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"A CO-RELATION OF FIRST TRIMESTER LEVELS OF PAPP-A (PREGNANCY ASSOCIATED PLASMA PROTEIN A) AND PIGF (PLACENTA INDUCED GROWTH FACTOR) WITH CO-RELATION OF PREECLAMPSIA AND FETOMATERNAL OUTCOME."

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ABSTRACT

Introduction: Preeclampsia is one of the major cause of maternal and fetal mortality. Pathogenesis of development of preeclampsia is still not clear but one of the cause is considered to be abnormal placentation. Various markers haven been found to be involved in process of placentation among which PAPP-A and PIGF have been found to be actively involved. PAPP-A and PIGF levels have not been studied in the Indian population in terms of preeclampsia prediction at 10-14 weeks of gestation, and we intend to study their levels for early preeclampsia prediction. **Methodology:** This observational study was carried out in obstetrics and gynecology OPD , Sir T Hospital , Bhavnagar from June-2021 to August 2022. Total of 100 antenatal patients attending OPD who were in first trimester taken after considering inclusion and exclusion criteria. Investigations for PAPP-A and PIGF were taken and patient followed up for development of preeclampsia till delivery. **Results:** Incidence of preeclampsia was found to be 22%. Majority of patients were found in age group of 26-30 years. More number of patients were multigravida who developed preeclampsia. PAPP-A during first trimester were found as 1.06 ± 0.20 MoM in overall patients, while PIGF found as 0.97 ± 0.18 MoM. Moreover, mean PAPP-A and PIGF of control and case group were found as (1.11 ± 0.22 MoM vs 0.91 ± 0.21 MoM; $p<0.0001$) and (0.99 ± 0.17 MoM vs 0.88 ± 0.20 MoM; $p<0.0001$) respectively. 90% of babies delivered full term. In women with preeclampsia 10% patients had preterm delivery. 50% babies were low birth weight in women who developed preeclampsia. **Conclusion:** Keeping the complications associated with preeclampsia, measurement of PAPP-A and PIGF levels in first trimester can be used as marker for prediction of preeclampsia in later months of pregnancy. Levels if found lower can help in taking regular follow up of patients and early diagnosis and management can be done. This can help us prevent maternal as well as fetal morbidity and mortality.

KEYWORDS : Preeclampsia , PAPP-A , PIGF

INTRODUCTION:

Pregnancy can be complicated by a variety of medical conditions. Hypertensive disorders of pregnancy are one of the leading causes of perinatal and maternal morbidity and mortality. Hypertensive disorders include Preeclampsia and Eclampsia. Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to extent of 140/90mmHg or more with protinuria after 20 weeks of gestation in previously normotensive and nonprotinuric woman.

In our population, the incidence of preeclampsia is commonly reported to be around 8-10%Preeclampsia is a multisystem disorder of pregnancy and is best described as pregnancy-specific syndrome that can affect virtually every organ system. Although the exact cause of PE remains elusive, the condition is thought to be predominantly due to defective implantation of the placenta within the uterine endometrium. The pathogenesis is hypothesised to occur in two main phases. The first phase begins with abnormal placentation, while the second phase is characterised by an abnormal maternal endothelial response, resulting in the clinical manifestations of the condition including hypertension, proteinuria and edema. PAPP-A and PIGF both are thought to be actively involved in the process during placentation.

The involvement of PAPP-A and PIGF factors in the cascade of events that leads to impaired placentation may be responsible for the development of clinical symptoms of the disease.PAPP-A (pregnancy associated plasma protein-A) is an insulin-like growth factor (IGF) binding protein 4 protease. Reduced fetal and placental growth is observed when PAPP-A levels are insufficient to cleave IGF, which remains bound and inactive. Placental growth factor (PIGF) is a member of the vascular endothelial growth factor (VEGF) family. It is primarily produced by the placenta and has strong proangiogenic properties.Low levels of PAPP-A and PIGF during first trimester have been associated to development of preeclampsia in later paregnancy.

OBJECTIVES:

To assess incidence of Preeclampsia in patients with lower PAPP-A, PIGF , to assess role of PAPP-A and PIGF in prediction of Preeclampsia and to assess Fetomaternal outcome in Preeclampsia patients.

