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Research Article

Pregnancy-associated plasma protein A - a level in first trimester and its impact on pregnancy outcome

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ABSTRACT

Background: To study the pregnancy outcome in relation to PAPP-A level in the first trimester of pregnancy.
Methods: Every patient visiting the antenatal OPD was counseled for testing of first trimester screening to assess fetal wellbeing. Patients who were registered for the delivery in the same hospital were taken into consideration for study. Blood samples were taken at 11-13 weeks of gestation and sent to lab for analysis. Results were expressed in multiple of median and the patients having MoM value less than 0.5 were carefully observed till the delivery, and a thorough neonatal examination was done by a pediatrician.
Results: 524 patients were included in the study, out of which 452 patients were found to have a normal PAPP-A level of >0.5 MoM. All these patients were followed further during the antenatal period where 18 patients developed preterm labour and few patients developed pregnancy induced hypertension (PIH). The obstetric outcome of patients with normal PAPP-A level was fairly uneventful as compared to others with a low PAPP-A level.
Conclusions: PAPP-A level in the first trimester of pregnancy (11-13 weeks) is an important predictor of further obstetrics outcome. Patients having a PAPP-A level < 0.5 MoM had a high risk for preterm delivery, fetal growth restriction and stillbirth along with increased incidence of hypertensive disorder of pregnancy. A low PAPP-A level is a useful indicator of risk of preterm delivery and future chance of development of PIH.

Keywords: PAPP-A in pregnancy, Preterm delivery, Fetal growth restriction, PIH

INTRODUCTION

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

A low PAPP-A is defined as maternal serum PAPP-A value < 0.4 MoM, with increased frequency of adverse obstetrical outcomes noted below this level.[2] PAPP-A is a large glycoprotein produced by the placenta and deciduas 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 fetal growth restriction,

fetal demise, preterm birth and pre-echlamsia in the third trimester.

The present study was aimed to study the pregnancy outcome in relation to variations of PAPP-A level in the first trimester of pregnancy.

METHODS

Every patient visiting the antenatal OPD was counselled for testing of first trimester screening to assess fetal wellbeing. Patients who were registered for the delivery in the same hospital were taken into consideration for study. Blood samples were taken at 11-13 weeks of gestation and sent to lab for analysis. Results were expressed in multiple of median and the patients having MoM value less than 0.5 were carefully observed till the delivery, and a thorough neonatal examination was done by a paediatrician.

RESULTS

We studied 524 patients in the first trimester of pregnancy by doing their PAPP-A level. A Papp level ≥ 0.5 MoM is considered normal, while levels less than 0.5 MoM are marked as low.

Normal MoM >0.5

452 patients were found to have normal levels and were further followed till delivery. 18 patients developed preterm labour (Figure 1) on their successive follow-up, while 12 patients had good neonatal outcome. 6 babies had extreme prematurity which required prolonged NICU admission and repeated surfactants.

Table 1: A comparison between the outcomes of patients in relation to PAPP-A levels.

PAPP-A level	No. of patients	Preterm labour	Fetal growth retardation	PIH	Still birth
Normal (>0.5 MoM)	452	18	12	3	nil
Low (0.5 MoM)	72	32	11	16	01

12 patients in the normal MoM study arm developed PIH, which in most of patients was well controlled with treatment, but 2 patients required termination of pregnancy in 8th month of pregnancy. No fetal growth restriction was documented in study arm, except in two to three patients where it was associated with PIH.

Low PAPP-A level <0.5 MoM

72 patients in the study group had PAPP-A level < 0.5 MoM. All of these patients were followed till the delivery. A significant number of patients in the study arm developed preterm labour 32 patients (Figure 2).

21 patients delivered during the 32-36 weeks of pregnancy where the outcome was comparatively better, while 11 patients delivered during the 28-32 weeks of pregnancy. Interestingly, most of the patients who developed preterm labour did not respond to the tocolytic agents and we could hardly buy any time for the any time for antenatal steroids to act and to enhance the fetal lung maturity.

16 patients in the study group developed PIH and 7 patients required termination of pregnancy for the severe pre-echlampsia.

11 patients in the study group had developed fetal growth restriction and did not have simultaneous PIH. Most of the patients had asymmetrical FGR suggesting increased uteroplacental resistance as a cause of fetal growth restriction.

