Relationship of Pregnancy Associated Plasma Protein A (PAPP-A) With Preterm Labour

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Abstract

Background: Aim of study: The purpose of the this study is to evaluate Pregnancy-associated plasma protein-A (PAPP-A) levels as a predictor of preterm birth in women with complaints of preterm labour or preterm painful contractions. **Methodology:** It was a prospective case control study carried out from the 1st of January 2018 to the 20th of march 2019 at Basra maternity and children hospital. A total of 150 patients (50 patient with preterm labour (28-37 weeks), 50 patients with threatened preterm labour and 50 patients term pregnancy in labor) Primary end point was delivery <37 weeks. All studied 3 groups were checked for serum maternal PAPP-A level on admission. **Results:** In all 50 Patients delivered before 37 weeks (GROUP l), 50 patients had symptoms of preterm labour but didn't deliver preterm (GROUP ll) and 50 patients (GROUP lll) delivered at term . mean PAPP-A level in preterm group and its matched control group were 32.56±17.2 miu/ml and 53.21±18.42 miu/ml respectively and the difference was statistically significant (P.value 0.002) , mean PAPP-A level TPL was 45.06±15.42 miu/ml and the difference was significant in compare to preterm labour but not significant in compare control group P.value 0.003 and P=0.74 respectively. **Conclusion:** PAPP-A level decrease in preterm labour, level <29.6 miu/ml was associated with increased risk of preterm birth where value of >33.6 miu/ml is more likely to be delivered at term .

1. Introduction

Preterm labour Preterm birth, defined as delivery before completed 37 weeks of gestation is an important complication of both singleton and multifetal pregnancies worldwide. Children born preterm are at increased risk of mortality and are more likely to have long-term neurological and developmental disorders than those born at term [1]. The incidence of preterm birth varies between countries with a range of 5-13%, resulting in 15 million preterm deliveries worldwide each year [2]. More than 60% of all preterm births occur in Sub-Saharan Africa and South(-eastern) Asia. where 13.4% of the children are born preterm. The preterm birth rate in Europe ranges from 5% to 10%, where relatively low rates are observed in Scandinavian countries and relatively high rates occur in Cyprus and Hungary [3].

In the women the levels of PAPP-A are highest during pregnancy, when plasma levels increase by a factor of about 150 as compared to the no pregnant state [60].PAPP-A is the most abundant in the maternal circulation with a mean vascular content of 250 mg at term [61].In women with singleton pregnancies PAPP-A was first detected in the maternal blood about 28 days post implantation [61]. Serum PAPP-A concentration increases exponentially with a doubling time of 3–4 days during the first trimester, then the levels continue to rise throughout pregnancy until delivery. It can be seen that the concentration rises up at a lesser gradient to 36 weeks after which the levels increase more steeply right up to term [62]. After parturition the clearance of PAPP-A from peripheral blood is slower than other molecules produced by the trophoblast, the average half-life of PAPP-A after normal delivery is 52.9 ± 25.8 hours. At termination in the first trimester the half-life is 51 hours. After surgical termination of ectopic pregnancy in patients with curetted decidua, PAPP-A disappeared significantly faster than in women with intact decidua. Then the half-life of PAPP-A is longer

in presence of the decidua then in absence. These results indicate that the production of PAPP-A continues by the decidua after removal of the trophoblast in early pregnancy [60]. Only minor pools of PAPP-A are distributed outside the maternal circulation. Trace amount of PAPP-A has been detected in amniotic fluid, colostrum and fetal blood. The concentrations seen in the fetal circulation are 1000 fold less and levels of PAPP-A in amniotic fluid are at least 10-fold less than in the maternal circulation [63].

The etiology of PTL and PPROM is multifactorial [67]. Most of the causes are still uncertain. It has been known for a long time that infection of the intraamniotic cavity with elevation of inflammatory cytokines plays an important role for those women complicated by PTL and PPROM [68]. However, not all pregnant women with preterm delivery have an evidence of infection. Therefore, some pathophysiologic processes other than infection should be involved in causing preterm delivery [68]. The following reports have indicated that vascular developmental defects in placentation may play a role in the pathogenesis of preterm delivery, especially in those with PPROM [69].

Maternal placental vasculopathy and infection were identified among those with pregnancies complicated by PTL as well as PPROM [69]. the failure of physiologic transformation in the myometrial segments of the spiral arteries was frequent in pregnancy with PPROM [69]. the maternal serum PAPP-A in the lowest fifth percentile at 8–14 weeks had an increasing risk of extremely premature delivery (24–32 weeks; odds ratio, 2.9) and moderately premature delivery (33–36 weeks; odds ratio, 2.4) [70]. This relationship was stronger in pregnancies with PPROM than those of PTL with intact membranes. lower concentrations of PAPP-A in the first trimester were associated with an earlier onset of spontaneous labor at full term [71].