MATERIAL & METHODS:

100 antenatal patients coming to obstetrics and gynecology OPD at Sir T. General Hospital during 11-13 weeks of pregnancy were taken during period of June- 2021 to August-2022 . PAPP-A and PIGF levels were done and followed up till delivery.

Inclusion Criteria:

Antenatal women in first trimester (11-13 week)

Exclusion Criteria:

1} Antenatal women with known case of Hypertension.
2}Patients with chronic hypertension, chronic renal disease, multiple pregnancy, connective tissue disorders.

RESULTS

In the present study, the incidence of pre-eclampsia was found to be 22% , while 78 patients did not develop pre-eclampsia during pregnancy. It was found that 51 (51%) of patients were in 26-30 years age group followed by 33 (33%) of patients in 21-25 years age group. Out of 100 patients taken 63 patients were multigravida of which 17 developed preeclampsia and from 37 primigravida patients 5 patients developed preeclampsia.Studying the gestational age at delivery, it was found in normotensive patients out of 78 patients all were delivered full term and from preeclamptic patients 10 delivered pre term and 12 had full term delivery and mean GA of control and case group have found statistically strong significant (38.21 ± 0.97 weeks vs 35.86 ± 2.73 weeks; $p<0.0001$) between the groups respectively. It was found that PAPP-A levels during first trimester were 1.06 ± 0.20 MoM in overall patients, while PIGF found as 0.97 ± 0.18 MoM. Moreover, mean PAPP-A and PIGF of control and case group

were found as (1.11 ± 0.22 MoM vs0.91 ± 0.21 MoM; p<0.0001) and (0.99 ± 0.17 MoM vs 0.88 ± 0.20 MoM; p<0.0001) statistically strong significant between the groups respectively. Also it was found that PAPP-A MoM have sensitivity, specificity, PPV and NPV as 68.2%, 74.4%, 42.9% and 89.2% respectively. While PIGF MoM have sensitivity, specificity, PPV and NPV as 81.8%, 39.7%, 27.7%, and 88.6%respectively.

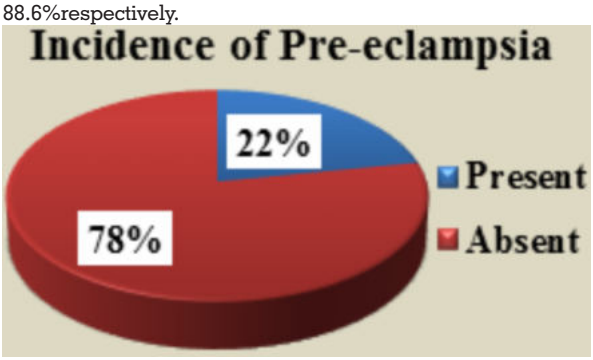

Figure 1: Incidence of preeclampsia

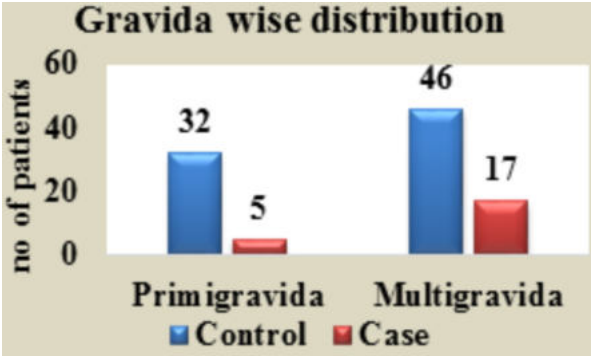

Figure 2 : Gravida Wise Distribution

Table 1: Maternal Age Wise Distribution

Age (yrs)	Control (n=78)	Case (n=22)	Total patients (n=100)
18-20	3 (3.84%)	0	3 (3%)
21-25	30 (38.46%)	3 (13.63%)	33 (33%)
26-30	34 (43.58%)	17 (77.27%)	51 (51%)
31-35	10 (12.82%)	2 (9.09%)	12 (12%)
> 35	1 (1.28%)	0	1 (1%)
Total	78 (100%)	22 (100%)	100 (100%)
Mean Age (yrs)	26.46 ± 3.57	27.68 ± 2.25	26.73 ± 3.35

