortality due to gestational hypertension. With this goal, this study was undertaken.

Patients and Methods

We conducted a prospective, observational cohort study at the Department of Obstetrics and Gynaecology at Gauhati Medical College and Hospital, Assam. The study was completed over a period of 1 year starting from October 2021, recruiting a total of 97 subjects. The initial sample size was 111, however as the kits provided had only 100 tests, the sample size was reduced to 100. For the calibration of instruments, 2 tests from each kit were used up and during the study one patient withdrew.

The inclusion criteria were as follows:

1. Primigravida with singleton pregnancy with a gestational age of 11–13 + 6 weeks as determined by last menstrual period or by ultrasound scan.
2. Antenatal women with first-trimester blood pressure records suggestive of normal blood pressure.
3. Women willing to participate in the study and ready to deliver in this hospital.

We excluded women with multifetal gestation and other medical disorders such as chronic hypertension, diabetes mellitus, kidney diseases, thyroid disorder, and autoimmune diseases. The Ethical Committee of Gauhati Medical College and Hospital approved the study on 22nd July 2021 (M/190/2007/Pt-II/July-2021/TH-34). Informed consent was taken from all the participants.

After enrolment in the study, proper history was taken. Socio-demographic history about age, gravida, menstrual cycles, past medical conditions, and surgical interventions was taken. General physical examination and systemic examination were done. Blood pressure was measured in the left recumbent position with her right arm at the level of the heart with an appropriate cuff after emptying her bladder. MAP was calculated using the formula MAP = DBP + 1/3(SBP-DBP) where DBP is diastolic blood pressure and SBP is systolic blood pressure. Obstetrical examination was carried out at each follow-up. Fundal height was palpated, and obstetrics grips assessment was done followed by auscultation of fetal heart rate (FHR). UAD was assessed by a transabdominal approach using the Mindray D-80 X-Insight USG machine. The mean PI was calculated.

Urinary proteinuria was checked and routine blood and urine investigations were sent which included:

- Complete blood count
- Blood sugar
- Thyroid function test
- Serum creatinine
- Viral markers
- Routine urine test and culture and sensitivity

Thereafter, blood samples were collected for serum-free ß HCG, PAPP-A, and PlGF, and serum-level estimation was done using the ROCHE Elecsys immunoassay using electrochemiluminescence technique. The results from these tests were converted to multiple of median (MOM). Thereafter 3 groups were made:

Group A-Only serum biochemical markers (Free *ß* HCG, PAPP-A, PlGF) were taken into consideration.

Group B-Only biophysical markers (MAP and UAD) were considered.

Group C-All variables were considered predictors of gestational hypertension.

Follow-up was done at 32–34 weeks and before delivery. Details including gestational age, blood pressure, mode of delivery, birthweight, any maternal or fetal adverse outcome, and NICU admission were documented.

Statistical Analysis

The sample size (n) is calculated according to the formula by Charan and Biswas (2013) [10]

$$n = z^2 \times p \times (1 - p)/e^2,$$

where

$z = 1.96$ for a confidence level (α) of 95%,

p = proportion (expressed as a decimal), taking 7.8% from literature [11]

e = margin of error.

$z = 1.96$, $p = 0.078$, $e = 0.05$.

$n = 1.962 \times 0.078 \times (1–0.078)/0.052$.

$n = 0.2763/0.0025 = 110.509$.

$n = 111$.

The sample size was equal to 111.

The data obtained were coded and entered into Microsoft Excel Worksheet version 2021 and analyzed using IBM-SPSS version 26. The normality of the data was determined using Kolmogorov–Smirnov test. Categorical data were expressed as frequency and proportion (percentages). Numerical data were represented with mean and standard deviation for parametric data, or median and IQR in case of non-parametric data. For determining the statistical correlation in categorical data, a Chi-square test or Fisher Exact test was applied. To calculate the significant mean difference for normally distributed continuous data, a student t-test was applied, whereas, for non-normal continuous data, the non-parametric test of Mann–Whitney U was applied. Receiver Operating Characteristic curves were used to find out sensitivity, specificity, positive predictive value, and negative predictive value. P-value < 0.05 was considered significant for all statistical comparisons.

Results

Of the 98 patients included in the study, one patient withdrew during follow-up. The minimum age included in the study was 19 years and the maximum was 37 years of age. The mean age of patients developing gestational hypertension was 30 ± 5 years. The mean maternal weight and height of those developing gestational hypertension were found to be 64.3 ± 12.5 kg ($p = 0.019$) and 155.8 ± 5.5 cm ($p = 0.046$), respectively. The mean BMI seen in the group developing gestational hypertension was 26.4 ± 4.1 which was not significant. Of the 97 patients that took part in the study, 21 patients (21.65%) developed only mild disease. However, 17 of them (17.53%) developed a severe form of the disease known as pre-eclampsia as defined by the ACOG 2019 Practice Bulletin [12].

