SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 7.
Issue: 4.
Page N. 93-98
Year: 2023

Original Article www.wjahr.com

EVALUATION OF THE LEVEL OF PREGNANCY ASSOCIATED PLASMA PROTEIN A IN THREATENED MISCARRIAGE

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Received date: 12 Februry 2023 **Revised date: 05** March 2023 **Accepted date: 26** March 2023

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ABSTRACT

Background: threatened miscarriage affects one in five women and associated with significant emotional distress. Uncertainty about prognosis of threatened miscarriage makes it a challenge to the healthcare professionals, various biochemical markers studied to predict the outcome of threatened miscarriage but the results were conflicting. Aim of the study: to evaluate the role of pregnancy associated plasma protein A in prediction of first trimester miscarriage in those with early pregnancy bleeding. Patients and methods: A prospective case control study carried out on 100 women, 50 of them were threatened miscarriage women (case group) and 50 were healthy pregnant women (control group). Age of participants ranged from 20-35 years, gestational age 6- 8 weeks. Venous blood samples were collected to measure pregnancy associated plasma protein A levels, comparison between these two groups done, and follow up them to 20 weeks of gestation. Results: there was no significant difference in pregnancy associated plasma protein A level observed between cases (1.075±0.2181) and controls (1.05±0.198), P-value =0.944, in addition, within the cases group, there was no significant difference in pregnancy associated plasma protein A level between cases that continued pregnancy to 20 weeks and cases ended with miscarriage (P-value 0.204). Conclusion: No significant difference in pregnancy associated plasma protein A levels between normal pregnancy and threatened miscarriage groups and even between pregnancies ended with miscarriage or continues their pregnancy within threatened miscarriage group, therefore pregnancy associated plasma protein A level cannot be recommended for predicting fetal loss in patient with first trimester bleeding.

KEYWORDS: Evaluation, Pregnancy, Plasma Protein, Threatened Miscarriage.

INTRODUCTION

Pregnancy loss before 20 weeks is called miscarriage. Threatened, inevitable, incomplete, complete, septic, and missed spontaneous miscarriage.[1] The Royal College of Obstetricians and Gynecologists defines miscarriage as spontaneous pregnancy loss before viability. According to the American College of Obstetricians and Gynecologists, miscarriage is a nonviable intrauterine pregnancy up to 20 weeks of gestation.[2,3] Vaginal bleeding before 20 weeks of gestation with a closed cervical os and no foetal or embryonic death is a threatening miscarriage. WHO defined a threatened miscarriage as pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilatation.[4] If the cervical os is opened, there is suspicion of extra-uterine pregnancy, an intrauterine pregnancy without a foetal heartbeat, or products of conception are passed, other forms of miscarriage may be investigated.[5] 25% of pregnant women have vaginal bleeding in the first and second trimesters, and almost 50% lose their pregnancies. Threatened miscarriages cause mild to severe bleeding. abdominal discomfort. Intermittent cramps, suprapubic discomfort, pelvic heaviness, or lower back pain.[6,7] Chromosomal and genetic disorders cause 50% of miscarriages. Almost 95% of chromosomally defective embryos miscarry.[8] Parental influences matter.[9] Correcting uterine structural abnormalities and reducing exposure to teratogens and infections before and during pregnancy may lower miscarriage risk. Chronic diseases including diabetes and thyroid disease, excessive weight, and tobacco, alcohol, and illegal drug use should be considered while maximizing maternal health.[10] Folic acid intake before and throughout early pregnancy may lessen the chance of spontaneous miscarriage.[11] Due to higher chromosomal abnormalities, paternal age is linked to pregnancy loss in many studies.[12] Women should

