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KEYWORDS :

Level of Papp-A in The First Trimester of Pregnancy & The Pregnancy Outcome

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ABSTRACT

Introduction : Abnormalities in maternal analyte levels and fetal measurements obtained during first trimester screening can be a marker not only for certain chromosomal disorders and anomalies in the foetus, but for specific pregnancy complications. In particular, low maternal serum pregnancy associated plasma protein-A (PAPP-A), at 11-13 weeks' gestation is associated with stillbirth, infant death, intrauterine growth restriction (IUGR), preterm birth and pre-eclampsia in chromosomally normal fetuses, whilst a raised nuchal translucency is associated with specific structural abnormalities and genetic syndromes.We have studied the serum Papp-A level in 176 pregnant patients (11- 13 wks gestation) registered at Bharati Hospital & Research Centre , Pune. All the patients undergoing testing were followed till the delivery & there neonatal outcome was also taken into the consideration. Aims & Objectives To study the pregnancy outcome in relation to the variations of Papp-A level in the first trimester of pregnancy. Material & Methods Every patient visiting the antenatal OPD are counseled for the testing of First Trimester Screening to asses the fetal well being. Patients who are registered for the delivery at our hospital are taken into the trial. Blood sample are taken at 11- 13 wks of pregnancy & sent to the PerkinElmer lab for analysis. Results were expressed in Multiple Of Median & patients having MOM value less than 0.5 were carefully observed till the delivery & thorough neonatal examination is done by paediatrician. Observations Only 17 patients were having Papp-A level less than 0.5 MOM out of which 6 number of patients had preterm delivery & two patients had fetal growth restriction. Those patients having MOM values more than 0.5 , eleven patients had preterm labor & recquired NICU for the neonatal resuscitation. Few number of patients (4 no.) have developed gestational hypertension but controlled with medication & had term deliveries. Conclusion Though Papp-A level in the First Trimester Of Pregnancy (11- 13 Wks) is an important predictor of future Obstetric outcome , it has poor positive predictive value. Papp-A MOM less than 0.5 in pregnant patients have higher risk of preterm delivery , fetal growth restriction & stillbirths along with increased incidence of hypertensive disorders of pregnancy. But alone Papp-A level can be poor predictor of future Obstetric outcome unless combined with other markers such as uterine artery Doppler velocimetry at 21 -22 wks of pregnancy, B-hcg serum concentration in pregnant mothers in the first trimester of pregnancy.

Introduction :

Abnormalities in maternal analyte levels and fetal measurements obtained during first trimester screening can be a marker not only for certain chromosomal disorders and anomalies in the foetus, but for specific pregnancy complications. In particular, low maternal serum pregnancy associated plasma protein-A (PAPP-A), at 11-13 weeks' gestation is associated with stillbirth, infant death, intrauterine growth restriction (IUGR), preterm birth and pre-eclampsia in chromosomally normal fetuses, whilst a raised nuchal translucency is associated with specific structural abnormalities and genetic syndromes[1, 2].

A low PAPP-A is defined as a maternal serum PAPP-A value <0.4MoM, with increased frequency of adverse obstetrical outcomes noted below this level [2].

PAPP-A is a large glycoprotein produced by the placenta and decidua thought to have several functions, including prevention of recognition of the fetus by the maternal immune system, matrix mineralization and angiogenesis. A low PAPP-A is therefore descriptive of poor early placentation resulting in complications such as foetal growth restriction, fetal demise, preterm birth and pre-eclampsia in the third trimester.

Aims & Objectives

To study the pregnancy outcome in relation to the variations of Papp-A level in the first trimester of pregnancy.