Table 2: Gestational Age At Delivery Wise Distribution

GA (weeks)	Control (n=78)	Case (n=22)	Total patients (n=100)
Preterm	0	10 (45.45%)	10 (10%)
Full term	78 (100%)	12 (54.54%)	90 (90%)
Total	78 (100%)	22 (100%)	100 (100%)
Mean GA (weeks)	38.21 ± 0.97	35.86 ± 2.73	37.7 ± 1.81
P Value	<0.0001		

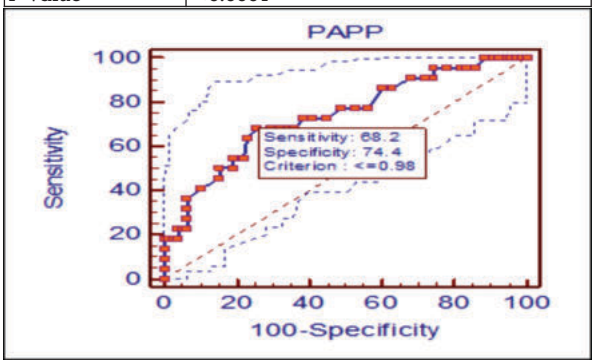

Figure 3: PAPP-A Sensitivity And Specificity

Table 3: PAPP-A And PIGF Distribution

Bio-markers	Control (n=78)	Case (n=22)	Total (n=100)	P value
PAPP-A MoM	1.11 ± 0.22	0.91 ± 0.21	1.06 ± 0.20	<0.0001
PIGF MoM	0.99 ± 0.17	0.88 ± 0.20	0.97 ± 0.18	<0.0001

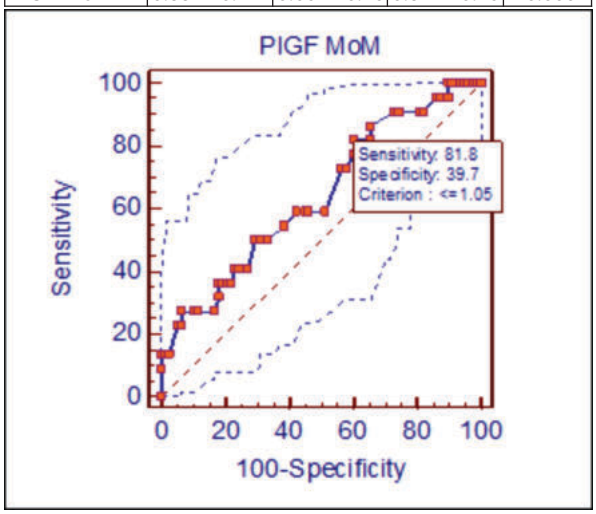

Figure 4: PIGF Sensitivity And Specificity

DISCUSSION:

PAPP-A and PIGF serum levels were found to be lower in the first trimester in patients who developed preeclampsia. Actual cause of preeclampsia is still unknown and is multifactorial. Abnormal placentation is one of the major cause. PAPP-A and PIGF are involved in abnormal placentation. In the present study, the incidence of pre-eclampsia found in 22 (22%) patients among 100 patients, which was lower incidence as compared to Kumar N et al[5] (32.14%) and higher as per Kaundal A et al[6] (14%) , Das E et al[12] (12.7%), Salem MA et al[9] (10%) and Jayamol A et al[8] (6.5%) respectively. It was found that (51%) of patients were in 26-30 years age group with mean age of control and case group have found to be (26.46 ± 3.57 yrs vs 27.68 ± 2.25 yrs; p=0.1325) respectively which was correspondingly with Sun XW et al[4] (28.36±4.82 vs 29.45±4.65 yrs) and Jayamol A et al[8] (24.08 yrs vs 24.38 yrs). In gestational age wise distribution, it was found that (90%) of babies were full term followed by (10%) of patients in preterm group. In addition, mean GA at delivery of control and case group have been found to be statistically strong significant (38.21 ± 0.97 weeks vs 35.86 ± 2.73 weeks; p<0.0001) between the groups respectively which was correspondingly with Salem MA et al[9] (38.7 ± 2.8 weeks vs 33.8 ± 2.55 weeks).