also be examined for relationship violence. Preconception counselling reduces risks.[13-15] Miscarriages vary by gestational age and mother age. 50% of biochemical pregnancies fail within 4 weeks of the latest menstrual period (LMP). pregnancies. At 6 weeks, 1 in 5 pregnancies are affected, and by the second trimester, 1 in 40.[16] Advanced mother and paternal age, past pregnancy loss, TORCH infections, DM, obesity, uncontrolled thyroid illness, severe stresses, usage of teratogenic drugs, and sub chorionic hemorrhage are risk factors for any miscarriage.[17] Vaginal bleeding in a pregnant woman under 20 weeks' gestation threatens miscarriage. Physical exam shows closed cervical os. Abdominal cramps, pelvic discomfort, pelvic pressure, and back pain may occur. Vaginal bleeding precedes stomach cramps hours to days later. Bleeding predicts pregnancy loss most accurately. Fetal heart activity reduces the incidence of spontaneous miscarriage in endangered pregnancies.[1] All miscarriage products should be histopathologically examined. Recurrent pregnancy loss patients should be offered karyotyping for products of conception to rule out chromosomal abnormalities as a cause of spontaneous miscarriage.[18] Pappalysin 1, PAPP-A, PAPPA1, SP4, high molecular weight alpha-2 mobile pregnancy-specific protein, IGFBP4 protease (IGFBP-4ase), PAPA.[19] Pregnancy-associated plasma protein-A (PAPP-A), a zinc-binding metalloproteinase from the super family of metalloproteases, was first found in pregnant women's blood in 1974 by Lin and his colleagues and then in multiple studies because low levels of PAPP-A were associated with adverse pregnancy outcomes like spontaneous miscarriage, chromosomal aneuploidy, premature birth, foetal growth limitation, preeclampsia, and stillbirth.[20] The aim of study is to evaluate the role of pregnancy associated plasma protein A in prediction of miscarriage in those with early pregnancy bleeding.

METHOD

This is a case control study was conducted in the department of Obstetrics and Gynecology in Babylon Maternity and Pediatric Teaching Hospital during the period from first of March 2020 to first of November 2020. The research included 100 pregnant women in their first trimester, ranging from 6-8 weeks, 50 of whom had light vaginal bleeding with or without lower abdomen discomfort and no cervical dilatation. Clinical symptoms and foetal heart activity on a Philips HD 11XE (Japan) abdominal or trasvaginal ultrasound confirmed impending miscarriage. The other 50 healthy pregnant women (control group) were symptom-free and ultrasound-viable. Because to follow-up losses, 47&45 participants remained. History and physical assessment selected patients. The questionnaire predicts risk factors based on age, LMP, gravidity and parity, prior miscarriage, symptoms at presentation, gynaecological history, past medical history, family history, and medication history. **Inclusion criteria**: Pregnant women in the first trimester, Singleton pregnancy, Dating confirmed. **Exclusion criteria**: Previous history of Congenital anomaly, Family history of chromosomal anomalies, known case of chronic diseases (coronary artery disease, chronic kidney disease, type II DM, hypertension, connective tissue disorder and thyroid dysfunction), Conception by assisted reproductive technique, Multiple pregnancies, Smoking. Ultrasound scan was performed for all patients and the control group. All patients and controls were followed-up until 20 weeks of gestations to determine those who miscarry or continue pregnancy beyond 20 weeks. Following history, physical examination, and ultrasound confirmed diagnosis, 5 ml of venous blood was taken using a gel tube and left to clot for 10-20 minutes at room temperature. Centrifuge at 2000 RPM for 20 minutes and store sera at -20°C until analysis. An ELISA KIT assessed serum PAPP-A. Maternal serum PAPP-A levels were assessed in nanogram/milliliter and translated into multiples of median MoM by dividing each result (ng/ml) from stored serum samples for each gestational age by the median marker level at that age. MoM numbers, rather than absolute levels, standardise data from diverse labs' tests and procedures.[21] SPSS 26 performed the statistical analyses. Continuous data were mean ± SD. Absolute numbers and percentages represent categorical variables. Kolmogorov-Smirnov test determined data normality. The Independent Samples T Test and Mann-Whitney U Test were used to compare continuous variables. A receiver operator characteristic (ROC) curve was utilised to analyse the PAPP-A level in identifying threatening miscarriage outcomes (spontaneous miscarriage) and determine its sensitivity, specificity, and appropriate cut-off value. Classified variables.

