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Original Research Article

Association of serum placental growth factor and pregnancy associated plasma protein A between 11 to 14 weeks and pre-eclampsia

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ABSTRACT

Background: Pre eclampsia complicates around 5-10% of pregnancies worldwide. Many countries in the world are far away of having interventions to predict and prevent preeclampsia. A number of biochemical, biophysical and sonographic parameters are emerging as a potential tool which can help us in a long way. This study was aimed to study association of biochemical markers of preeclampsia in early pregnancy with the development of preeclampsia.
Methods: This cohort study was conducted over a period of one year in the Department of Obstetrics and Gynecology at King George's Medical University, Lucknow.
Results: Total number of women enrolled at 11-14 weeks were 56. The mean age of women enrolled was 28±4.2 years. Out of total 44.6% women were nulliparous. Mean crown rump length at testing was 60.55±11.26mm. There was a significant correlation between the levels of Placental growth factors and development of PE ($p<0.01$) and especially severe early onset disease, however we did not found a significant correlation between Pregnancy associated plasma protein and Preeclampsia.
Conclusions: Placental growth factor is an emerging marker which could be incorporated in essential bundle of care at 11 to 14 weeks testing in order to enhance the detection rates of preeclampsia.

Keywords: PAPPA, PlGF, Preeclampsia

INTRODUCTION

Preeclampsia complicates around 5 to 10% worldwide however the incidence varies with developing countries having higher incidence.[1,2] Majority of patients who are referred to tertiary care centre are actually sent when they have already developed severe form of disease or with complications. Many countries in the world are far away of having interventions to predict and prevent preeclampsia. Albeit is it not so clear but a number of biochemical, biophysical and sonographic parameters are emerging as a potential tool which can help us in a long way. More research is needed in specific ethnic population before we provide a valid arrangement of screening and prevention of preeclampsia. Preeclampsia and eclampsia related deaths worldwide are estimated to be 50000-60000 per year.[2]

The possibility of complications is higher when the disease is severe and of early onset requiring delivery before 37 weeks gestation. Numerous known complications include like eclampsia, HELLP syndrome, placental abruption, disseminated intravascular coagulation, fetal growth retardation, intrauterine death and iatrogenic preterm delivery. The aetiology of preeclampsia has been reported to be due to abnormal placentation.

If we could identify the disease by biochemical and biophysical parameters and intervene timely, we can have some reduction in the prevalence of the disease and its complications. This study was planned to assess levels of PAPPA, PLGF between 11-13 weeks 6 days and correlate levels with mean arterial pressure, uterine artery PI, development and severity of PE.

METHODS

This was a prospective cohort study conducted in the Department of Obstetrics and Gynaecology, King George Medical University. The pregnant patients attending the outpatient department meeting the inclusion criteria were enrolled in the study after a written consent. The study was carried over a period of one year. Women with multifetal gestation chronic hypertension and autoimmune diseases were excluded from the study. The biochemical test was carried out by Kryptor Immunoassays, Thermofisher scientific private limited. 1st trimester uterine artery PI, mean arterial pressure and biochemical markers has been shown to be affected by gestational age at screening, maternal weight, racial origin, history of pre-existing diabetes mellitus and IVF and were consequently expressed as MoM after adjustment for these factors.

The measurement of mean arterial pressure and uterine Doppler was carried out in the Department of Obstetrics and Gynaecology.

RESULTS

A total 60 pregnant women were enrolled in the study after meeting inclusion criteria. Out of those, four were lost to follow up. Mean mage of women enrolled was 28 ±4.29 years. Mean body mass index of women was 25.37 ±5.72. Out of 56 women there were 26 primigravida and 30 were multigravidas. Gestational diabetes was present in 14 (25%) and 3 (5.4%) had history of PE in previous pregnancies. Table 1 shows various parameters recorded.

All the parameters were filled in Foetal medicine foundation software for determination of risk of preeclampsia. Pregnant women were followed till delivery.

Table 1: Various parameters measured between 11 to 14 weeks of pregnancy.

