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A correlation of first trimester serum levels of PAPP-A and PlGF with preeclampsia in western Indian population

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Abstract

Preeclampsia till today is a leading cause of serious maternal morbidity as well as maternal mortality. Prevention of preeclampsia is the mainstay of controlling various maternal and fetal complications as cure for it is not available. Early identification of preeclamptic patients is helpful in prevention of serious morbidities. Various biochemical markers were studied for prediction of preeclampsia but the sensitivity and specificity were found to be low. We intend to study the serum levels of pregnancy associated plasma protein-a (PAPP-A) and placental growth factor (PlGF) at 10-14 weeks of period of gestation for early prediction of development of preeclampsia. In a prospective observational study carried out from Aug 2014 to Jul 2016 at a tertiary care hospital where 323 patients participated. Serum levels of PAPP-A and PlGF at 10-14 weeks were collected and followed up till the time of delivery for development of preeclampsia. Incidence of preeclampsia was 6.5%. Maternal characteristics and obstetric factors were comparable in cases and controls. Serum levels of PAPP-A in cases and controls were 14.34 ug/ml & 18.96 ug/ml and for PlGF it was 27.86 pg/ml & 38.56 pg/ml respectively. There was statistically significant difference between the cases and controls in serum levels of PAPP-A and PlGF. Low serum levels of PAPP-A and PlGF at 10-14 weeks were observed in patients who developed preeclampsia at later gestation.

Keywords: Preeclampsia, PAPP-A, PlGF

Introduction

Pregnancy can be complicated by various medical disorders. One of the leading causes of perinatal and maternal morbidity & mortality is hypertensive disorders of pregnancy. Hemorrhage, infection and hypertensive disorders are making the deadly triad of maternal morbidity and mortality [1]. Though the incidences of hemorrhage and infections are reducing but hypertensive disorders are common and still a major factor for maternal morbidity. The incidence of preeclampsia is commonly cited to be about 8-10% and mainly seen in late pregnancy that is at more than 30 – 32 weeks period of gestation in our population [2].

The etio-pathogenesis of preeclampsia is still not clear. Various conditions like anti phospholipid antibody (APLA) syndrome, protein S deficiency, activated protein C resistance, multiple pregnancy, hydatidiform mole and hyperhomocysteinaemia are commonly seen in patients who develop preeclampsia [3]. Counselling for future pregnancies and pharmacotherapy has a definite impact in patients who all are identified with these

preexisting conditions. Identification of high risk groups at an early stage could potentially improve the outcome by directing such pregnancies to the specialist clinics for close monitoring. For reduction of the prevalence of the disease this would be the basis for future studies to investigate the potential role of pharmacological interventions.

Pregnancy associated plasma protein-A (PAPP-A) is a protease for insulin like growth factor (IGF) binding protein 4. Diminished fetal and placental growth are seen in situation where levels of PAPP-A is insufficient to cleavage IGF, it remains bound and inactive form. Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family. It is produced mainly by the placenta, and has potent proangiogenic effects. Maternal serum levels of PAPP-A and PlGF decrease in the early part of the gestation [4] and during the placentation it is believed that both of them are actively involved in the process [5]. Development of clinical symptoms of the disease may be due to involvement of PAPP-A and PlGF factors in the cascade of events that lead to impaired placentation [6]. Along with the biochemical markers especially PAPP-A and PlGF which are altered in the early part of the gestation and combining them with maternal history and examination can improve the performance of the screening of pregnant women who subsequently develop the disease. PAPP-A

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and PIGF levels are not studied in Indian population in regarding prediction of preeclampsia at 10-14 weeks period of gestation and we intend to study their levels for early prediction of preeclampsia.

The objective of our study is to study the serum levels of Pregnancy Associated Plasma Protein A (PAPP-A) and Placental Growth Factor (PIGF) during early gestation and correlate their value with development of preeclampsia.