RESULTS

Our investigation found no significant differences in maternal ages between patients with threatening miscarriage (26.26±2.94) and controls (27.24±4.195), p-value=0.517. Parity was not significant, p-value 0.051, and most were nulliparous. Threatened miscarriage patients and the control group had similar gestational ages, p-value 0.6, and more than 50% were 8 weeks. These two groups differed in prior miscarriage, p-value 0.033. Case group had 36% miscarriage history, control group 15%. Table (1) listed demographics of examined groups.

Table 1: The Demographic criteria of case and control groups.

Parameters		Case(n = 47)	Control (n=45)	*P* value
Maternal age(mean±SD)		**26.26±2.94**	**27.24±4.195**	**0.517****
Gestational age(weeks)	6-6+6 weeks	8(17%)	11(24.4%)	0.6*
	7-7+6 weeks	15(31.9%)	11(24.4%)	
	8-8+6 weeks	24(51.1%)	23(51.1%)	
Parity	nullipara	32(68.1%)	22(48.9%)	0.051*
	1	11(23.4%)	10(22.2%)	
	2	4(8.5%)	13(28.9%)	
Previous miscarriage	0	30(63.8%)	38(84.4%)	
	1	14(29.8%)	7(15.6%)	0.033***
	2	3(6.4%)	0(0%)	

*Pearson's chi-squared test
**Mann-Whitney U Test
***Fisher's Exact Test

Five from 47 patients with threatened miscarriage had pregnancy failure while the other 42 patients and all patients in control group had pregnancies that progress beyond 20 weeks of gestations.as showed in figure (1).

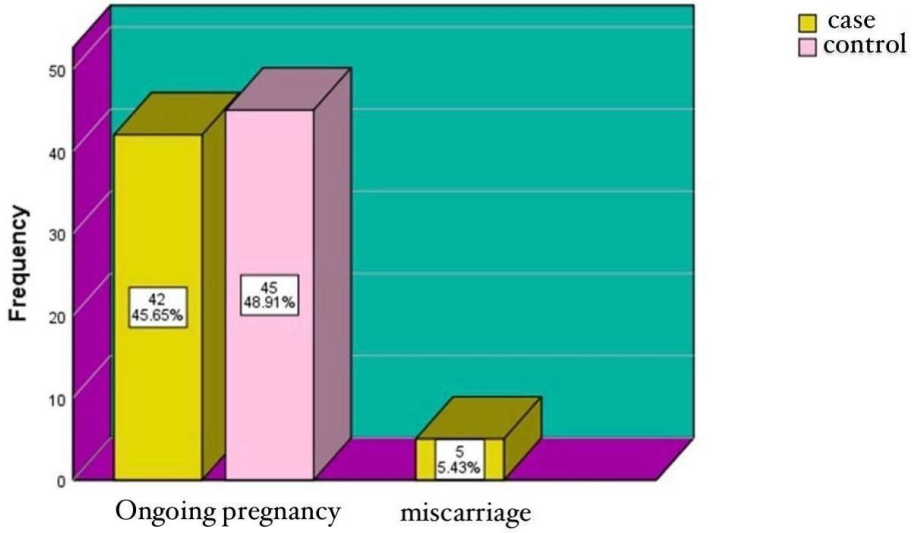

Figure 1: Distribution of fate of pregnancy in both case and control.

Serum PAPP-A level was compared between cases and controls. No significant difference in PAPP-A level was observed between cases (1.07±0.218) MOM and controls (1.05±0.198) MOM, P-value =0.944.

Table 2: PAPP-A level in case and control groups.

