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Original Research

Elevated Second Trimester Alpha-Fetoprotein Increases the Risk of Placenta Accreta

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Abstract

Background: Placenta previa-accreta constitutes an increasing clinical problem, whose diagnosis remains challenging in obstetrics. The current work aimed to assess whether second-trimester serum alpha-fetoprotein (AFP) amounts are altered in pregnant women with placenta previa-accreta versus control values. **Methods**: A retrospective chart review was performed for 504 pregnant women treated between 1 January 2016 and 28 February 2021. This cohort included 105 placenta previa-accreta and 122 placenta previa control cases, as well as 277 body mass index (BMI)-matched individuals with healthy pregnancy. The multiple of the median (MoM) for AFP was obtained from clinical records. **Results**: Markedly elevated MoM for AFP was detected in the placenta previa-accreta group compared with the placenta previa control and healthy pregnant control groups (both $p < 0.001$). Serum AFP levels had a significant positive association with placenta accreta after adjustment for age, BMI, and gestational week at blood collection ($\beta = 0.60$; 95% confidence interval [95% CI]: 0.52, 0.68; $p < 0.001$). In addition, previous cesarean delivery history ($\beta = 3.41$; 95% CI: 2.18, 5.34; $p < 0.001$) also had a significant association with placenta accreta. **Conclusions**: Elevated second-trimester serum AFP had a positive association with placenta accreta. Such finding suggests a potential role for AFP in detecting pregnancies at high-risk of placenta accreta. This second-trimester biomarker of AFP may help classify women into the high- and low-risk groups for placenta accreta. In addition, we have validated a previous history of cesarean section as a risk factor for accreta in patients with placenta previa.

Keywords: alpha-fetoprotein AFP; placenta accreta; second trimester serum; association

1. Introduction

Placenta accreta features an abnormal invasion of the placenta into, but not beyond, the myometrium. Placenta accreta, a serious obstetric complication, carries significant risks for the mother and the offspring, including excessive hemorrhage, serious bleeding, shock, uterine perforation, secondary infection, and even death [1]. Its incidence currently shows an increasing trend worldwide [2]. According to recent reports, placenta accreta affects 0.91% of pregnant women, which indicates a significant increase from 0.12% to 0.31% over the past 30 years [3,4]. In addition, invasive placenta has evolved into an important issue in obstetrics, killing about 7% of the affected individuals [4].

Severe hemorrhage can be life threatening, and often a hysterectomy is required [5,6]. Due to substantial morbidity and adverse outcomes related to placenta accreta, correct prenatal diagnosis before the onset of symptoms is essential. Obtaining an accurate diagnosis would facilitate delivery at a tertiary institution with the help of multidisciplinary experts, which is crucial for managing placenta accreta. Currently, prenatal diagnosis of placenta accreta is mostly carried out with high-resolution ultrasound and magnetic resonance imaging (MRI). Despite recent advances in imaging methods, including the development of high-resolution ultrasound and MRI, the diagnosis of placenta accreta remains greatly challenging in clinic [7]. In addition, the diagnostic accuracies of MRI and other imaging tools in placenta accreta remain controversial, as their sensitivities and specificities range from 33% to 93%, and 71% to 100%, respectively [7–10]. Nevertheless, many patients may not have an opportunity to receive an antenatal examination in a high-risk prenatal diagnosis center [11–13]. Therefore, it is urgent to improve the detection of pregnancies that are specifically at high-risk for placenta accreta with a sensitive and convenient prenatal diagnostic mode. Various studies have previously assessed the potential risk factors and predictive markers of some adverse outcomes [14–16].

Maternal serum markers may help improve prenatal diagnosis in placenta accreta. Further, an early understanding of the potential risk may contribute to interpretation accuracy for data generated by these imaging tools, thereby improving pregnancy outcomes. Alpha-fetoprotein (AFP), an important circulating protein synthesized during human gestation, represents an excellent biomarker of many adverse pregnancy outcomes, e.g., preeclampsia, placental abruption, and preterm delivery [17]. However, the association of second-trimester serum AFP levels with placenta accreta remains unclear. Therefore, we aimed to assess the association of a second-trimester serum marker (AFP) with placenta accreta in this study.

