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Original Research Article

Relationship of first trimester pregnancy associated plasma protein: A levels with intrapartum fetal distress

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Abstract

PAPP-A is a glycoprotein released from the placenta, and was first obtained from the plasma of pregnant women in 1974 by Lin *et al*. 21 Its level in the maternal bloodstream increases as pregnancy advances, 8 reflecting the placental activity. 7 It is produced by the syncytiotrophoblast and is also expressed in ovarian granulose cells as well as in the non-reproductive tissues, like fibroblasts, osteoblasts and vascular smooth muscle cells. Every patient visiting the antenatal OPD with a period of gestation of 11-14 weeks was counselled for the testing of first trimester screening to assess fetal well-being. An informed consent was taken from all the participants. In all cases, the mothers were followed up for the duration of their pregnancies. Majority of the patients (62.4%) had a normal CTG at the time of delivery, with only 30 patients (32.3%) showing fetal distress. There is a significant association between CTG and levels of PAPP-A.

Keywords: First trimester pregnancy, plasma protein-a, intrapartum fetal distress

Introduction

The aim of first trimester maternal serum screening is to recognize mothers at increased risk of delivering a baby affected with Down syndrome, Patau syndrome and Edward syndrome. 5 There is a well-known association between advanced maternal age and increased risk of trisomy 21 and pregnant women older than 35 years age are routinely offered invasive prenatal diagnostic testing. Amniocentesis is the most commonly used test for genetic diagnosis, but the rate of spontaneous fetal loss related to amniocentesis averages to about one in every 200 procedures [1]. This risk has made serum analyte testing a crucial, non-invasive initial step in identifying patients at risk of congenital anomalies. Studies available on first trimester maternal serum screening shows that the double marker test, which includes measuring the thickness of nuchal translucency and serologic tests, which measure the level of serum pregnancy associated plasma protein A (PAPP-A) and free beta-hCG (b-hCG), helps in identifying 90% of pregnant women at risk of Down syndrome, 94% of all major chromosomal abnormalities like Patau syndrome, Edward syndrome, triploidy and Turner

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syndrome, as well as 60% of other chromosomal defects that include deletions, partial trisomies, unbalanced translocations and sex chromosome aneuploidies other than turners. A second trimester quadruple test which additionally measures unconjugated estriol (uE3) and inhibin A to the double test, has been established and is reserved as an alternative test in pregnant women with first prenatal visits to the hospital after 13 weeks and 6 days of gestation [2].

PAPP-A is a glycoprotein released from the placenta, and was first obtained from the plasma of pregnant women in 1974 by Lin *et al*. Its level in the maternal bloodstream increases as pregnancy advances, reflecting the placental activity. It is produced by the syncytiotrophoblast, and is also expressed in ovarian granulose cells as well as in the non-reproductive tissues, like fibroblasts, osteoblasts and vascular smooth muscle cells. It is a specific protease for insulin-like growth factor binding protein-4 and 5 (IGFBP-4,5) and helps in the release of IGF from these binding proteins so that it can interact with its cell receptor. IGF is thought to play a major role in trophoblast invasion, and regulates glucose and amino acids transport in the placenta, thus aiding early development and vascularization of the placenta and the placental bed [3, 4].

PAPP-A is a relatively large molecule with 750000 daltons molecular weight, 8 and is secreted as a disulfide-bound homodimer with each subunit derived from pre-pro PAPP-A having 1,627 residue proteins that are processed into mature PAPP-A of 1,547 amino acid residues and 14 putative N-glycosylation sites. Following intracellular cleavage of the C-terminal side of PAPP-A polypeptide, it is secreted as an active protease. It is a zinc binding metalloproteinase that belongs to the metzincin superfamily of metalloproteinases, and the residues coordinate the catalytic zinc ion of the active site as well as a structurally important methionine residue located downstream in the so-called Met-turn [5]. Metzincins have a remarkably similar tertiary structure, but have only limited sequence identity. Because of a characteristic residue that directly follows the zinc-binding motif, and the unusual distance from the zinc-binding motif and the Met-turn, PAPP-A is distinct from the other four metzincin groups (astacins, serralysins, adamalycins or reprolysins and matrix metalloproteinases). PAPP-A circulates in the plasma either as a free form or as a heterotetrameric complex of the proform of eosinophil major basic protein (proMBP) known as PAPP-A/proMBP, with all proMBP synthesized in extravillous. In addition to a single heparan sulfate moiety, ProMBP is substituted with both N-and O-linked carbohydrate, and is believed to occupy the PAPP-A cell-surface binding site, in the circulating PAPP-A/proMBP complex. Murine and human PAPPA shows an overall sequence identity of 91%, assigned to human chromosome 9q33.1 that spans over 200 kb of DNA, and contains exons, with the coding of all residues of the zinc binding and Met-turn consensus conserved in exon [6].