Material and Methods

The study was carried out at a tertiary level care teaching hospital of armed forces, India from Aug 2014 to Jul 2016 and it was a prospective observational study. Institutional ethical committee had approved the study protocol. The study included all pregnant women willing to participate and registered during first trimester in our antenatal outpatient dept (OPD). Patients with preexisting hypertension, multiple pregnancy, systemic lupus erythematosus (SLE), diabetes mellitus, known anti phospholipid antibody (APLA) syndrome, hyperhomocystenemia, severe anaemia (Hb < 8 gm%) were excluded from the study.

Informed consent was taken from all women enrolled in the study. Detailed history taking and examination including blood pressure and body mass index (BMI) was carried out. Period of gestation (POG) was calculated from last menstrual period and correlated with ultrasound. First trimester USG-EDD (expected date of delivery) was taken to calculate period of gestation (POG) in cases of unsure dates. 8 hrs fasting blood samples were collected from all patients at 10 -13+6 weeks POG for measurement of their serum PAPP-A and PIGF levels. The PAPP-A and PIGF levels were measured by ELISA technique. Blood was stored at -20°C and the samples were analysed afterwards. All the cases were followed up till the end of pregnancy for development of preeclampsia. Preeclampsia was defined as a rise in blood pressure combined with proteinuria after 20 weeks gestation. Hypertension was defined as a sustained blood pressure (BP) reading of $\geq 140/90$ on at least two occasions 6h apart in a previously normotensive woman. Proteinuria was defined as a protein dipstick measurement of $\geq 1+$ on a midstream urine sample at least twice (24 h apart) or a 24h urine excretion ≥ 0.3 g protein in the absence of a urinary infection. Data so obtained were statistically analysed by available statistical software.

Statistical analysis

Sample size was calculated from referring study "Maternal Serum Placental Growth Factor, Pregnancy-Associated Plasma Protein-A and Free - Human Chorionic Gonadotrophin at 30–33 Weeks in the Prediction of Pre-Eclampsia" [4] with following specification for PAPP-A and PIGF:

1. Level of significance: 5%
2. Power of study: 80%

Sample size calculated for PAPP-A and PIGF were 18 & 10 respectively. Therefore we had planned to study at least 30 cases and controls more than 30. Incidence of preeclampsia in our population is 8-10%, hence to get 30 cases we had planned to study 300 pregnant women.

Statistical analysis was carried out by SPSS 22. Normality test was applied to all quantitative data to test whether these variables

follow normal distribution or not. Non parametric test (Mann Whitney test) was applied for all the variables which do not follow normal distribution. Logistic regression analysis was applied to dependent variable preeclampsia and independent variables like PAPP-A, PIGF and preterm delivery.

Results

Total 352 pregnant women at 10-14 weeks POG were recruited for the study after meeting the inclusion and exclusion criteria. During the follow up period, 29 patients were lost to follow up and data of 323 patients were analysed. Among the 323 patients studied, 21 of them had preeclampsia and making the incidence of preeclampsia in this study was 6.5%.

Maternal characteristics were showed in table 1 and there were no statistical difference in both the groups. The obstetric factors were shown in table 2. Among the obstetric factors, more number of caesarean deliveries was carried out in the preeclampsia group which was found to be statistically significant.

Serum levels of PAPP-A and PIGF among the cases and controls are shown in Figure 1a and 1b. Analysis of serum levels of PAPP-A and PIGF between both the groups showed that serum levels were statistically significant in preeclampsia group as compared to patients who did not develop preeclampsia (Table 3).

Logistic multivariate analysis between various factors was carried out as shown in table 4 and none of them found to be statistically significant.

Table 1. Maternal characteristics in the cases and controls

Characteristics	Controls (Mean) n= 302	Cases (Mean) n= 21	P value
Age (Yrs)	24.08	24.38	> 0.05 (NS)
BMI (Kg/ m ²)	20.54	21.23	> 0.05 (NS)
Systolic BP (mm of Hg)	112.11	110.20	> 0.05 (NS)
Diastolic BP (mm of Hg)	71.35	72.26	> 0.05 (NS)
Blood samples taken at POG (Days)	86.06	85.28	> 0.05 (NS)
Primipara (Total no)	138	11	> 0.05 (NS)
Multipara (Total no)	164	10	> 0.05 (NS)

