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Maternal Serum Alpha Feto Protein Level May Predict Morbidly Adherent Placenta in Women with Placenta Previa

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Abstract

Background In situations of a morbidly adherent placenta, studies have shown that maternal serum alfa feto protein (AFP) is clinically high.

Objective To examine the association of morbidly adherent placenta (MAP) in pregnant women with placenta previa (PP) and their serum AFP biomarker.

Methods A prospective observational study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk, Iraq during the period from Feb. till Nov. 2019. It included 82 pregnant women those between 14-20 weeks of gestation with singleton pregnancy, viable fetus, and diagnosed with low lying placenta, with and without vaginal bleeding. A blood sample from all women was taken to investigate for serum AFP level after confirming the diagnosis of low-lying placenta by early abdominal ultrasound (U/S) scan. All the enrolled pregnant women were followed by Doppler U/S at gestational age 28-32 weeks, underwent targeted screening for MAP and were divided into two groups according to the status of placenta: MAP group included 11 pregnant women and PP group alone included 71 pregnant women.

Results In this study, MAP was diagnosed in 13.4% of cases. Mean of serum AFP biomarker in women with MAP was significantly higher than that in women with PP. Serum AFP biomarker in early pregnancy >200 ng/ml is predictive for diagnosis of MAP in late pregnancy.

Conclusion Maternal serum AFP biomarker may play an important role at early pregnancy in prediction of placental adherence at late pregnancy in cases of early low-lying placenta.

Keywords Morbidly adherent placenta, alpha feto protein, previa, pregnancy, Iraq

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List of abbreviations: AFP = Maternal serum α-fetoprotein, AUC = Area under curve, BMI = Body mass index, C/S = Cesarean section, DCR = Damage control resuscitation, MAP = Morbidly adherent placenta, MRI = Magnetic resonance imaging, PP = Placenta previa, ROC = Receiver operating characteristics, SPSS = Statistical package for social sciences, TAS = Transabdominal sonography, TVS = Transvaginal sonography, U/S = Ultrasound

Introduction

The morbidly adherent placenta previa (MAP) (placenta accreta, increta, and percreta) is a developing obstetric issue, and a link has been found between this kind of placentation and previous lower segment cesarean section [(1)]. It is one of the most dangerous pregnancy problems. Women with a morbidly adherent placenta have been documented to have maternal morbidity in up to 60% of cases and mortality in up to 7% of cases. Another risk factor is the mother's age. The increased rate of caesarean births around the world has resulted in an increase in the incidence of both placenta previa (PP) and MAP [(2)]. The term "placenta accreta" refers to the

trophoblastic attachment of the placenta to the myometrium without the presence of an intervening decidua. A placenta increta occurs when the trophoblast invades the myometrium, and a percreta occurs when the trophoblast invades the myometrium beyond the serosa and into neighboring structures such as the bladder. The word "placenta accreta" is frequently used to describe a wide range of disorders, including accreta, increta, and percreta, as well as cases of clinically evident MAP [3,4]. The incidence of placenta accreta varies from 1 in 300 to 1 in 2000 pregnancies. This large range of results could be due to diagnostic challenges (histopathology) in distinguishing between difficult manual removal and abnormally attached placentas [5]. Currently, the prenatal course of women with MAP is compared to that of women with PP. The ability to diagnose MAP antenatally using imaging [ultrasound (U/S) color Doppler and magnetic resonance imaging (MRI)] allows for multidisciplinary planning in the hopes of reducing maternal and newborn morbidity and mortality. Interventional radiological techniques aid in the preservation of the uterus and thus the patient's future reproductive prospects [2]. The traditional surgical therapy for MAP is a intrapartum hysterectomy following the delivery of the fetus through an upper segment incision that leaves the placenta in place, however conservative treatment, particularly in women who want to preserve their reproductive potential, is also an option [1]. In addition to the lengthy surgical operations necessary, MAP is linked to significant bleeding during birth, which frequently necessitates substantial blood transfusions, putting the mother at risk for hypothermia, acidosis, and coagulopathy, among other catastrophic problems [6]. Recently, resuscitation in MAP shifted toward Damage Control Resuscitation (DCR) protocols, which is used in massive trauma and consists of three steps: abbreviated surgery to control the hemorrhage and contamination, resuscitation in the intensive care unit, and planned re-operation with definitive surgery. This protocol includes early use of packed red blood cell and fresh frozen plasma in 1/1 ratio to avoid over-infusion with crystalloids [6]. Doppler U/S has been a standard practice for a long time. It is a simple, precise, and safe method to visualize the placenta that can often be used in conjunction with transvaginal sonography (TVS) when available [7]. In cases of suspected PP on transabdominal sonography (TAS), the patient should undergo TVS to more accurately delineate the relationship between the placenta and the endocervical os [3]. Maternal serum alpha fetoprotein (AFP) is being utilized to predict fetal quality. It is among the most widely used diagnostic biomarkers, based on its use for screening for malignancies and prenatal abnormalities. Its presence in the amniotic fluid could indicate anencephalus or neural tube abnormalities. Furthermore, studies have shown that in situations of a MAP, maternal serum AFP is clinically high, and it is a secondary indicator of PP [8].