	Mean	SD	Median	Minimum	Maximum
CRL mm	60.55	11.26	60.85	45.90	81.60
Mean arterial pressure	83.26	8.16	84.00	65.00	106.00
uterine artery PI mean	1.83	0.60	1.83	0.80	3.85
PLGF pg/ml	37.94	26.19	31.77	3.00	128.00
PAPPA IU/L	5.23	5.95	3.24	0.39	32.64
POG	37.27	2.14	37.40	30.00	41.00

Table 2: Association between markers of predictors of PE and development of PE.

	Development of preeclampsia				P value
	Yes		No		
	Mean	SD	Mean	SD	
Mean arterial pressure	85.49	5.41	82.65	8.71	0.289
Uterine artery PI mean	1.91	0.67	1.81	0.58	0.595
PLGF pg/ml	18.06	11.91	43.36	26.48	0.002
PAPPA IU/L	3.07	2.72	5.82	6.45	0.157

Table 3: Association between markers of predictors of PE and development of PE.

	Development of severe PE				P value
	Yes		No		
	Mean	SD	Mean	SD	
Mean arterial pressure	83.93	4.48	83.18	8.52	0.833
uterine artery PI mean	1.97	0.77	1.81	0.58	0.537
PLGF pg/ml	10.61	5.72	41.22	25.78	0.006
PAPPA IU/L	2.12	1.52	5.60	6.17	0.178

Out of 56 women, three women (5.3%) were found to have risk of early onset PE while 16 (28.5%) were found to develop late onset disease. On follow up, total 18 women develop PE, out of which, severe PE was found in 10.7% women. Non severe disease was seen in 12 women, (21%). 5 (8.9%) women required care in high dependency unit. Maternal complications were seen in form of acute kidney injury (1.8%), placental abruption (1.8%) and HELLP (5.4%). All these four biomarkers

were analysed and Table 2 shows association of these markers with development of PE. A significant association was seen between placental growth factor and development of PE.

A significant correlation was seen between PLGF and development of severe PE as shown in Table 3. On analysing association between the markers and need of High dependency unit care as shown in Table 4, the levels of PlGF were found to have a significant association (p=0.008).

On analysing the markers and need of NICU, as shown in Table 5, significant association was seen with the rising Uterine artery PI (0.023) and falling PLGF (0.036).

Period of gestation at the time of delivery was correlated with markers as shown in Table 6. There was significant positive correlation between prolonged gestational age with higher PlGF levels. Also, there was negative correlation between rising mean arterial pressure and uterine artery PI with rising period of gestation at delivery.

Table 4: Association between uterine artery PI and PlGF levels and need of HDU and NICU

	Need of high dependency unit				P value
	Yes		No		
	Mean	SD	Mean	SD	
Mean arterial pressure	82.32	2.37	83.35	8.52	0.790
uterine artery PI mean	1.99	0.86	1.81	0.58	0.529
PLGF pg/ml	8.90	4.37	40.79	25.70	0.008
PAPPA IU/L	2.23	1.68	5.52	6.14	0.241

Table 5: Association between Uterine artery PI and PlGF levels and need of NICU.

	Need of NICU				P value
	Yes		No		
	Mean	SD	Mean	SD	
Mean arterial pressure	82.33	2.89	83.31	8.37	0.842
uterine artery PI mean	2.58	0.38	1.79	0.58	0.023
PLGF pg/ml	7.25	4.93	39.68	25.83	0.036
PAPPA IU/L	2.79	2.07	5.37	6.07	0.470

Table 6: Correlations between the period of gestation at delivery and mean arterial pressure, uterine artery PI, PlGF and PAPPA levels.

		POG at delivery	Mean arterial pressure	uterine artery PI mean	PLGF pg/ml	PAPPA IU/L
POG	Pearson correlation	1	-0.059	-0.246	0.404	0.164
	Sig. (2-tailed)		0.665	0.068	0.002	0.227
	N	56	56	56	56	56

DISCUSSION

A combination of maternal demographic characteristics, including medical and obstetric history, serum markers, uterine artery pulsatality index (PI) and mean arterial pressure (MAP) at 11-13 weeks gestation have been studied and reported to identify a high proportion of pregnancies at high-risk for preterm PE.[3-6]

Uterine artery PI is an indirect measure of utero placental perfusion and the postulated hypothesis is that high PI implies impaired placentation with consequent increased risk of developing preeclampsia, fetal growth restriction, abruption and stillbirth.[7-9] The uterine artery PI and mean arterial pressure is considered to be increased if it is above the 90th centile.