The aim of this study was to assess the relationship between maternal serum PAPP-A level in pregnancies complicated by preterm labour and term pregnancies .

2. Methodology

2.1 Study setting and patients

It was a prospective case control study carried out from the 1st of January 2018 to the 20th of march 2019 at Basra maternity and children hospital which is the main tertiary referral hospital serving the southern part of Basra and to some extent it might reflect the Basra governorate . it included 150 pregnant woman who were admitted for the purpose of delivery or severe uterine contraction in the hospital while on duty .
These woman were divided into 3 groups: group one include 50 women who had preterm labour (28-37 weeks) and they are in imminent preterm labour with rupture membranes, group two include 50 women with uterine contraction but not in active preterm labour and intact membrane, while group three , include 50 women with labour pain (more than 37 weeks).

We diagnose a preterm labour if they had a regular painful contractions coming 3 times/10 minutes on monitor and had cervical dilatation ≥ to 3 cm or effacement more than 80% and had rupture membrane and their gestational age (28-37 weeks) while the second group had irregular uterine contraction and intact membrane and their gestational age between (28-37 weeks), in the third group they are >37 weeks in establish labor .

2.2 Exclusion criteria

Women were excluded from the study if they had multiple pregnancies, maternal disorder such as diabetes, hypertension, pre-eclampsia, placental haemorrhage, history of cervical cerclage, history of uterine malformation, IUGR and known fetal abnormality .

2.3. Data Collection

The demographic character of the studied group was determined such as age, parity, weight, blood pressure, pregnancy outcome, neonatal weight and smocking status were recorded . Preterm labour management were offered to all our preterm patients according to the standard practise in our hospital and it includes, dexamethasone administration with 24-48 hours tocolytics with MgSo4 was prescribed and it was unrelated to the maternal serum level of PAPP-A. The gestational age was determined accurately from the date of the last menstrual period (LMP) , also ultrasound estimation was required in all studied women .

2.4 Clinical Examination

A blood simple 5 cc . at time of admission taken from the patient the analysis were done using Snibe Malgumi 1000 analyzer with the following principles Sandwich immunoluminometric assay: Use an anti-PAPP-A monoclonal antibody to label ABEI, and use another monoclonal antibody to label FITC. Sample, calibrators, or control, with FITC label and magnetic microbeads coated with anti-FITC are mixed thoroughly and incubated at 37℃ and cycle washing for 1 time. Then add ABEI Label, incubation and form a sandwich, then washing for the 2nd time. Subsequently, the starter reagents are added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as RLU (relative light unit) within 3 seconds and is proportional to the concentration of PAPP-A present in samples.

2.5 Ethical approval

All women included in the study group informed consent and the study was approved by the scientific committee of our hospital.

2.6 Statistical analysis

The significance of the difference between the three studied groups were assessed by chi-square test and student t-test as appropriate , statistical significance was defined as $P<0.05$, $P<0.01$ and $P<0.001$.