The aim of this study was to examine the association of MAP in pregnant women with PP and their serum AFP marker.

Methods

Study design, setting, and time

This was a prospective observational study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk, Iraq, during the period of 10 months from February till November 2019.

Study population and sample size

The study included initially 96 pregnant women between 14-20 weeks gestational age, first attended the outpatient clinic or the emergency department with singleton pregnancy, viable fetus, and diagnosed with low lying placenta, with and without vaginal bleeding. Patients who had fetus with aneuploidies, neural tube defects, abdominal wall defects, patients with multiple pregnancy, maternal hepatic disease, and maternal ovarian cancer were excluded from the study.

Gestational age was calculated at the time of presentation according to first day of last menstrual period and confirmed by early abdominal U/S examination as having low-lying placenta at gestational age 14-20 weeks and blood was taken for AFP examination at first visit then they followed up by abdominal U/S scan at 2nd visit for checking the persistence of PP between 24-27 weeks gestation, then after by Doppler U/S in 3rd visit at 28-32 weeks Gestation. Fourteen participants were lost to follow up, so the total number of participants included in the analysis was 82. All the patients signed an informed consent that allows us to review their medical records for research purposes as long as the patient anonymity and confidentiality of their medical records are maintained. Detailed history by questionnaire, obstetrical history, past medical and surgical histories were taken for all patients. Information about previous pregnancies (number, abortion, outcome, and mode of delivery either vaginal delivery or cesarean section) were taken. Ultrasound findings (2D U/S, Color Doppler U/S) as position of the placenta and grade of PP were recorded. A general (vital signs) and abdominal examinations were done for all study patients.

Sample collection and serum AFP marker test procedure

A five ml of blood was drawn from the volar surface of the forearm from all study participants at presentation to test for serum AFP marker. The test used the sandwich immunodetection method; the detector antibody in buffer binds to antigen in sample, forming antigen-antibody complexes. The cut-off (reference range): ≤10.9 ng/ml.

Follow up

All the enrolled pregnant women were followed up by U/S and Doppler U/S in 3rd visit at gestational age between 28-32 weeks, underwent targeted screening for morbidly adherent placenta and were divided into two groups according to the status of placenta:

1. MAP group: Included 11 pregnant women diagnosed with morbidly adherent placenta during the 3rd trimester of pregnancy or during delivery.
2. PP group: Included 71 pregnant women diagnosed with PP.

Diagnosis of MAP

It was done by:

- U/S study which was performed by experienced ultra-sonographer in Azadi Teaching Hospital and reported findings associated with placental invasion in the 2nd and 3rd trimesters (gray-scale abdominal U/S) [9] include:
  1. The presence of PP.
  2. Echolucent space between the placenta and uterus with myometrial thinning.
  3. Multiple placental lacunae.
  4. Extension of the villi into the myometrium or beyond.
  5. Interruption of the posterior bladder wall-uterine interface.
  6. Hypervascularity of the adjacent bladder wall.
  7. Decreased retroplacental space (less than 1 mm).
- Color Doppler findings associated with MAP include [9,10]:
  A. Turbulent lacunar blood flow.
  B. Increased subplacental vascularity.
  C. Vessels bridging the placenta to the uterine margin, and gaps in myometrial blood flow.

The sensitivity and specificity of both 2nd- and 3rd-trimester U/S for the identification of MAP has been reported to be as high as approximately 80-90% [9,10].

Statistical analysis

The data analyzed using statistical package for social sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Receiver operating characteristic (ROC) curve analysis was constructed for serum AFP marker level as a predictor of MAP. Pearson's correlation test

(r) was used to assess correlation between continuous variables accordingly. A level of P – value less than 0.05 was considered significant.