In normal pregnancy the uterine artery PI decreases with fetal crown-rump length and maternal weight and it is increased in women of African racial origin. In assessing whether a measurement is normal or not these maternal characteristics should be taken into consideration. In a study done by Plasencia et al., they reported that uterine artery screening PI at 11+0 to 13+6 weeks and the change in uterine artery PI between 11+0 to 13+6 and 21+0 to 24+6 weeks of gestation provided significant independent

contribution to the prediction of preeclampsia with the detection rates of early and late-onset preeclampsia being 90.9% and 31.0%.[7] In our study, we did not find a

significant difference of uterine artery PI in women who developed PE compared to those who did not. However, this might be due a smaller sample size but there was a significant correlation of raised uterine artery PI with earlier gestational age at delivery as shown in Table 6 (p=0.068).

Mean arterial pressure of women who develop preeclampsia has been reported to be higher than those who did not. In a study by Poon, they evaluated the performance of screening for preeclampsia (PE) by maternal medical history and mean arterial pressure (MAP) at 11 weeks to 13 weeks 6 days.[10] The detection rate of PE by log multiple of the median MAP and maternal variables was 62.5% for a false-positive rate of 10%. The mean arterial pressure was affected by ethnic origin, body mass index and personal history of PE. Literature has shown that the predictive strength of mean arterial pressure is moderate.[4] In our study also, we did not notice a significant difference in the baseline mean arterial pressure measured between 11 to 14 weeks between n women who developed PE compared to those who did not (p=0.289).

Soluble fms-like tyrosine kinase-1 (sFlt-1), pregnancy associated plasma protein A (PAPPA) and Placental growth factors (PlGF) are new emerging makers in PE. These markers predominantly define and govern angiogenesis. Aditi R Saxena et al measured sFlt-1 levels and PAPPA in 427 women with singleton pregnancies in all three trimesters.[11] First trimester PAPP-A was significantly lower in preeclamptic (n=19), versus normal pregnancies (p=0.02). Although mean third trimester sFlt-1 levels were significantly higher in preeclampsia (p=0.002), first trimester sFlt-1 levels were lower in women who developed preeclampsia, compared with normal pregnancies (p =0.03).

They also found PAPP-A levels correlated significantly with serial sFlt-1 levels. We did not find a significant association of PAPPA in predicting PE (p=0.157). Few studies have not reported effective results and challenged their benefit in early gestation. Francisco J. Schneuer et al did a study to assess the accuracy of first trimester soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PLGF) in predicting pregnancy hypertension and pre-eclampsia upon 2,681women with singleton pregnancies in New South Wales, Australia.[12]

They realized that maternal first trimester serum concentrations of sFlt-1 and PLGF do not predict hypertensive disorders in pregnancy any better than routinely collected clinical and maternal risk factor information. They also concluded that parity and previous diagnosed hypertension had better predictive accuracy than serum biomarkers. However much more studies have shown a significant correlation of PlGF in first trimester with development of PE (p=0.002) and severe PE (p=0.006).

PE is estimated to affect 8,370,000 woman worldwide every year and is a major cause of maternal, foetal and neonatal morbidity and mortality.[13,14] We tried to look for the association of biomarkers with maternal morbidity. There was significant association with levels of PlGF and need for admission in high dependency unit (p=0.008). Development of PE also has impact on the neonate owing to the complications and prematurity. We found a significant association between levels of PLGF and need of NICU (p=0.036).

Yliniemi et al evaluated the efficacy of first-trimester markers including pregnancy-associated plasma protein A (PAPPA), free human chorionic gonadotropin β (fhCGβ), alpha-fetoprotein (AFP), placental growth factor and soluble tumour necrosis factor receptor-1 (sTNFR1) together with maternal characteristics for prediction of early-onset preeclampsia and found that together they have a very good predictive value.[15] They detection in first trimester is lesser owing to predominant rise of all these markers in second trimester. We analysed PAPPA and PlGF where PlGF emerged as an excellent biomarker even in first trimeter.

Kyung UK, Sung et al did a prospective observational study on 175 pregnant women.[16] The women's maternal history was recorded, PlGF and PAPP-A levels at 11 to 13 gestational weeks were measured. They found that PlGF and PAPP-A are potentially useful as first-trimester markers for SGA infants and some hypertensive disorders of pregnancy.

