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Research Article

MATERNAL SERUM BETA HCG AND PAPP-A LEVELS IN EARLY PREGNANCY AS A SCREENING TEST FOR PREDICTION OF PIH AND FGR

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ABSTRACT

Aims and objectives: To study role of PAPP-A and Beta HCG in early pregnancy for prediction of hypertensive disorders of pregnancy and intra uterine fetal growth restriction later in pregnancy.

Materials and methods: This prospective cohort study was conducted in the Deptt. Of obstetrics and gynecology Safdarjung hospital which is a tertiary care centre over a period of 6 months from January 2017 to June 2017.After taking due consent, maternal serum Beta HCG and PAPP-A was measured in the antenatal women coming for routine antenatal visit between 11-14 weeks of gestation, the test value was noted down. Normal range of PAPP-A and Beta HCG levels were taken as 0.003 MOM and 0.879 mom as per previous studies. These women were followed up until delivery and looked for development of pregnancy induced hypertension (PIH) fetal growth restriction (FGR) and low birth weight (LBW). Outcome record for women developing PIH, FGR and LBW were matched with their respective first trimester biochemical markers.

Results: We found out that sensitivity of serum Beta HCG estimation as a predictor of pre-eclampsia is only 33.33% and specificity 53.53%, positive predictive value being 5.49% and negative predictive value being 90.82%. Due to low sensitivity this test may not be considered as routine screening test. The sensitivity and specificity of maternal serum PAPP-A estimation between 11-14 weeks of pregnancy as a predictor of preeclampsia is 60% and 72.97% respectively. Positive predictive value of maternal serum PAPP-A is 15.25% but negative predictive value is as high as 95.74%.

Conclusion: Between 11- 14 weeks of pregnancy, Serum PAPP-A levels could be used for predicting pregnancy outcomes of PIH and FGR while beta hcg measured during this period does not play any significant role. The advantage of predicting PIH in early pregnancy is that it allows early intervention of low dose aspirin in pregnant women with low serum PAPP-A levels for subsequent prevention of PIH.

INTRODUCTION

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad along with haemorrhage and infection that result in maternal morbidity and mortality related to pregnancy.Hypertensive disorders account for 16 % of maternal deaths in developed countries.[1]Around 3-10% of babies are growth restricted and fetal growth restriction (FGR) is associated with substantial perinatal morbidity and mortality.[2]As PIH and FGR have a high magnitude of problem, so early prediction of these entities can prevent their occurrence by intervention early in pregnancy and potential to improve the feto-maternal outcome.[3]Most of the interventions have commenced in 2nd and 3rd trimester and have been found to be ineffective. Several tests are in research like serum Beta Human Chorionic Gonadotropin, PAPP-A, placental protein - 13 and uterine artery Doppler to detect pregnancies at high risk for preeclampsia and FGR.[4]

Although preeclampsia manifests in 2nd and 3rd trimester of pregnancy the underlying pathology starts in the first trimester itself. There is insufficient placentation in preeclamptic women due to impaired cytotrophoblastic invasion of spiral arteries in myometrium, which restricts the blood supply to the fetus and placenta and causes placental ischemia. [5]Since the origin of the preeclampsia is believed to be lying in the placenta, hence many investigators hypothesized a relationship between the PAPP-Aand β-hCG levels and preeclampsia. Both β-hCG and PAPP-A are placental products thatare primarily produced by syncytiotrophoblasts. PAPP-A is a large glycosylated protein and β-hCG is a glycoprotein hormone. PAPP A has been used in first and second trimester serum screening for downs

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syndrome. Besides screening tool for Downs syndrome, abnormal values of these hormones have been associated with preeclampsia. [6,7]Thereis an increase in adverse obstetrical outcomes and occurrence of preeclampsia in women with low levels of maternal serum PAPP-A. [8,9]

Maternal serum β-hCG elevation, defined as cut-offs varying from 2.0 MoM to 4.0 MoM, has been found to have correlation with subsequent occurrence of pre-eclampsia.[10]

We measured maternal serum β HCG and PAPP-A levels between 11-14 weeks as a screening test and observed these women for development of PIH or FGR later in pregnancy. We did this study to find if maternal serum β HCG and PAPP-A act as predictors for PIH and FGR.