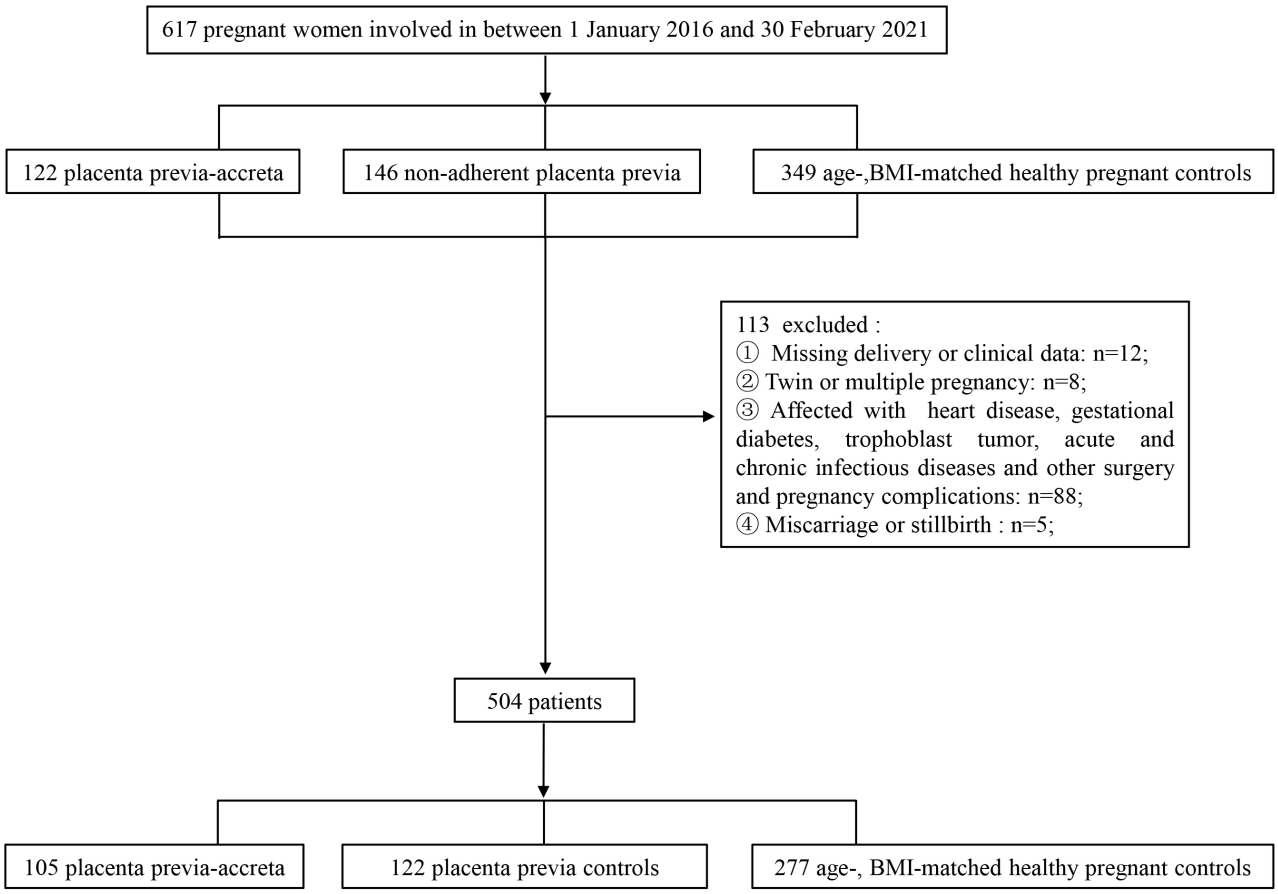

Fig. 1. Study flowchart. BMI, body mass index.