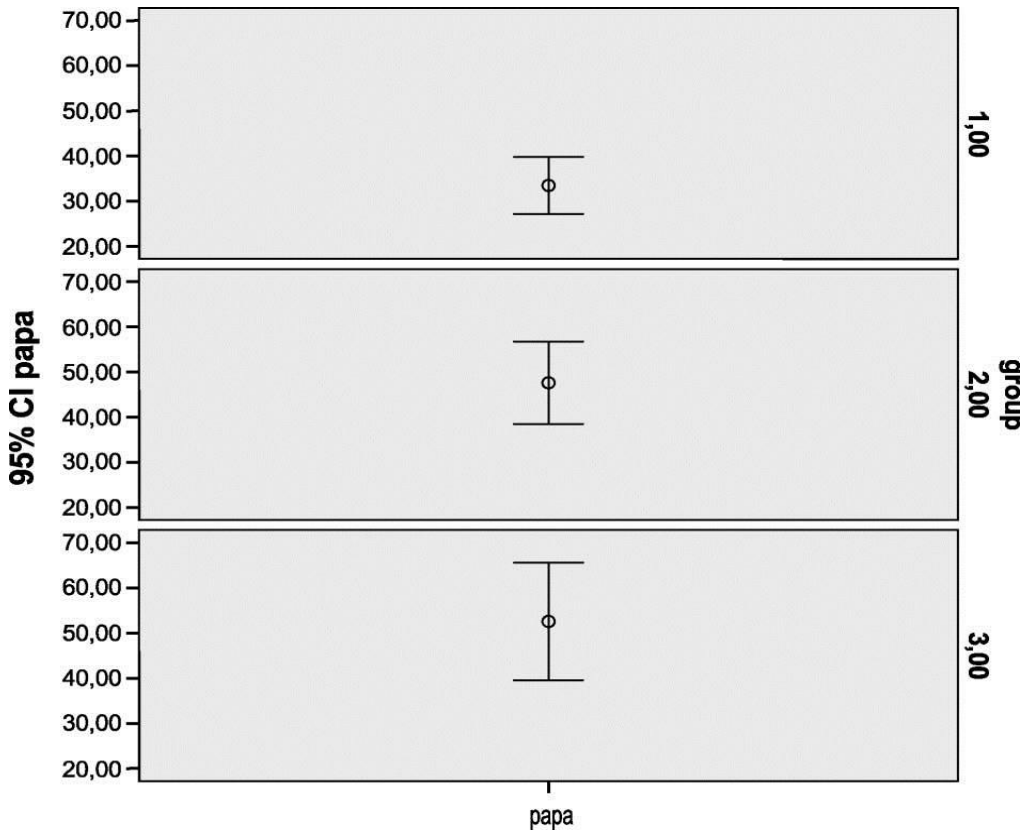
3. Results

During the study period 150 patients were considered eligible for study and they were divided into 3 groups , (group I) consist of 50 patients who delivered preterm , the (group II) consist of 50 patients having symptoms of preterm labour but not delivered preterm and was called threatened preterm labour (TPL) while the third group consist of 50 patients neither having symptoms of preterm nor delivered preterm and regarded as control group (group III) .

Table 1 show the demographic characteristics of the study group and it was found there were no statistical significant difference between the three groups apart from increase the rate of admission to paediatric intensive care unit (PICU) and low Apgar score in the first group , low birth weight and the difference was statically significant .

Table 1 : demographic character of the studied groups

	Group I	Group II	Group III	*p*- value
Age	27.4±5.7	26.8±4.9	28.1±5.5	N.S
Parity	3.4±1.6	2.9±1.8	3.1±1.7	N.S
BMI	26.6±3.4	27.2±2.8	27.5±3.2	N.S
Gestational age at admission	30.4±2.6	31.1±1.8	31.9±0.6	N.S
ANC	20/50	21/50	30/50	N.S
Smocking	5/50	4/50	3/50	N.S
Caesarean section rate	20	18	16	N.S
Gestational age at delivery	34±1.8	38.4±1	38.8±1.8	N.S
Birth weight in KG	2.2±0.6	3.2±1.2	3.6±0.6	< 0.001
Apgar Score at 1 minute	3.1±1.2	8.6±0.8	8.6±1.4	< 0.001
Apgar Score at 5 minutes	5.1±0.2	7.3±0.6	9.1±0.2	< 0.001
PICU admission	23	19	6	< 0.001



Mean PAPP-A level in preterm labour(Group l) when compared to control term pregnancy (Group lll) where controlled 32.56±17.2 miu/ml and 53.21±18.42 miu/ml respectively and the difference was statically significance P.value= 0.002 .

While mean PAPP-A level in threatened preterm labour group (Group ll) was 45.06±15.42 miu/ml and the difference were significant compare to preterm labour but not significant when compared to control term group P.vlaue = 0.003 and p= 0.74 respectively .

Table 2 : cut off value PAPP-A for prediciting of preterm labour and control groups

Cut off	Sensitivity	Specificity	Likelihood ratio	PPV	NPV
29.70	0.70759	0.51319	1.468	0.5310	0.7100
30.20	0.6785	0.51219	1.398	0.5298	0.660
30.50	0.63414	0.51219	1.341	0.5106	0.659
31.10	0.57972	0.51217	1.1905	0.4998	0.621
33.90	0.55893	0.5429	1.182	0.4781	0.6112

Table 3 : cut off value PAPP-A for predicating of preterm labour and threatened preterm labour

Cut off	Sensitivity	Specificity	Likelihood ratio	PPV	NPV
33.60	0.6970	0.5415	1.483	0.5463	0.675
33.80	0.6725	0.540	1.425	0.532	0.662
34.10	0.6590	0.6590	1.463	0.536	0.675
34.60	0.6590	0.5752	1.552	0.545	0.682
35.00	0.6590	0.6085	1.675	0.569	0.695
36.50	0.6590	0.6920	1.681	0.580	0.706