Study group	Mean ± Standard deviation(MOM)	*P* value
Case (n = 47)	1.07±0.218	0.944*
Control (n = 45)	1.05±0.198	

*Mann-Whitney U Test

Within case group, another comparison was performed between cases who continue their pregnancy until 20 weeks and those who ended with miscarriage regarding PAPP-A level. No significant difference was observed between cases that continued their pregnancies (1.056±0.218) MOM and cases ended with miscarriage (1.188±0.2) MOM, p-value 0.204, as show in table (3)

Table 3: PAPP-A level in case group according to fellow up results.

Threatened pregnancy	Mean ± Standard deviation	(MOM)	*P* value
Ongoing pregnancy(n = 42)	1.056±0.218		0.204
Miscarriage (n = 5)	1.188±0.2		

Another association was studied between the PAPP-A level and the gestational age, no significant difference was observed between the gestational age and PAPP-A level, p-value 0.92.

Table 4: Association of PAPP-A level with gestational age.

Parameters	Gestational age (6-6+6weeks)	Gestational age (7-7+6weeks)	Gestational age (8-8+6weeks)	*P value
PAPP-A Mean ± SD	1.05±0.158	1.05±0.219	1.08±0.239	0.92

*Mann-Whitney U Test

To differentiate women who had pregnancy failure from those who had progressed pregnancy to 20 weeks, ROC curve was constructed based on 47 patients with threatened miscarriage and showed area under the curve of 0.729 (95% CI, 0.545-0.912) with optimized cut-off value of 1.042. This cut off value gave 80% sensitivity and 69% specificity, positive predictive value (PPV) of 24% and negative predictive value (NPV) of 97%, as showed in table (4) and illustrated in figure (2).

Table 5: Predictive accuracy of PAPP-A in threatened pregnancy outcome.

Marker	Optimal Cut-off value (MOM)	area under curve (95% CI)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
		0.729	80%	69%	24%	97%
PAPP-A	1.042	(0.545-				
		0.912)				

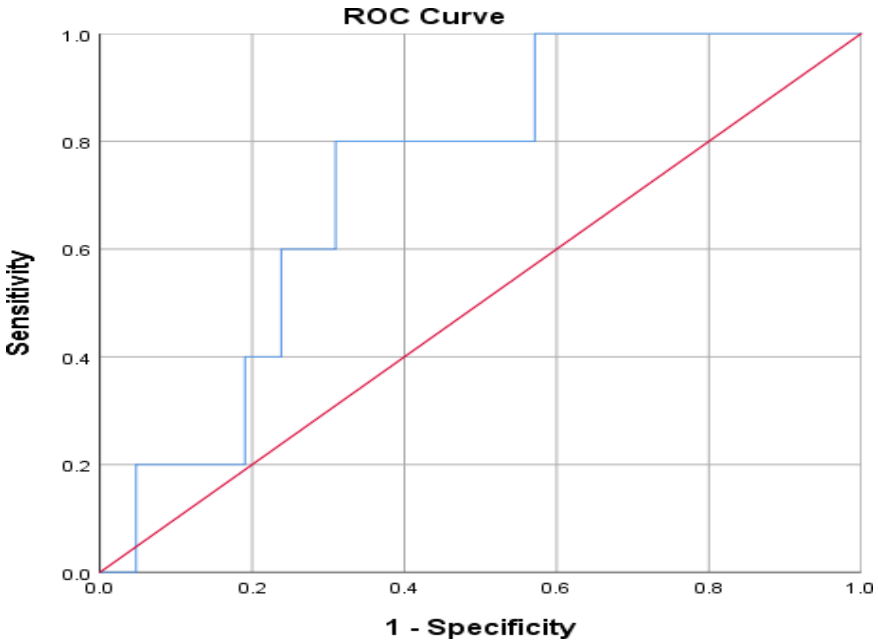

Figure 2: Receiver operating curves for PAPP-A in threatened pregnancy.