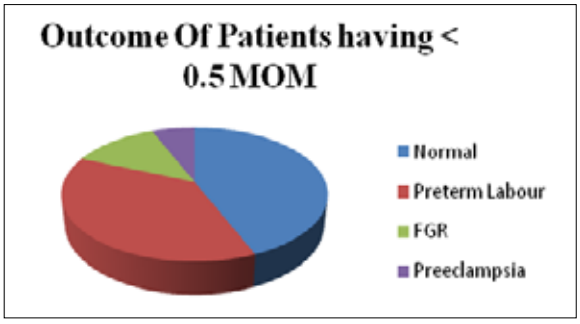
Material & Methods

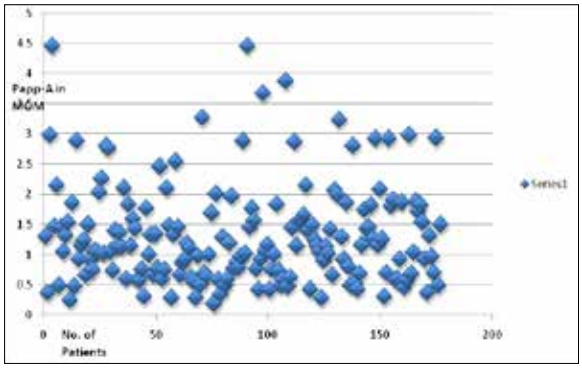
Every patient visiting the antenatal OPD are counseled for the testing of First Trimester Screening to asses the fetal well being. Patients who are registered for the delivery at our hospital are taken into the trial. Blood sample are taken at 11- 13 wks of pregnancy & sent to the PerkinElmer lab for analysis. Results were expressed in Multiple Of Median & patients having MOM value less than 1 are carefully observed till the delivery & thorough neonatal examination is done by paediatrician.

Observtations

10 % of the total patients studied have MOM values less than 0.5. We have all total 17 patients having MOM values less than 0.5 . These patients were followed till delivery & we have found 6 patients had preterm deliveries & 2 patients have developed fetal growth restriction. One patients had Pre-eclampsia & recquired termination of pregnancy because of the uncontrolled hypertension.

Rest of the 8 patients were delivered at full term & had healthy babies.





However we have also monitored rest of the 159 patients in whom the Papp-A levels were more than 0.5 MOM. Eleven patients in this class had preterm deliveries & the neonate recquired NICU admission. Gestational hypertension developed in four patients having MOM values more than 0.5 & 1 patient had intrauterine death of the fetus.

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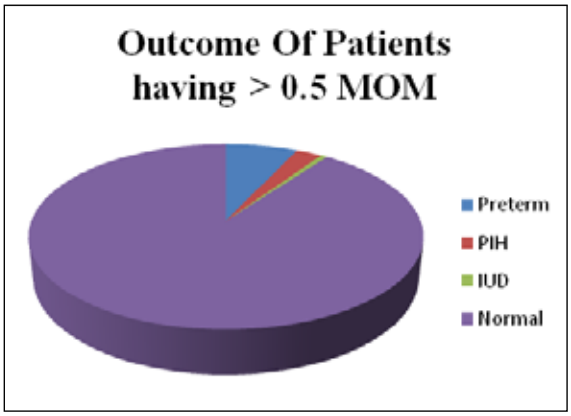

So the positive predictive value of low Papp-A level in our study is 52 % to anticipate future obstetrical complications such as preterm deliveries , fetal growth restrictions & stillbirths.

While those patients having Papp-A level more than 0.5 MOM also developed preterm deliveries but the incidence is only 6 % comparable to the general population.

While the incidence of gestational hypertension was relatively high in patients with Papp-A level less than 0.5 MOM. As the number of patients was a limitation of the study but further ongoing multicentre studies will focus more light on the association of 1st trimester Papp-A level & the pregnancy outcome.

Discussions :

A low PAPP-A level is poorly sensitive, as although these associations exist at the lower end of the PAPP-A distribution, the majority of patients with these adverse outcomes do not have a low PAPP-A. In addition, it has a low positive predictive value as few patients with a low PAPP-A actually have an adverse outcome3. However, the likelihood of an adverse outcome does increase as the PAPP-A level decreases, with extremely low levels of PAPP-A having very high positive predictive value, as follows: <0.45 MoM (5th percentile)

1. 1 to 4% risk of pregnancy loss before 20 weeks .
2. increased risk of intrauterine growth restriction, positive predictive value 14% (OR 2.7, 95% CI 1.9-3.9)
3. increased risk of preterm delivery before 34 weeks (OR 2.3, 95% CI 1.1-4.7)

<0.29 MoM (1st percentile) : significantly increased risk of intrauterine growth restriction, with positive predictive values of 24% 4, 5 .

