Correlates between the Pregnancy Associated Plasma Protein A (PAPP-A) and Preterm Labour

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Abstract
Background: Preterm labor, which is defined as giving birth before 37 weeks of gestation, is a significant global complication of pregnancies including both singletons and multiple fetuses. Premature babies have a higher chance of dying.
Aim of study: Investigate the relationship between pregnancy-associated plasma protein-A (PAPP-A) levels and preterm birth in women who report experiencing premature labor.
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 patient's 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 and Discussion: In all 50 patients delivered before 37 weeks (Group I), 50 patients had symptoms of preterm labour but didn't deliver preterm (Group II) and 50 patients (Group III) 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 reduction in preterm labor was linked to an increased risk of preterm birth; a value of < 33.6 miu/ml indicates a higher likelihood of a term delivery.

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1. Introduction

Premature labor Preterm birth is a major global complication of singleton and multifetal pregnancies, defined as delivery before 37 weeks of gestation. Compared to children born at term, preterm babies have a higher chance of dying and developing long-term neurological and developmental issues [1]. There are 15 million preterm births globally each year due to the 5–13% variation in preterm birth incidence between nations [2]. Sub-Saharan Africa and South (eastern) Asia account for more than 60% of all preterm births. There the preterm birth rate is 13.4%. Europe has a preterm birth rate of 5% to 10%; Scandinavia and Hungary have comparatively low rates, while Cyprus and Hungary have quite high rates [3].

During pregnancy, when plasma levels rise by a factor of roughly 150 in comparison to the non-pregnant state, women's PAPP-A levels are at their highest [4]. At term, the mean vascular concentration of PAPP-A in the mother's circulation is 250 mg, making it the most abundant [5]. In pregnant ladies who are singletons PAPP-A was initially found in the mother's blood approximately 28 days after the implantation [5]. During the first trimester, serum PAPP-A concentration rises dramatically with a doubling time of 3–4 days. After that, levels climb steadily until birth. It is evident that the concentration increases more gradually up to 36 weeks, at which point the levels climb more sharply all the way to term [6]. PAPP-A has an average half-life of 52.9±25.8 hours following a normal delivery; it is cleared from peripheral blood from the trophoblast more slowly than other molecules after parturition.

The half-life is 51 hours at first trimester termination. PAPP-A vanished much more quickly in patients with curetted decidua following surgical termination of ectopic pregnancy than in women with intact decidua. Therefore, when decidua is present, PAPP-A has a longer half-life than when it is not. These findings suggest that after the trophoblast is removed in the early stages of pregnancy, the decidua continues to produce PAPP-A [4]. PAPP-A is only dispersed in small pools outside of the mother's circulation. PAPP-A has been found in trace amounts in fetal blood, colostrum, and amniotic fluid. PAPP-A concentrations in amniotic fluid are at least ten times lower than those in the mother's circulation, while concentrations in the fetal circulation are 1000 times lower [7].

PTL and PPROM have a complex etiology [8]. The majority of the causes remain unknown. Long recognized is the significant impact that intraamniotic cavity infection and elevated inflammatory cytokines play in women with PTL and PPROM complications [9]. Not every pregnant woman who gives birth prematurely exhibits signs of infection though. Therefore, preterm birth should be caused by a pathophysiologic process other than infection [9]. According to the following reports, premature delivery may have vascular developmental problems during placentation, particularly in cases when PPROM is present [10].

It has been demonstrated that maternal placental vasculopathy and infection occur in PPROM and PTL-complicated pregnancies [10]. Failure of physiologic transition in the myometrial portions of the spiral arteries was often linked to pregnancy with PPROM [10]. Maternal blood PAPP-A in the lowest fifth percentile at 8–14 weeks was linked to an elevated risk of extremely early delivery (24–32 weeks; odds ratio, 2.9) and moderately premature delivery (33–36 weeks; odds ratio, 2.4) [11]. There was a greater correlation between this and pregnancies with PPROM than with PTL pregnancies with intact membranes. An earlier beginning of spontaneous labor at full term was linked to lower levels of PAPP-A in the first trimester [12]. The purpose of this study was to ascertain if maternal serum PAPP-A levels in pregnancies complicated by premature labor were associated with 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 practice in our hospital and it includes, dexamethasone administration with 24-48 hours tocolytics with $MgSO_4$ 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 use a monoclonal antibody against PAPP-A to label ABEI and a different monoclonal antibody to label FITC in a sandwich immuno luminometric test. After carefully mixing the sample, calibrators, or control with FITC label and anti-FITC-coated magnetic microbeads, they are incubated at 37°C and cycled through washing once. After adding the ABEI label, forming a sandwich, and incubating, wash one more time. Following the addition of the beginning reagents, a flash chemiluminescent reaction is started. In less than three seconds, a photomultiplier measures the light signal as a relative light unit (RLU), which is directly correlated with the amount of PAPP-A in the samples.

2.5. Statistical analysis

$p<0.05$, $p<0.01$, and $p<0.001$ were considered statistically significant. The significance of the difference between the three groups under examination was assessed using the relevant chi-square and student t-tests.

3. Results

150 patients were deemed eligible for the study during that time, and they were split into three groups: (Group I) consisted of 50 patients who delivered prematurely; (Group II) consisted of 50 patients who had preterm labor symptoms but did not deliver prematurely, which was referred to as threatened preterm labor (TPL); and (Group III) consisted of 50 patients who neither delivered prematurely nor had preterm symptoms and were considered the control group. (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 pediatric 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 I) when compared to control term pregnancy (Group III) 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.