An extensive review by Poon LC and Nicolaides has shown an excellent model of care where effective screening for the development of early onset PE can be provided in the first-trimester of pregnancy by screening by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler, maternal serum pregnancy-associated plasma protein-A and placental growth factor and this can identify about 95% of cases of early onset PE for a false-positive rate of 10%.[17]

Kate E, Duhig et al did a stratified analysis of the PARROT trial where 1006 women were included.[18] PlGF <100pg/ml identified women with more marked hypertension, increased adverse maternal outcomes and preterm delivery rates, and higher rates of small for gestational age infants. There was a reduction in adverse maternal outcomes in women whose results were revealed when PlGF levels were 12-100pg/ml compared to usual care (3.8% vs 6.9%; a OR 0.15(95% CI 0.03-0.92).

There was no significant difference in gestation at delivery between concealed or revealed groups in any PlGF categories. Low PlGF concentrations are associated with severe preeclampsia. The reduction in severe adverse maternal outcomes may be mediated through quicker diagnosis and intensive surveillance, as

recommended by the management algorithm for those at increased risk.

PlGF is particularly beneficial in those who test 12-100pg/ml, as these may be women with silent multi-organ disease who otherwise may go undetected. In our study we found the mean PlGF level to be 37.94pg/ml with minimum of 3pg/ml and maximum 128pg/ml. We found that levels below 30pg/ml were more associated with development of PE. This emphasizes on the ethnic population difference which needs to be identified.

Edward Antwi et al did a prospective cohort of 1010 pregnant women attending antenatal clinics in two public hospitals in Accra, Ghana.[19] Normotensive pregnant women were recruited at a gestational age between 8 and 13 weeks and serum, biomarkers PAPP-A and PlGF concentrations were measured by the Auto DELFIA immunoassay method. Three hundred and seventy-three women participated in this study. They found that adding the biomarkers PAPP-A and PlGF to maternal characteristics to a prediction model for gestational hypertension improved predictive ability.

We analysed the correlation between the biophysical and biochemical markers of PE with gestational age at delivery using Pearson's correlation. There was a significant negative linear correlation between the MAP MoM with gestational age at delivery (-0.059) and also there was a negative linear correlation between the uterine artery PI MoM with gestational age at delivery (-0.246). Similar findings were reported by Wright D et al.[20] In this study we noticed a significant positive correlation between levels of PlGF levels and gestational age at delivery (0.002). We realize that combination of these markers in first trimester can prove to be an important and cost effective tool to detect those women at high of risk of PE so that intervention like aspirin can be started and later in pregnancy these can be repeat along to predict the need of early delivery , vigilant follow up, early admission and antihypertensive or antiseizure medication particularly important for developing countries where women are still dying of hypertensive disorders in pregnancy.

In a very recent study conducted by A. Mazer Zumaeta A et al, the study population was composed of 60,875 singleton pregnancies, including 1736 (2.9%) that developed PE.[21] The main finding was that the performance of first-trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PlGF is superior to that of screening by maternal factors, MAP, UtA-PI and PAPP-A. Addition of serum PAPP-A does not improve the prediction of PE any further. There is immense variation in risk cut-off and screen-positive rate to achieve a given fixed detection rate of PE according to the racial composition of the study population.

The most preferred biochemical marker is PlGF. Incorporation OF PlGF might help not only to have a more vigilant follow up of women with high risk of PE in order to prevent maternal complications and time delivery but also opens up the possibility of interventions in form of aspirin.[22]

CONCLUSION

The present was a small pilot study on Indian population to look at the role of Placental growth factor and pregnancy associated plasma protein A as a marker for prediction of PE.

Exiting biophysical predictors of PE like mean arterial pressure and uterine artery PI. We noticed a significant association of PlGF with development of PE and a significant determinant of timing of delivery in women with PE.

There are not many Indian studies which have actually compared the trends of PAPPA and PLGF together at early gestational ages and their potential role in differentiating between a severe and non-severe disease.

If these newer markers are found to have a good prediction in our population, their incorporation in our system of healthcare can be of great help to identify that group of patients who are at high risk of severe disease so that a better care and timely referral can be planned to deal with expected complications.

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