Studies have shown that in combination with a low PAPP-A level, second trimester monitoring of fetal growth, placental size and Doppler indices can help to identify women at high risk of adverse obstetric outcomes[1, 2, 5, 6, 7], and improve accuracy. In addition, a normal ultrasound examination does not rule out an adverse pregnancy outcome [6].

PAPP-A is produced by the placental trophoblasts, especially, by the extravillous cytotrophoblasts(Handschuh, et al., Placenta 2006;27 suppl A:S127-34).

It is a 'protease' for insulin-like growth factor (IGF) binding proteins 4 and 5 (Boldt and Conover. Growth Horm IGF Res. 207;17:10-18). This means it has the ability to help release IGF from these binding proteins so that it is free to interact with its cell receptor (Laursen, et al., Mol Endocrinol 2007;21:1246-57). IGF is thought to play an important role in trophoblast invasion and hence the early development and vascularization of the placenta and the placental bed. These early events in formation of the placenta are critical to pregnancy outcome and, when abnormal, are associated with miscarriage, intrauterine growth restriction (IUGR) of the baby, pregnancy-induced hypertensive disorders, fetal death in utero, premature delivery, and even cesarean section for indications of fetal or maternal compromise. It has been postulated that low levels of PAPP-A, resulting in less release of IGF, could be a pathway by which placentation abnormalities occur that culminate in these poor pregnancy outcomes.

Recent studies would support this association between low PAPP-A levels in first trimester and risk for poor pregnancy outcome. Spencer and colleagues (Ultrasound Obstet Gynecol 2006;28:637-43) evaluated first trimester markers in 54,722 chromosomally normal singleton pregnancies. At the 5th percentile of PAPP-A (0.415 MoM), the odds ratios for fetal loss before 24 weeks, at or above 24 weeks, and at any gestational age were 3.3, 1.9, and 2.8. In other words, there was about a three-fold risk of losing a baby with low PAPP-A levels. Cowans and Spencer (Prenat Diagn 2007;27:264-71) recently confirmed the association between low PAPP-A and low for gestational age birth weight babies as well. Indeed, they found a linear relationship between the severity of growth restriction and the decrease in PAPP-A levels – in other words, the lower the PAPP-A, the smaller the babies at any gestational age.

Several other studies confirm the association of the other 'pregnancy complications' noted above with low levels of PAPP-A. For example, as a spin-off of the results in the First and Second Trimester Evaluation of Risk (FASTER) trial, it was found that women with PAPP-A at or below the 5th percentile "were significantly more likely to experience fetal loss at less than or equal to 24 weeks, low birth weight, preeclampsia, gestational hypertension, preterm birth (P < .001) and stillbirth, preterm premature rupture of membranes, and placental abruption (P < .02)." (Dugoff, et al., Am J Obstet Gynecol 2004; 191:1446-61).

Conclusion

Though Papp-A level in the First Trimester Of Pregnancy (11- 13 Wks) is an important predictor of future Obstetric outcome , it has poor positive predictive value. Papp-A MOM less than 0.5 in pregnant patients have higher risk of preterm delivery , fetal growth restriction & stillbirths along with increased incidence of hypertensive disorders of pregnancy. But alone Papp-A level can be poor predictor of future Obstetric outcome unless combined with other markers such as uterine artery Doppler velocimetry at 21 -22 wks of pregnancy, B-hcg serum concentration in pregnant mothers in the first trimester of pregnancy. So further multicentre studies will be required involving large sub group of pregnant patients to determine the association of Papp-A level & its outcome.

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