In the present study, it was found that PAPP-A during first trimester were found as 1.06 ± 0.20 MoM in overall patients, while PIGF found as 0.97 ± 0.18 MoM. Moreover, mean PAPP-A and PIGF of control and case group were found as (1.11 ± 0.22 MoM vs 0.91 ± 0.21 MoM; p<0.0001) and (0.99 ± 0.17 MoM vs 0.88 ± 0.20 MoM; p<0.0001) statistically strong significant between the groups respectively. In addition, it was found that PAPP-A MoM have found sensitivity, specificity, PPV and NPV as 68.2%, 74.4%, 42.9% and 89.2% respectively. While PIGF MoM have found sensitivity, specificity, PPV and NPV as 81.8%, 39.7%, 27.7%, and 88.6%respectively.

Similarly, Salem MA et al[9] have found Serum PAPP-A concentration showed significant decrease in preeclamptic women (0.97 ± 0.2) when compared to healthy women (1.1 ± 0.3). The optimal cutoff PAPP-A value using the ROC curve was B0.96 MoM, resulting in a sensitivity of 63.3% and a specificity of 90.4%, a PPV of 42.2%, a NPV of 95.7% and an accuracy of 88%. Moreover, Serum PlGF concentration showed significantly decrease in preeclamptic women (0.85 ± 0.2) when compared to healthy women (1.02 ± 0.3). The optimal cutoff PlGF value using the ROC curve was 0.91 MoM,

resulting in a sensitivity of 90%, a specificity of 82.6%, a positive predictive value of 36.5%, a negative predictive value of 98.7% and an accuracy of 83%.

In addition, the study by DG EY et al[11] have found that mean PAPP-A and PlGF of control and case group were found as (0.643 ± 0.02 MoM vs 0.361 ± 0.04 MoM; p<0.0001) and (26.4 ± 1.4 pg/ml va 9.8 ± 0.6 pg/ml p<0.0001) statistically strong significant. The analysis of PlGF (<12 pg/ml) have found that sensitivity, specificity, PPV, NPV as 63.15%, 92.82%, 50%, and 96.91% while, PAPPA have found that (<0.45 MOM) with sensitivity, specificity, PPV, NPV as 42.1%, 93.11%, 32%, and 95.43% respectively.

Another study by Das E et al[12] have found that the mean first trimester PAPP-A MoM values of those who developed hypertensive disorders of pregnancy (0.67) were significantly lower than the mean PAPP-A MoM of those who did not (1.21, p<0.001). As per the receiver operator characteristic (ROC) curve for PAPP-A MoM (Figure 2), the area under the curve was 0.319. The best cut-off that maximized sensitivity and specificity was 0.41. The first trimester PAPP-A as a screening tool had a sensitivity of 28%, specificity of 90.6%, PPV of 38.89%, NPV of 85.48%, and a DR of 79.58%.

According to Jaymol A et al[8] have found that Analysis of serum levels of PAPP-A (14.34 ugm/ml vs 18.96 ugm/ml) and PlGF (27.86 pg/ml vs 38.56 pg/ml) between both the groups showed that serum levels were statistically significant in preeclampsia group as compared to patients who did not develop preeclampsia (p<0.0001). As regards preeclampsia, early prediction could potentially improve the outcome by close surveillance of the patient and would be the basis of the prophylactic medications such as aspirin, starting from the first trimester to improve placental invasion, uteroplacental circulation and so decreasing the prevalence of the disease.

CONCLUSION:

Measurement of PAPP A and PIGF levels in first trimester can be used as markers for prediction of pre eclampsia in later months of pregnancy. Levels if found lower, interventions like regular follow up of patients, patients counseling regarding symptoms of pre eclampsia, aspirin therapy , early diagnosis and early management can be done.

This can help us to reduce complications related to pre eclampsia like Preterm labour, abruption placenta, acute renal failure, HELLP syndrome, DIC, pulmonary edema and prevent fulminant complication like eclampsia. This can significantly reduce maternal morbidity and mortality.

Also fetal complications like preterm birth , fetal growth restriction , low birth weight, oligohydroamios , intrauterine fetal death can be prevented thus decreasing fetal mobidity and mortality.

However keeping in mind the cost:benefit ratio, cost of these tests are a major issue. Also we need more studies on larger and variable population on weather these markers can be used for prediction of pre eclampsia as not enough studies are done in Indian population to prove their role.

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