Receiver Operating Characteristic curves were used to illustrate the diagnostic ability of each variable individually to predict gestational hypertension at less than 34 weeks and at the time of delivery. Following this, data for the combinations of variables as mentioned earlier as Group A, Group B, and Group C were analyzed.

The sensitivity of Group A combination in detecting gestational hypertension at less than 34 weeks was 100% (CI 0.590–0.782) and specificity was 38.37% (CI 0.590–0.782) with p-value < 0.0001 which is highly significant. PPV was 17.2% and NPV was 100%. The sensitivity of Group A combination in detecting gestational hypertension overall was 89.47% (CI 0.591–0.783) and specificity was 49.15% (CI 0.591 to 0.783). PPV was 53.1% and NPV was 87.9%. ($p < 0.0001$).

In Group B, it was observed that the sensitivity of the combination in detecting early onset gestational hypertension was 90.91% (CI 0.672–0.848) and specificity was 62.79% (CI 0.672–0.848) ($p < 0.0001$). PPV was 23.8% and NPV was 98.2% (Fig. 1). The sensitivity of the combination in detecting gestational hypertension overall was 63.16% (CI 0.560–0.756) and specificity was 69.49% (CI 0.560–0.756). PPV was 57.1% and NPV was 74.5% ($p < 0.0011$) (Tables 1 and 2).

It was observed that the sensitivity of Group C combination in detecting gestational hypertension at less than 34 weeks was 100% (CI 0.536–0.735) and specificity was 27.91% (CI 0.536–0.735). PPV was 15.1% and NPV was 100%. ($p < 0.0001$). It was observed that the sensitivity of

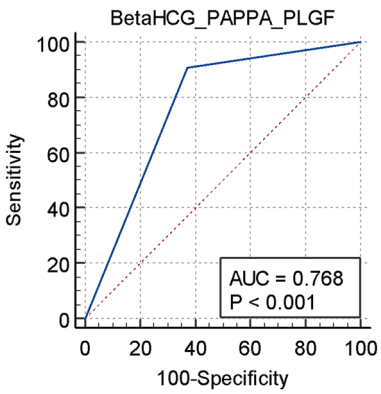

Fig. 1 ROC of Group B for early prediction (< 34 weeks)

Table 1 Comparison of diagnostic ability of Group A, Group B, and Group C for early onset PIH and overall prediction

	Early Onset (< 34 weeks)				Overall			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Group A	100	38.37	17.2	100	89.47	49.15	53.1	87.9
Group B	90.91	62.79	23.8	98.2	63.16	69.49	57.1	74.5
Group C	100	27.91	15.1	100	97.37	38.98	50.7	95.8

PPV positive predictive value, *NPV* negative predictive value

Table 2 Comparison of true positive for pre-eclampsia in Group A, Group B, and Group C

	Sensitivity	True positive	False negative
Group A	89.47	34	4
Group B	63.16	24	14
Group C	97.37	37	1

A total of 38 patients developed gestational hypertension in the study

Group C combination in detecting gestational hypertension overall was 97.37% (CI 0.579–0.773) and specificity was 38.98% (CI 0.579–0.773). PPV was 50.7% and NPV was 95.8%. *p*-value was < 0.0001 which is highly significant (Fig. 2 and Tables 1 and 2).

In the recent guidelines by ACOG (2019) for diagnosis of pre-eclampsia it has been stated that the disease may be diagnosed even in the absence of proteinuria [12]. The validity of this guideline is very aptly observed in our study. Only one patient out of the 17 that developed severe form of the disease, i.e., pre-eclampsia had proteinuria 2 + on examination. The rest of the subjects with pre-eclampsia were diagnosed with the guidelines which can be used in the absence of proteinuria.

A statistically significant, strong, negative correlation between the level of serum PAPP-A and adverse fetal outcome was seen, i.e., the lower the level of PAPP-A in serum, higher the chance of adverse fetal outcome such as IUGR, IUFD, fetal distress, early preterm and preterm birth. The correlation coefficient was − 0.7748 with a *p*-value of 0.0001 (CI − 0.8438 to − 0.6805) (Fig. 3).

A statistically significant, mild, negative correlation was also seen between the serum level of PlGF and the severity of gestational hypertension. The correlation coefficient was found to be − 0.3375 with a 95% CI (− 0.5932 to − 0.02002). The *p*-value is 0.0382 which is statistically significant. Therefore, a lower-level serum PlGF may result in severe forms of gestational hypertension (Fig. 4).