Results

Study participants' age was ranging from 19-42 years with a mean of 31.8±6.3 years. The highest proportion of study participants was aged ≥35 years (40.2%), 41.5% were presented <18 weeks of gestation; 47.6% of them had more than three children; 47.6% were obese; 11% were current smokers, and 8.5% were hypertensive (Table 1).

The rate of previous C/S in MAP was higher than PP alone but this difference was not significant (P= 0.201) as shown in table (2).

Table 1. Distribution of study participants by general characteristics

Variable		Number	Percentage
Age (Year)	<25	19	23.2
	25-34	30	36.6
	≥35	33	40.2
Parity	Nulliparous	12	14.6
	1-3	31	37.8
	>3	39	47.6
Gestational age (weeks)	> 18	34	41.5
	$18\text{-}27^{+6}$	32	39.0
	28-32	16	19.5
Smoking	Yes	9	11.0
	No	73	89.0
BMI Level	Normal	16	19.5
	Overweight	27	32.9
	Obese	39	47.6
Medical history	No	71	86.6
	Hypertension	7	8.5
	Diabetes Mellitus	4	4.9
Type of placenta	Morbidly adherent placenta	11	13.4
	Placenta Previa	71	86.6

N=82, BMI=Body mass index

Table 2. Association between status of placenta and previous cesarian section

Previous cesarian section	Morbidly adherent placenta N=11 N (%)	Placenta Previa N=71 N (%)	Total N=82 N (%)	P Value
Yes	8 (72.7)	37 (52.1)	37 (45.1)	0.201
No	3 (27.3)	34 (47.9)		

Means of parity and serum AFP marker in women with MAP were significantly higher than that in women with PP (5.92 versus 2.24 weeks, P= 0.001; and 286.34 versus 134.1 ng/ml, P= 0.001 respectively). No significant differences (P ≥ 0.05) in means of age and BMI between study groups as shown in table (3).

Table 3. Comparison in certain parameters according status of placenta

Variable	Morbidly adherent placenta N=11 Mean±SD	Placenta Previa N=71 Mean±SD	P value
Maternal age (years)	33.5±5.2	30.9±6.7	0.084
BMI (kg/m^2)	31.22±4.8	29.6±5.2	0.176
Parity	5.92±1.27	2.24±1.7	0.001
Serum AFP marker (ng/ml)	286.34±52.3	134.1±81.0	0.001

BMI=Body mass index, AFP=Alpha feto protein

ROC curve analysis was constructed for serum AFP marker level as a predictor of MAP. As shown in figure (1), the cut point of serum AFP marker was 200 ng/ml, so serum AFP marker in early pregnancy >200 ng/ml is predictive for diagnosis of MAP in late pregnancy as a large significant area under the curve (AUC = 91.8%) indicating significant association between higher level of serum AFP marker and diagnosis of MAP. The sensitivity was 100% and the specificity was 85.2%.

No significant correlations (P ≥ 0.05) between AFP marker and both of age and BMI as shown in table (4).