Aims and Objectives

To study role of PAPP-A and β HCG levels in early pregnancy in predicting development of hypertensive disorders of pregnancy and intrauterine fetal growth restriction later in pregnancy.

MATERIALS AND MEHODS

Study settings-The present study was conducted in the Deptt. Of Obstetrics and Gynecology of Safdarjung hospital which is a tertiary care center over a period of 6 months from January 2017 to June 2017. It was a prospective observational study. Clearance was taken from the ethical committee of the hospital.

Sample size- Assuming prevalence of pre-eclampsia as 8% from existing evidence, using the formulae 4PQ/d2 sample size is calculated as 117(d=5). Assuming 20 % attrition rate the sample size is 200

Study procedure- Total 200 antenatal women who registered in first trimester between 11 - 14 weeks who agreed to undergo dual marker test were enrolled in the study. Any women with history of chronic hypertension was excluded from the study. The blood samples for dual marker test were drawn after informed consent. PAPP-A and free β-hCG levels were converted to multiples of the median (MoM). Normal range of PAPP-A and Beta hcg levels were taken as 0.903 mom and 0.879 mom as per previous studies. [8,10]The test values were noted down and the women were followed up until delivery and observed for the development of PIH, FGR. Pre-eclampsia was defined as blood pressure of >140 mm Hg systolic and/or 90 mm Hg diastolic on two or more occasions after 20 weeks gestation in a woman with previously normal blood pressure. [11] The patients were divided in two groups, those who did not develop preeclampsia were taken as controls and those who later developed preeclampsia were considered as cases. Outcome for people who did and did not develop PIH were matched to their respective first trimester biochemical markers. The women who did not develop PIH were taken as controls and those who developed PIH later were considered cases. The birth weights were recorded.

The data was entered in MS excel sheet and analysed by SPSS software. Pearson chi-squared or Fisher's exact tests were used for the comparison of categorical variables, and Student's t-tests were used for continuous variables.

RESULTS

Table 1 Demographics of cohort with PIH and without PIH

Variable	Group	N	Mean	SD	P-VALUE
Maternal age	Control	185	28 YRS	3.69	0.9
	Case	15	27.93	5.32	
Total		200			

Table 2 BMI distribution in pregnant women with preeclampsia (case) and without preeclampsia (control)

Variable	Group	N	Mean	SD	P-value
BMI	Control	186	29.14	2.76	0.809
	Case	15	29.0461	2.15	

Table 3 Distribution of gestational age at delivery in pregnancy with PIH (case) and without PIH (control)

Variable	Group	N	Mean	SD	P-Value
Gestational	Control	185	37.75	1.296	0.77
Age at delivery	Case	15	27.33	0.819	

The maternal age, BMI and gestational age at delivery of cases and controls was comparable as the p values were > 0.05.

Out of 200 patients enrolled in the study, 15 patients later developed preeclampsia and these 15 cases were taken as cases and those who did not develop preeclampsia were taken as controls.

Table 4 Association between maternal serum β-hcg in women who developed Preeclampsia and those who did not develop Preeclampsia

		Pre eclampsia		
		Control	Case	P value
β HCG	>0.879	99	10	0.325
	<0.879	86	05	

There was no association between maternal serum β hcg and in pregnant women who later did or did not develop preeclampsia with p value- (0.325)

Table 5 Table to show association between maternal serum levels of PAPP-A in pregnant women with pre-eclampsia(case) and without pre- eclampsia (control)

		Pre-eclampsia		P value
		Control	Case	
PAPP-A	>0.903	135	6	0.007
	<0.903	50	9	

Maternal serum PAPP-A levels < 0.903 in early pregnancy were associated with later development ofpre-eclampsia with p-value <0.05. This difference was statistically significant. This tells the importance of serum PAPP-A levels in predicting the future risk of preeclampsia and FGR.

Table 6 Distribution of baby weight of PIH patients on basis of PAPP-A levels

Variable	PAPP-A	Mean birth wt.(kg)	SD	P-value
Baby weight	< 0.903	2.9	0.27	0.31
	>0.903	2.4	0.48	

As shown in above table there is no significant statistical difference between maternal serum PAPP-A level above and below the cut-off levels and baby weight, p - value >0.05. This means that, PAPP A was a poor predictor of FGR and preeclampsia.