Methodology

Study design: Cohort study.
Study setting: Department of Obstetrics and gynaecology.
Study population: All singleton pregnancies in their first trimester (11-14 weeks of gestation), visiting the OPD Medical College Hospital, for their antenatal check up, over a period of 1 year was requested to give an informed consent to be enrolled in the study.

Inclusion criteria

- Singleton pregnancies.
- 11-14th week of gestation.

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Exclusion criteria

- Multiple pregnancies.
- Cases with abnormal fetal karyotype.
- Cases with antenatal complications in pregnancy.
- All preterm deliveries.

Sample size

Z1-α/2= 1.96 [at 5% α] Z1-β = 0.84 [at 20% β] P1= 68% and P2 = 42% 7 n= 57 in each group.

Sampling technique: Convenient sampling.

Statistical analysis

All categorical variables were summarized using frequency and percentage. Quantitative variables were summarized using mean and standard deviation if data follows normality, else median and interquartile range.

Method of collection of data

Every patient visiting the antenatal OPD with a period of gestation of 11-14 weeks was counselled for the testing of first trimester screening to assess fetal well-being. An informed consent was taken from all the participants. In all cases, the mothers were followed up for the duration of their pregnancies.
Eligible mothers had their blood samples taken and the serum levels of PAPP-A were tested and value was adjusted according to the maternal weight, insulin-related diabetes and smoking habits. Measurement of PAPP-A in maternal serum was done using Enzyme Immunoassay 85 They were divided into 2 groups based on their first trimester PAPP-A MoM values as <0.5MoM (group 1) or >0.5MoM (Group 2). The demographic features, gender, birth weight, mode of delivery and indication for C/S were recorded. 7 These mothers were monitored continuously with CTG while in labour and any abnormality was noted. Fetal distress was diagnosed by the interpretation of CTG traces according to the NICE guidelines. 84 Patients with pathological and suspicious CTG according to NICE guidelines were diagnosed to have fetal distress.

Results

Table 1: Association between PAPP-A and Mode of delivery

PAPP-A	Mode of Delivery			Total	Chi-Square	p value
	EM LSCS	FTND	Outlet Forceps			
Low PAPP-A	5 (12.2%)	35 (85.4%)	1 (2.4%)	41 (100%)	1.742	0.419
Normal PAPP-A	9 (19.1%)	35 (74.5%)	3 (6.4%)	47 (100%)		
Total	14	70	4	88		

Majority of the patients (62.4%) had a normal CTG at the time of delivery, with only 30 patients (32.3%) showing distress.

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Table 2: CTG of study population

CTG	Frequency	Percent
Distress	30	32.3
Normal CTG	58	62.4
Lost follow up	5	5.4
Total	93	100.0

Here Pearson Chi-Square Test is used to test the association between CTG and level of PAPP-A. The frequency distribution of the CTG across the levels of PAPP-A. Around 37% subjects are distressed with low PAPP-A. And for the subjects with normal PAPP-A, only 27% are distressed and 72% are in good condition with CTG. The calculated Chi-square value is 7.248 with p value < 0.05. So, there is a significant association between CTG and levels of PAPP-A.

Table 3: Frequency distribution of the CTG across the levels of PAPP-A

Group	CTG			Total	Chi-Square	p value
	Lost follow up	Distress	Normal CTG			
Low PAPP-A	5 (10.9%)	17 (37.0%)	24 (52.20%)	46 (100%)	7.248*	0.027
Normal PAPP-A	0 (0.0%)	13 (27.7%)	34 (72.30%)	47 (100%)		
Total	5	30	58	93		

The calculated Chi-square value for meconium stained amniotic fluid is 8.949 with p value < 0.05. So there is a significant association between MSAF and levels of PAPP-A.

Table 4: Association between PAPP-A and MSAF

Group	Meconium Stained Amniotic Fluid				Total	Chi-Square	p value
	No	Moderate	THIN	THIC K			
Low PAPP-A	37 (90.2%)	0 (0.0%)	0 (0.0%)	4 (9.8%)	41 (100%)	8.949*	0.030
Normal PAPP-A	42 (89.4%)	3 (6.4%)	2 (4.3%)	0 (0.0%)	47 (100%)		
Total	79	3	2	4	88		

Pearson Chi-Square Test, *Significant at 0.05 level.