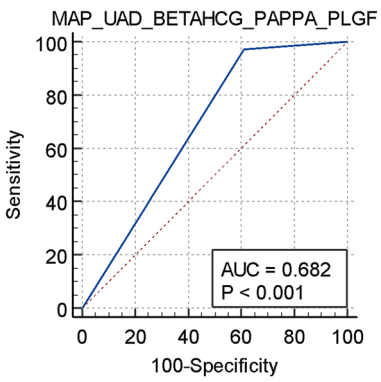

Fig. 2 ROC for Group C for overall prediction

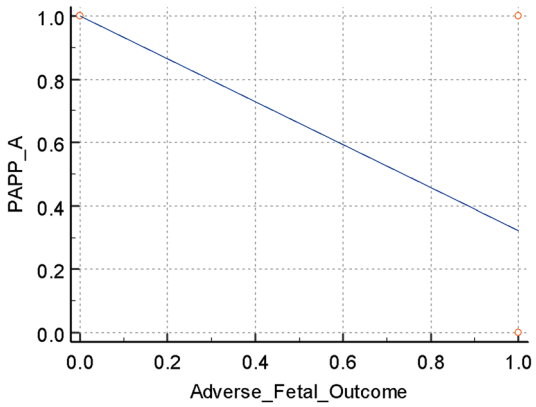

Fig. 3 Correlation between PAPP-A level and adverse fetal outcome

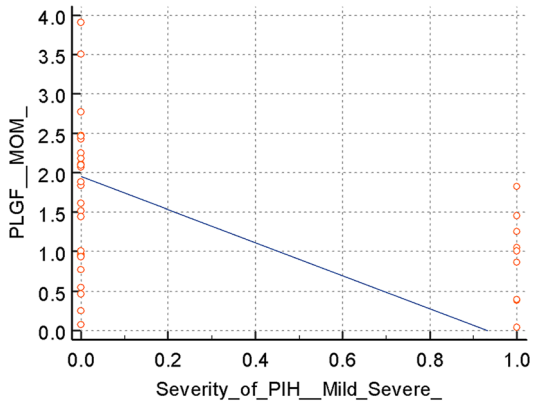

Fig. 4 Correlation between PlGF levels and severity of PIH

Discussion

Out of the 97 patients who participated in the study, 59 patients did not witness any rise in blood pressure. However, 38 patients developed gestational hypertension. 17 out of which progressed to preeclampsia. 11 of these 38 patients developed early onset gestational hypertension, i.e., before 34 weeks of gestation. In a study done by Gasse C et al., out of the 4700 subjects who were followed up completely out of 4749 eligible participants, gestational hypertension without pre-eclampsia was observed in 250 (5.3%) participants, and pre-eclampsia in 241 (5.1%), including 33 (0.7%) preterm PE and 10 (0.2%) early onset pre-eclampsia [13]. Our study has shown a higher prevalence of gestational hypertension probably due to the small sample size. Also, we have included only primigravidae in the study, which is a high-risk factor for gestational hypertension.

It was observed that the sensitivity of Group A in detecting gestational hypertension at less than 34 weeks was 100% however the specificity was only 38.37%. The sensitivity of Group A as an overall predictor was 89.47% and the specificity was 49.15%. The sensitivity of Group B in detecting gestational hypertension at less than 34 weeks was 90.91% and specificity was a favorable 62.79% but the sensitivity and specificity as an overall predictor were 63.16% and 69.49%, respectively. The sensitivity of Group C in detecting early-onset gestational hypertension was 100% and the specificity was 27.91%. It was observed that the sensitivity of the Group C combination in detecting gestational hypertension overall was 97.37% and specificity was 38.98%.

Trilla C et al. in their two-phase study in June 2022, included maternal factors, MAP, UtA-PI, and PAPP-A for 1st stage risk assessment. Three groups were defined (high-, medium-, and low-risk). Cut-off levels for the contingent screening model were chosen in the first and second stages of screening to achieve a performance with sensitivities of 100% and 80% for early-onset and preterm PE detection, respectively, with a 15% false positive rate [14].

Analysis of the data showed a statistically significant, strong, negative correlation between serum PAPP-A level and adverse fetal outcome. The correlation coefficient was − 0.7748 (p-value 0.0001). In their study done in 2020 to analyze pregnancy outcomes with low maternal PAPP-A ($\leq$ 5th percentile) at the FTAS screening test in Southern India, Shah et al. found that the total rate of preterm deliveries (OR:2.1), small-for-gestation-age fetuses (OR:2.3), and low birth weight babies (OR: 2.12) was significantly higher in the study group. A positive likelihood ratio of 1.4 for PTD, 2 for < 5th percentile birth weight, and 1.7 for < 10th centile birthweight was found [15].

The study reveals that at 11 to 13 + 6 weeks gestation, prediction of early-onset gestational hypertension is best done by a combination of free β HCG, PAPP-A, and PlGF as it has high sensitivity and favorable specificity. As an overall predictor, the combination of all five biomarkers has excellent sensitivity, with a favorable positive predictive value and a good negative predictive value. The study also shows the importance of these serum markers in preparing us for probable adverse maternal and fetal outcomes.

Conclusion

In conclusion, Group B seems to be a better screening test for early-onset gestational hypertension. However, Group C turns out to be the best screening test for predicting an overall chance of development of gestational hypertension. These screening tests will allow prompt management of at-risk patients, thereby preventing the dreaded consequences.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of Gauhati Medical College and Hospital on 22nd July 2021 (M/190/2007/Pt-II/July-2021/TH-34). Declaration of Helsinki was followed in all procedures.

Consent for Publication Informed consent was taken from all participants before enrolling in the study.

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