The group II, which was threatened with preterm labor, had a mean PAPP-A level of 45.06±15.42 miu/ml. This difference was significant when compared to preterm labor, but not significant when compared to the control group (*p*-value = 0.003 and *p* = 0.74, respectively).

The ROC analysis used to distinguish between the control group and the preterm group revealed that the cut off value for PAPP-A was 29.70 miu/ml. This value was found to have a sensitivity of 70.7%, specificity of 51.3%, PPV of 53.1%, and NPV of 71.0% for the prediction of preterm labor. The results of this analysis are shown in (Table 2 and Figure 1).

Table 2: Cut off value PAPP-A for predicting 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

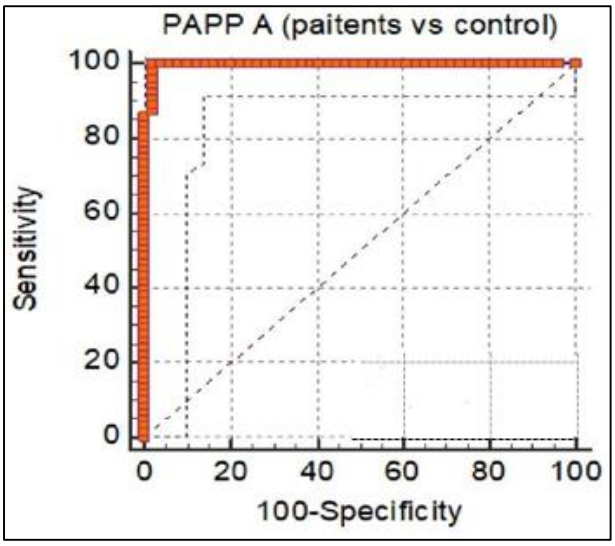

Fig 1: ROC Curve of preterm labour Vs. Control group

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 3 and Figure 2).

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

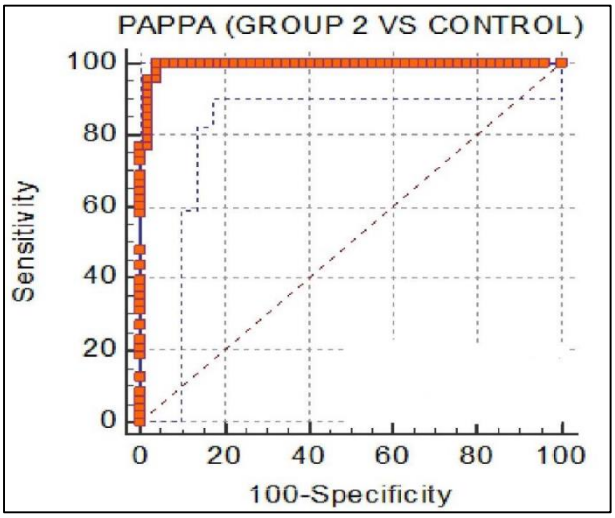

Fig 2: ROC Curve of preterm labour Vs. TPL group

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 [13, 14].

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. Due to the fact that PAPPA is highly expressed in the placenta's syncythiotrophoblast, which is the primary source of circulating PAPP-A during pregnancy, the placenta's impaired function may prevent trophoblastic invasion through the decidua and cause the mother's spiral arteries' small, elastic walls to grow larger, allowing for an increase in blood flow that could reduce placental perfusion in the event of low PAPP-A levels, 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 [15-17], 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 [18, 19].

Therefore, the purpose of our study was to determine if a low maternal blood level of PAPP-A assessed during the second half of pregnancy may be used as a predictor factor for these outcomes by being associated with a later risk of spontaneous preterm labor 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 2), in compared to (Table 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 Grisaru-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 [20].

In order to distinguish a real control group from a threatened preterm labor group, we used three groups in our study. We reasoned that pathogenic elements might still exist even in cases when the threatened preterm group successfully achieves a term pregnancy. According to our research, a PAPP-A cut-off value of more than 33.6 miu/ml increases the likelihood of a term delivery, but a cut-off value of less than 29.6 miu/ml increases the likelihood of a preterm delivery, necessitating more intensive management. The control group's mean PAPP-A serum level was 53.21 ± 18.42 miu/ml, while the mean in preterm labor was 32.56 ± 1.72 miu/ml. This difference was statistically significant, with a *p*-value of 0.002.

With a *p*-value of 0.003 and a *p*-value of 0.74, the PAPP-A level in the threatened preterm group was 45.06 ±15.42 miu/ml, and this difference was significant when compared to preterm labor but not with the control group. Our study's prospective design, which allows us to follow up with patients from the time of admission to the hospital until delivery, is one of its strongest points.

5. Conclusion

PAPP-A level reduction in preterm labor was linked to an increased risk of preterm birth; a value of < 33.6 miu/ml indicates a higher likelihood of a term delivery. In order to assess the likelihood of a woman having a threatened preterm labor, a low level of PAPP-A in the mother's serum is considered to be a good predictive value and an indicator that the woman may experience a preterm labor.

Ethical approval

The study was approved by our hospital's scientific council and all of the ladies who were part of the study group gave their informed consent.

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