Table 5: PAPP-A level in mothers of NICU admitted babies

NICU Admission Indication	Low PAPP-A		Normal PAPP-A	
	Frequency	Percent	Frequency	Percent
Hypoglycemia Meningitis	0	0.00	1	7.69
Hypoglycemia	1	9.09	0	0.00
Low Cord PH	6	54.55	7	53.85
Mod MSAF	0	0.00	3	23.08
Thick MSAF	4	36.36	0	0.00
Thin MSAF	0	0.00	2	15.38
Total	11	100	13	100

The calculated Chi-square value is 0.008 with p value > 0.05. So, there is no significant association between NICU Admission and levels of PAPP-A.

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Table 6: Association between NICU admission and PAPP-A level

PAPP-A	ICU Admission		Total	Chi-Square	p value
	Yes	No			
Low PAPP-A	11 (26.8%)	30 (73.2%)	41 (100%)	0.008	0.930
Normal PAPP-A	13 (27.7%)	34 (72.3%)	47 (100%)		
Total	24	64	88		

Pearson Chi-Square Test

Table 7: Association between RD and levels of PAPP-A

Group	Respiratory Distress		Total	Chi-Square	p value
	Yes	No			
Low PAPP-A	9 (22%)	32 (78%)	41 (100%)	2.095	0.148
Normal PAPP-A	5 (10.6%)	42 (89.4%)	47 (100%)		
Total	14	74	88		

Discussion

According to this study, 70 patients (75.3%) underwent full term normal delivery, whereas forceps and emergency LSCS was done for 4 (4.3%) and 14 (15.05%) patients respectively. Majority of the patients (62.4%) had a normal CTG at the time of delivery, with only 30 patients (32.3%) showing fetal distress. There is a significant association between CTG and levels of PAPP-A. In a study by Ajah *et al*. the 8.9% of the parturients had caesarean section due to fetal distress [7]. This was similar to studies by Abakaliki and Nnewi, with LSCS rates of 10.4% and 11.7% respectively [8, 9]. In an environment with high aversion to caesarean section and poor health seeking behaviour, the future obstetric career of this group of women may be in jeopardy as some of them may avoid skilled birth attendant in their subsequent deliveries with its dire consequences [7]. With previous caesarean section being the commonest indication for caesarean section in this environment [10], these unnecessary caesarean sections due to clinical diagnosis of fetal distress, may predispose these women to caesarean sections in their subsequent deliveries. Some of these parturients may also develop other complications from the procedure [7]. Ucella *et al*. found that the rate of non-elective LSCS deliveries indicated by fetal distress was higher among mothers with low PAPP-A levels (16.2%) than among mothers with normal PAPP-A (7.9%) levels. Thus, low PAPP-A levels may be not only related to antenatal complications like preeclampsia, intrauterine growth retardation, preterm delivery and loss of pregnancy, but also may be a risk factor for acute intrapartum fetal distress related to abnormal placentation and placental dysfunction, leading to more emergency LSCS deliveries.

42 patients (45.2%) were of normal weight whereas 51 patients (54.8%) were overweight. None of the patients were underweight or obese. A significant association was seen between BMI and levels of PAPP-A. According to a study by Ajibade *et al*., majority of patients with low PAPP-A has low BMI (<25), with no incidence in patient with BMI >40 [11]. Meconium Stained Amniotic Fluid (MSAF) was seen only in 9 cases, out of which majority (4.3%) were thick. A significant association was found between MSAF and levels of PAPP-A. This was similar to a study by Desai *et al*., in which there was a strong association between meconium stained liquor and fetal distress [12]. In contrast to this, Wong *et al*. reported lack of significant association between fresh meconium stained liquor and fetal distress. Fetal distress was presented as respiratory Distress in 14 babies (15.1%), low birth weight, brady/tachycardia, decreased SpO_2 and hypo/hyperthermia. But none of this had a significant association with low PAPP-A level.

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Conclusion

Though PAPP-A level in the first trimester of pregnancy is an important predictor of obstetric outcome, it has poor positive predictive value and may not be used as a marker in such a highly selected patient group. Further studies with more study populations are required to elucidate this relationship between PAPP-A and presence of adverse perinatal outcomes.

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