DISCUSSION

Pregnancy often causes threatened miscarriage. Several patients miscarried again after ultrasound viability confirmation. A sensitive and specific biomarker might help women avoid emotional trauma by predicting pregnancy outcomes.[20] This research examined the predictive power of serum PAPP-A in threatening miscarriage women. Several investigations have used blood hCG, progesterone, activin A, and inhibin A to predict imminent miscarriage.[22] These investigations have different cut-off values, sensitivity, and specificity. PAPP-A has been shown to predict miscarriage in recent research.[23] This research found no significant difference between factors (gestational age, maternal age and parity). Hanita et al revealed no significant link between maternal age, gravidity, and parity.[20] In our investigation, serum PAPP-A levels did not vary between normal pregnancy (1.05 ± 0.198) MOM and impending miscarriage (1.07 ± 0.218), p value 0.944, or between patients that continued their pregnancy until 20 weeks (1.056 ± 0.218) or terminated by miscarriage (1.188 ± 0.2), p value 0.204. Hadizadeh-Talasaz Z et al. agree at 2020 which found no link between PAPP-A and pregnancy loss.[24] Quattrocchi et al. conducted a retrospective case–control research between 8th and 11th weeks of pregnancy to determine whether low first-trimester PAPP-A levels are related with unfavourable pregnancy outcomes. Only miscarriages, gestational hypertension, and preeclampsia (PE) changed across groups[25], contradicting our conclusion. Our findings

correspond in part with Hanita et al, which likewise revealed no significant difference in PAPP-A levels between cases and controls, although that study reported considerably low PAPP-A levels in impending miscarriage patients, which contradicts our study.[20] In the 2020 Shah et al. research, spontaneous miscarriage was greater.[27] Karim et al indicated that women with low serum PAPP-A were 5.0 times more likely to miscarry or have a stillbirth than those in the control group.[26] In 2020, Shah et al. discovered no significant association between PAPP-A levels and gestational age[27] also supported a 2015 Quattrocchi et al. research that found no link between PAPP-A levels and gestational age.[25] PAPP-A threshold values for poor pregnancy outcomes varied between research. Our study's cut-off was 1.042 MOM. Hanita et al. discovered a 0.66 cut-off value for pregnancy failure.[20] In 2014, Imcha et al. reported that low levels less than 0.4 MOM were descriptive of inadequate early placentation and might be an independent risk factor for problems linked with bad obstetric outcomes.[28] Karim et al. (2011) found the same PAPP-A cutoff value to predict unfavourable pregnancy outcomes.[26] Different PAPP-A measuring methods may explain cut-off values. Most studies employed automated immunoassay. Our investigation employed precise ELISA technique. Several studies found varied sensitivity and specificity for PAPP-A prognosis. Our research demonstrated 80% sensitivity and 69% specificity. Hadizadeh-Talasaz Z et al. obtained 57% sensitivity and 83% specificity in 2020. In their 2016 systematic review, Pillai and colleagues showed that PAPP-A had a low sensitivity (25–64%) but good specificity (88–94%).[29] Our sensitivity and specificity results differed. Balcı (2016) studied 158 singleton pregnancies till delivery with regard to PAPP-A levels at 11–14 weeks. The PAPP-A cutoff point of 0.72 MOM had 82.4% sensitivity and 29.8% specificity for poor pregnancy outcomes.[30] The ROC curve shows the prediction capacity and sensitivity of impending miscarriage outcomes precision and cut-off. Sensitivity vs. specificity. ROC analysis determines AUC. Our research's AUC was 0.729, similar to Hadizadeh-Talasaz Z et al, which had an AUC of 0.85.[24]

CONCLUSION

No significant difference in PAPP-A levels between normal pregnancy and threatened miscarriage groups. PAPP-A cannot be recommended for predicting fetal loss in patient with threatened miscarriage. The cutoff values of PAPP-A to predict miscarriage was 1.042 MOM.

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