Table 7 Distribution of baby weight of PIH patients on basis of βHCG levels

Variable	β hcg	Mean (kg)	SD	p-value
Baby weight	<0.879	2.4	0.41	0.09
	>0.879	2.8	0.36	

As shown in above table there is no significant statistical difference between maternal serum Beta HCG levels above and below the cut off, p value(<0.05).

Table 8 Sensitivity and specificity, positive predictive value and negative predictive value of Beta HCG, PAPP-A for pre-eclampsia

		PRE ECLAMPSIA		Sensitivity	Specificity	PPV	NPV
		CASE	CONTROL				
β HCG	<.879	5	86	33.33	53.3	5.49	96.8
	>.897	10	99				
PAPP-A	<.903	9	50	60	72.97	15.25	95.74
	>.903	6	135				

This table shows that both the markers have a low positive predictive value. This means that subjects with positive screening test may not develop disease. High negative predictive value for both the tests means that patients with negative screening test are unlikely to develop disease.

Sensitivity of maternal serum β HCG estimation as a predictor of preeclampsia is 33.33% and specificity 53.53% positive predictive value being 5.49 and negative predictive value being 90.82%. due to lower sensitivity this test may not be considered as a routine screening test. As the table shows the sensitivity of maternal serum PAPP-A estimation as a predictor of preeclamsia is 60% and specificity is 72.97%. positive predictive value being 15.25% and negative predictive value being 95.74%

DISCUSSION

Results from our study confirm the previously established association between first-trimester low levels of PAPP-A and the subsequent development of pre-eclampsia.

In a large, multicenter study of 34,271 women, Dugoff *et al.* in 2004 also demonstrated similar results demonstrated that women with low first-trimester PAPP-A levels were significantly more likely to experience pre-eclampsia along with other adverse obstetric outcomes. β-hCG was not found to be associated with pre-eclampsia in that study. [8]

In year 200, Similarresults were obtained from a study of 5,584 patients in which low PAPP-A levels was significantly associated with pregnancy complications including pre-eclampsia. In contrast to our results, this study also reported a significant association between first trimester free β-hCG levels ≤10th percentile and the subsequent development of pre-eclampsia. [9]

In 2011, Goetzingeret al in a study of 3,741 patients observed that first trimester low levels of PAPP-A was associated with subsequent development of pre-eclampsia; but there was no association between extreme levels of free β-hCG and pre-eclampsia.[12]

Our study found that there was no statistical difference in association between maternal Beta HCGmeasured between 11-14 weeks in pregnant women who did and did not develop PIH as shown in table 4.

Our study also showed that maternal serum PAPP-A levels is a good predictor of PIH with FGR but not a good indicator of only FGR .A study done by Ong et al on maternal serum PAPP-A and β-hcg in first trimester concluded that maternal serum PAPP-A levels <10th centile was associated with development of PIH and FGR later in pregnancy.[9]

Ozkan ozdamar et al in 2014 showed that mean PAPP-A MOM was 1.252 in control group and 0.920 in preeclampsia group. Further each unit decrease in PAPP-A value caused 3.9 fold increase in the risk of developing preeclampsia with sensitivity of 70% and specificity of 65.5%. There was significant differences in maternal serum PAPP-A concentration at 11+0 to 13+6 weeks of gestation between the normotensive pregnancies and those that subsequently develop pre-eclampsia. [13]

Our study also compared the birth weight as a secondary outcome, we compared the serum levels of PAPP-A and βhcg with birth weight of baby. Results showed that pregnant women with PAPP-A levels<0.903 had mean birth weight of 2.9kg and women with PAPP-A levels >0.903 had mean birth weight of baby as 2.4 kg. There was no change in birth weight with different values of Beta hcg.

CONCLUSION

Maternal serum PAPP-A is a fair indicator for PIH and a good indicator for PIH with FGR. Low serum PAPP-A levels is significantly associated with development of PIH therefore it can be used as a prognostic marker for pregnancy induced hypertension. On the contrary, βhcg does not predict occurrence of preeclampsia or FGR later in pregnancy.

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