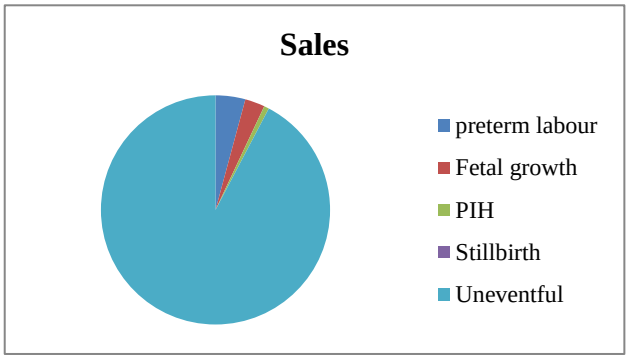

Figure 1: Outcome of patients having PAPP-A level >0.5 MoM.

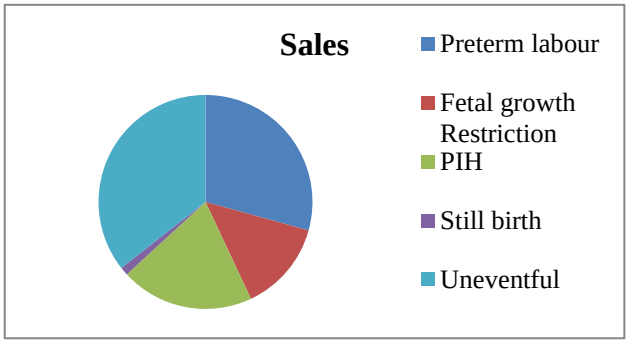

Figure 2: Outcome of patients having PAPP-A level <0.5 MoM.

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 and stillbirth. While those patients having a PAPP-A level >0.5 MoM also had preterm deliveries, fetal growth restrictions and PIH in patients with low PAPP-A level in the first trimester of pregnancy.

DISCUSSION

A low PAPP-A level is poorly sensitive, although these associations exist at the lower outcomes and improve accuracy.[1,2,5-7] 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 extravillous cytotrophoblasts.[8] It is a protease for insulin like growth factor (IGF)-binding protein 4 and 5.[9] 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.[10] IGF is thought to play an imp role in trophoblast invasion and hence the early development and vascularisation of placenta and placental bed. These early events in the formation of the placenta are critical to the pregnancy outcome and when abnormal, are associated with miscarriage, IUGR of baby, PIH, fetal death in utro, 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 placental abnormalities occur that culminate in these poor pregnancy outcomes.

Recent studies would support these associations between low PAPP-A levels in the first trimester and risk of poor pregnancy outcome. Spencer and colleagues evaluated that first trimester markers in 54,722 chromosomally normal singleton pregnancies.[11] At the 5th percentile of PAPP-A (0.415 MoM), the odds ratios for fetal lose before 24 weeks, at or above 24 weeks and at any gestational age were 3.3, 1.9 and 2.8 respectively. In other words, there was about a threefold risk of losing a baby with low PAPP-A levels. Cowan and Spencer recently confirmed the association between low PAPP-A and low for gestational age birth weight babies as well.[12]

Indeed, they found a linear relationship between the severity of growth restriction and decrease in PAPP-A levels. In other words the lower the PAPP-A; the smaller the babies at gestational age.

Several other studies confirm the association of the other "pregnancy complications" noted above with the levels of PAPP-A e.g. as a spin-off 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 $\leq$ 24 weeks, low birth weight, pre-echlampsia, gestational hypertension, preterm birth ($p<0.001$) and stillbirth, preterm premature rupture of membranes and placental abruption ($p<0.02$).[13]

CONCLUSION

Though PAPP-A level in the first trimester of pregnancy (11-13 weeks) is an important predictor of future obstetric outcome, it has poor positive predictive value. Patients having PAPP-A level less than 0.5 MoM have a higher risk for preterm delivery, fetal growth restriction and still birth along with increased incidence of hypertensive disorders of pregnancy. Lower the MoM value of PAPP-A level, more the chances of adverse obstetrical outcome. In our study we have found an increased incidence of preterm labour and PIH in patients having a Papp level <0.5 MoM. While the patients having a PAPP-A level >0.5 MoM had fairly uneventful obstetric outcome except for a few of them who had preterm labour and PIH, which is comparable to the population mean. So, further larger studies will be required involving large subgroups of pregnant patients to determine the association of PAPP-A level and its outcome.

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