Table 2. Obstetric factors in cases and controls

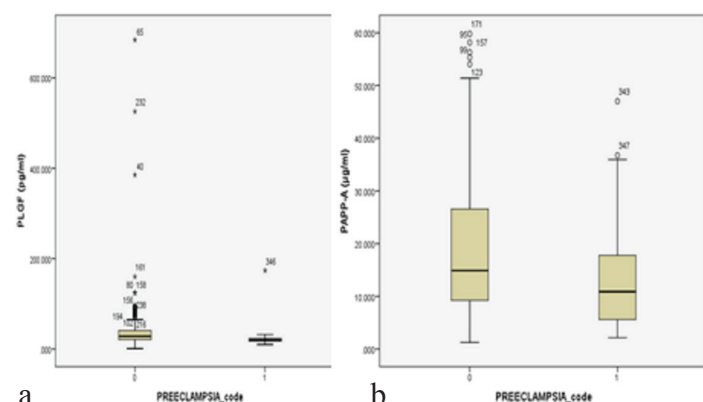
Obstetric factors	Controls (n= 302)	Cases (n= 21)	Significance
Delivery at POG (Days)	270.45	253.71	> 0.05 (NS)
Normal delivery (Total no)	229 (75.8%)	11 (52.38%)	> 0.05 (NS)
Caesarean delivery (Total no)	68 (22.51%)	10 (47.61%)	< 0.05 (NS)
Abruptio	2	0	-
Vacuum delivery (Total no)	5 (1.65%)	0	-
Neonatal birth weight (Kg)	2.82	2.68	> 0.05 (NS)
NICU admission	23	3	> 0.05 (NS)

Table 3. Maternal serum PAPP-A and PIGF levels in cases and controls

Serum levels	Controls (Mean) n= 302	Cases (Mean) n= 21	Significance
PAPP-A (ugm/ml)	18.96	14.34	< 0.05 (S)
PIGF (pg/ml)	38.56	27.86	< 0.05 (S)

Table 4. Logistic multivariate analysis

Variables	Significance
Age	P = 0.135
Socioeconomic status	P = 0.67
BMI	P = 0.41
PAPP-A	P = 0.117
PIGF	P = 0.379
Delivery at POG	P = 0.627

**Figure 1.** Box and Whisker plot after excluding extremes for PIGF (a) and PAPP-A (b)

Discussion

In our study, first trimester serum levels of PAPP-A and PIGF were found to be lower in patients who developed preeclampsia. The precise etiology of preeclampsia remains unknown, but it is believed to be likely multifactorial. Placenta and its pathology play a central role in development of preeclampsia [7]. Various hypotheses are described for development of preeclampsia including as a consequence of some kind of immune maladaptation between the fetus and mother during the first few weeks of pregnancy. Abnormal trophoblastic invasion, endothelial cell activation, nutritional and genetic factors also plays important role in pathogenesis. Incidence of preeclampsia in our population is about 8% [2]. In this study, incidence of preeclampsia found to be 6.5% among the data analysed for 323 patients.

Nulliparous and younger women are more vulnerable for development of preeclampsia and advanced maternal age is associated with chronic hypertension and superimposed preeclampsia. According to western literature African-American and Hispanic mothers are more susceptible to preeclampsia [8]. In our study, average age of preeclamptic women was 24.38 years and marginally higher than the controls but statistically insignificant. Among the 21 pregnant women who developed preeclampsia, 11 of them were primipara in the present study.

Among the various risk factors of preeclampsia, there is a progressive relationship between maternal weight and risk of

preeclampsia. The incidence of preeclampsia increases from 4.3% to 13.3% when body mass index (BMI) increases from 35 Kg/m² [9]. In this study, BMI of preeclamptic women were 21.23 Kg/m² as compared to 20.54 Kg/m² in women who did not develop preeclampsia but this difference were statistically insignificant. Smoking causes various adverse pregnancy outcomes but it has consistently been associated with reduced risk for hypertension during pregnancy because smoking upregulates placental adrenomedullin expression, which regulates volume homeostasis [10]. No one from our study population gives history of smoking before or during pregnancy.