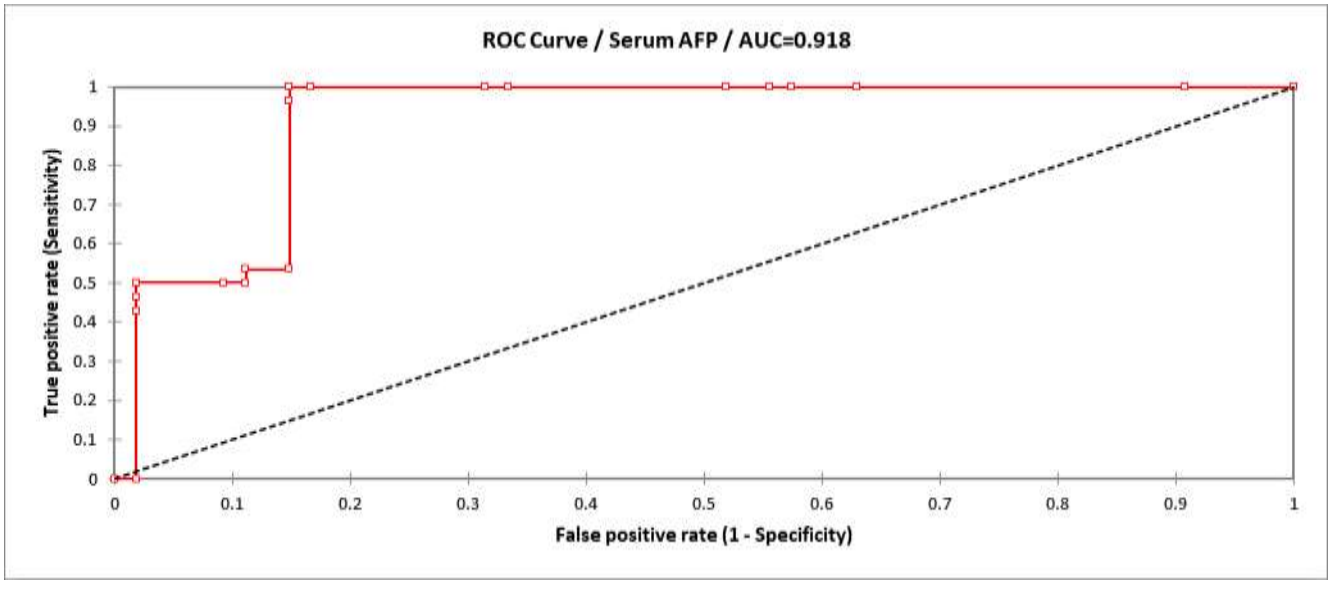

Figure 1. ROC curve for AFP as a marker of MAP

Table 4. Correlation between AFP marker and both of age and body mass index

Variable	AFP (ng/ml)	
	r	P value
Age (Year)	- 0.06	0.595
BMI (kg/m^2)	0.064	0.566

BMI=Body mass index

Discussion

MAP is becoming a more common pregnancy complication, owing to an increase in the rate of C/S during the last 50 years [11]. It is the most frequent indication for peripartum hysterectomy [12]. Furthermore, preterm birth and fetuses that are small for gestational age increase the risk of perinatal problems [13]. Antenatal diagnosis of accreta is critical, as it can reduce maternal morbidity by enabling for a scheduled delivery [14]. Elevated maternal-serum AFP and beta-human chorionic gonadotropin (β-HCG) levels in the second trimester have been linked to MAP [15]. In the current study, MAP was diagnosed in 13.4% of cases, and 86.6% were diagnosed as PP alone, mean of parity was significantly higher in MAP group compared to PP group, and no significant differences in means of age and BMI between study groups. Differently, lower results observed in Lyell et al. study in 2015, in which patients with MAP represented only 5% of the study patients [8]. Results of studies conducted by Berezowsky et al. in 2019 [16] and by Farquhar et al. in 2017 [17] were disagreed to this study results when observed that women with pathological placentation in the form of placenta accreta were more likely to be older. Sample size enrolled in each study, gestational age at presentation, parity, previous cesarean or pelvic surgery and obstetrical morbid conditions can have explained the differences observed among above studies.

In the present study, no significant associations (P = 0.201) between status of placenta and previous C/S, which disagreed by and by Chattopadhyay et al. study in 1993 [18] and Shi et al. study in 2018 [19] when demonstrated that C/S was associated with significantly increased risk of placenta accreta in a subsequent pregnancy complicated with PP. The association between C/S and placental pathology can explained by fact that a uterus during labor has been subjected to contractions, which might shorten the wound, diminish damage to the endometrium, and render the tissue with more potential for healing [20].

In the current study, mean of serum AFP marker in women with MAP was significantly higher than that in women with PP and serum AFP marker in early pregnancy >200 ng/ml is predictive for diagnosis of MAP. Furthermore, no significant correlation between AFP marker and both of age and BMI. These results agreed with results found by Lyell et al. study in 2015 (8), Dreux et al. study in 2012 [15] and Berezowsky A et al study in 2019 [16] when they found that risk for MAP was associated with higher level of maternal-serum AFP. In a small subset of patients at high risk, serum indicators may provide further information (In the second trimester, an unexplained elevation of maternal serum AFP, β-HCG, and/or inhibin-A or a decreased level of maternal serum AFP and/or unconjugated estriol are associated with an increased frequency of adverse obstetrical outcomes). Elevated maternal serum AFP levels in the second trimester have been linked to MAP. Its overexpression could be linked to high levels of placental invasion and MAP. While it isn't known to be linked to poor obstetrical outcomes [21].

In conclusion, maternal serum AFP biomarker may play an important role at early pregnancy in prediction of placental adherence at late pregnancy in cases of early low-lying placenta, ± vaginal bleeding. In women with a low-lying placenta and vaginal bleeding, the maternal serum AFP biomarker represents an early, non-

invasive, and good predictor of MAP that can be used if further investigations confirm it.

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Author contribution

Dr. Ghalib: Put the research plan. Dr. Hassan: Did the sampling, wrote the manuscript and did the statistical work.

Conflict of interest

The authors declare there is no conflict of interest.

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