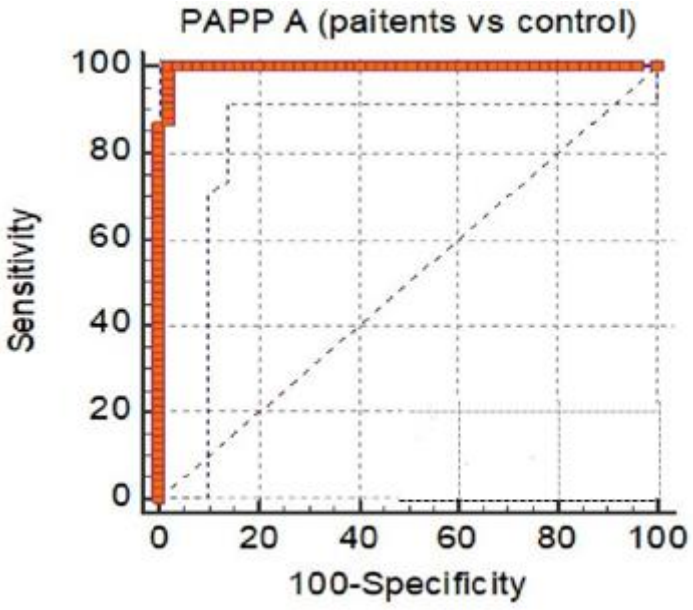


Figure 2 : ROC Curve of preterm labour Vs. Control group

ROC analysis differentiate control group Vs. preterm one showed that 29.70 miu/ml as Cut off value for PAPP-A and had sensitivity 70.7 % , 51.3 % specificity , 53.1 % PPV and 71.0 % NPV for prediction of preterm labour while the cut off value for PAPP-A for prediction of preterm labour Vs. control group (Group lll) are shown in table 2 .

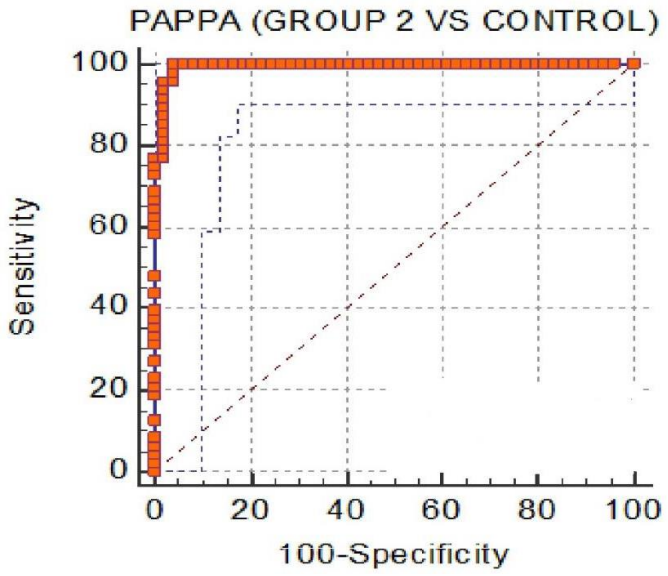


Figure 3 : ROC Curve of preterm labour Vs. TPL group

ROC analysis show that cut off value 33.60 miu/ml , with a sensitivity 69.0 % , specificity 54.1 % , PPV 54.6 % and NPV 67.5 % . While the cut off value of PAPP-A predicating preterm labour Vs. threatened preterm labour was shown in table No. 3 .

4. Discussion

Preterm labour is birth that happen too soon or before completing 37 weeks of pregnancy as was reviewed by literature in the introduction (1). In recent years it was found that treatment of preterm labour was change in many important ways such as development of new classes of safe tocolytics agents with routine use of antenatal steroid therapy (72.73) .

So, in our study we want to find late pregnancy PAPP-A serum level would be helpful in predicting preterm delivery and avoid risk of prematurity, as PAPPA highly expressed in syncythiotrophoblast of placenta which is the main source of circulating PAPP-A in pregnancy, so impaired function of placenta inhibiting trophoblastic invasion through the decidua and transformation of small muscular wall of maternal spiral arteries into larger and more elastic one to allow the increment in blood flow which might result in decrease placental perfusion with low PAPP-A level, so many studies done to evaluate the level of PAPP-A serum level on pregnancy outcome such as fetal loss, small gestational age, preterm birth and preeclampsia (74,75,76). which was in agreement to our study which was found that there is a significant correlation between premature labour and PAPP-A maternal serum level while other studies unable to found this correlation (77,78).

So our study aim was done to evaluate whether a low maternal serum level of PAPP-A measured in the second half of pregnancy associated with the risk of spontaneous preterm labour of which later on can be used as predictor factor for these outcomes and it was confirmed in our results when we found that cut-off value of 29.70 miu/ml of PAPP-A have 70.8% sensitivity, 51.3% specificity, 53.1% positive predictive value, 71 % negative predictive value for prediction of preterm labour as shown in table No. 2 , in compared to table no. 3 which found that cutoff value 33.60 miu/ml has 69.7% sensitivity , 54.1% specificity , 54.6 % positive predictive value and 67.5% negative predictive value. in determining threatened preterm labour form preterm labour was in agreement with study done by Granuvescy et.al who shows that value less than 30 miu/ml at time of admission for predicting preterm labour has 88% specificity , 85% sensitivity , 81% positive predictive value, 62% negative predictive value (79) .