For early prediction of preeclampsia, various biochemical markers were studied during first trimester of pregnancy and low levels of PAPP-A and PIGF were found to be associated with preeclampsia. Whether the low maternal serum levels of PAPP-A and PIGF act as a marker of preeclampsia or both of them are implicated in the pathogenesis of impaired placentation is still not clear. Both first trimester maternal serum PAPP-A and PIGF were reduced but maternal free beta-HCG levels were not significantly different in preeclamptic women when compared with normal pregnancies as per study reported by Lai et al [11]. Uterine artery doppler pulsatility index as an indirect measure for placental perfusion has shown an inverse relationship with serum PAPP-A and PIGF levels [12]. Both the study shows that maternal serum PAPP-A and PIGF levels plays an important role in the placentation process but normal levels of beta-HCG cannot be explained which is also produced by the placenta as reported by Lai et al [11]. In our study, both the serum levels of PAPP-A and PIGF were lower in cases of preeclamptic women as compared to patients who did not develop preeclampsia and the levels were statistically significant.

Once severe preeclampsia is diagnosed, induction of labour is ideal. Headache, nausea, vomiting, visual disturbances, or epigastric pain are indicative that convulsions may be imminent, and oliguria is another ominous sign. Antihypertensive drugs are commonly used in cases of severe preeclampsia and many patients require anticonvulsant therapy & magnesium sulphate is the drug of choice, followed by delivery. In 21 pregnant women who developed preeclampsia in our study, 09 of them received anti hypertensive for control of blood pressure in an average 32 weeks period of gestation and 10 of them received magnesium sulphate as anticonvulsant during the time of delivery. Once severe preeclampsia is diagnosed, induction of labour and vaginal delivery is considered ideal. In the metaanalysis of observational studies, it is found that one third cases were delivered vaginally after induction of labour in early onset severe preeclampsia cases and even the very low birth weight infants were delivered successfully [13]. According to Langenveld et al [14], newborns delivered before 36 weeks had higher caesarean section and more neonatal respiratory complications. In our study, 47% of preeclamptic patients underwent caesarean section as compared to 24% in non preeclamptic cases and it was statistically significant. Average gestation of delivery in preeclamptic cases were 36 weeks. Neonatal birthweight in both the groups was more than 2.5 Kg and comparable in both the groups. We did not have any neonatal mortality in both the groups and one neonate from each group required ventilator support. 3 neonatal intensive care unit (NICU) admissions from preeclampsia group were mainly due to low birth weight and majority from control group were due to

transient tachypnoea of newborn and low birth weight.

Prospective design and high follow up rates are the strengths of our study. Decreased first trimester maternal serum levels of PAPP-A and PIGF were seen before the development of clinical manifestation of preeclampsia. We used logistic regression to adjust for a number of confounders. We also used fasting blood samples to determine PAPP-A and PIGF concentrations. Similar socio economic status and education provided parity between the two groups. Interpretation of this study should be done with contemplation of certain significant limitations. Firstly, longitudinal studies signifying serial measurements of maternal PAPP-A and PIGF concentrations are required to explicate their pattern levels, the factors affecting these changes and the consequences of patho-physiologic variations of such alterations during pregnancy. Secondly, the number of patients with pre-eclampsia in our study was 21 patients, this reasonably small number of patients stalled deduction from some of our data. Thirdly due considerations were taken to include maximum potential confounders but exclusion of other potential cofounders cannot be ruled out from unmeasured covariates. Lastly, an additional limitation of this study was that it was based on data compiled from solitary medical centre.

Conclusion

Lower serum levels of PAPP-A and PIGF were observed during first trimester in patients who developed preeclampsia later in gestation. Because of fewer numbers of preeclampsia cases and single centre study, further large prospective multicenter studies are required to know their potential as predictor of preeclampsia.

Competing interests

The author confirms that this article content has no conflict of interest.

Financial Disclosure

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Ethical approval

Consent of ethics was approved by the local ethics committee.

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