2. Materials and Methods

2.1 Study Design

A retrospective review was carried out at the Obstetrics Department of the affiliated hospital of Jining Medical University over a 5-year period (1 January 2016 to 28 February 2021). A total of 617 participants were enrolled per the eligibility criteria below prior to screening. Inclusion criteria were as follows: (1) In the placenta previa-accreta group, pregnant women with prenatal diagnosis of placenta previa by ultrasound, and subsequently as placenta accreta by histological assessment according to the Federation International of Gynecology and Obstetrics (FIGO) criteria. (2) In the placenta previa controls (non-adherent placenta previa group), placenta previa was detected by ultrasonography, but with no adhesion abnormalities developing later. (3) Normal pregnant controls group were pregnant women whose age- and body mass index (BMI)-matched to placenta accreta and previa (Fig. 1). Exclusion criteria included: (1) pregnant women with gestational diabetes, trophoblast tumors, acute or chronic infection, and further surgical and pregnancy complications; (2) twin/multiple pregnancy; (3) missing delivery or clinical data; (4) miscarriage or stillbirth (Fig. 1). In brief, 504 cases were finally examined, of which 105 placenta previa-accreta, 122 placenta previa control, and 277 BMI-matched, healthy pregnant control cases. Pregnancy dating was determined from the last menstrual period. All pregnant women in the study were tested for maternal serum AFP levels during the second trimester, as requested by their attending doctors. Blood sample collection was performed at pregnancy week 17 of gestation. Multiple of the median (MoM) values for second-trimester serum AFP were obtained from the laboratory data files of the Affiliated Hospital of Jining Medical University. Additionally, maternal information, including maternal demographic, obstetrical, and medical histories, were retrieved from the data system of medical records. To protect patient privacy, this report did not include participants' identifiable data. The study had approval from the Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China) (2023-08-C001).

2.2 Statistical Analysis

Continuous variates with normal skewed distributions were presented by mean ± standard deviation and medium (range), respectively. Categorical variates were presented as number (frequency or percentage). The χ^2 test (categorical variates), one-way ANOVA (normally distributed con-

Table 1. Baseline characteristics of subjects.

Characteristic	① Placenta previa-accreta (n = 105)	② Placenta previa controls (n = 122)	③ Healthy pregnant controls (n = 277)	$p^{\#}$ value	p^{*} value
Age (years)[a]	30.83 ± 4.75	30.13 ± 5.21	29.62 ± 4.12	p = (①–②) = 0.590 p = (①–③) = 0.036 p = (②–③) = 0.838	0.208
Height (cm)[a]	162.37 ± 4.41	162.75 ± 4.70	163.10 ± 4.32	p = (①–②) = 0.547 p = (①–③) = 0.242 p = (②–③) = 0.845	0.523
BMI (kg/m^2)[a]	28.15 ± 4.33	28.08 ± 4.53	28.12 ± 3.38	p = (①–②) = 0.889 p = (①–③) = 0.976 p = (②–③) = 0.825	0.988
Gestational week at time of blood sampling (weeks)[a]	17.10 ± 1.07	17.11 ± 1.05	17.16 ± 0.76	p = (①–②) = 0.776 p = (①–③) = 0.032 p = (②–③) = 0.996	0.015
Delivery pregnancy week (weeks)[a]	37.63 ± 2.43	36.98 ± 3.25	38.88 ± 1.60	p = (①–②) = 0.137 p = (①–③) < 0.001 p = (②–③) < 0.001	<0.001
Neonatal weight (kg)[a]	3.06 ± 0.60	3.02 ± 0.76	3.35 ± 0.49	p = (①–②) = 0.931 p = (①–③) < 0.001 p = (②–③) < 0.001	<0.001
Previous cesarean section history[a]	67 (63.81%)	43 (35.25%)	93 (33.57%)	p = (①–②) < 0.001 p = (①–③) < 0.001 p = (②–③) = 0.975	<0.001
AFP MoM[b]	1.49 ± 0.54	0.97 ± 0.52	0.98 ± 0.60	p = (①–②) < 0.001 p = (①–③) < 0.001 p = (②–③) = 0.909	<0.001
Vaginal bleeding[a]	43 (40.95%)	52 (42.62%)	23 (8.30%)	p = (①–②) = 0.799 p = (①–③) < 0.001 p = (②–③) < 0.001	<0.001
Blood transfusion[a]	34 (32.38%)	13 (10.66%)	3 (1.08%)	p = (①–②) < 0.001 p = (①–③) = 0.001 p = (②–③) = 0.909	<0.001
Cesarean hysterectomy at the time of delivery[a]	2 (1.90%)	0 (0.00%)	0 (0.00%)	p = (①–②) = 0.547 p = (①–③) = 0.075 p = (②–③) = 0.909	0.043

[a], normally distributed variates shown as mean ± standard deviation (SD); [b], skewedly distributed variates presented as median (Min-Max); categorical data are shown as number and percentage (n, %); One-way ANOVA (Bonferroni correction) was utilized for data analysis; p^{*} and $p^{\#}$ are among and between groups, respectively; AFP, alpha-fetoprotein; MoM, multiple of the median; BMI, Body Mass Index. $p < 0.015$ was deemed to indicate statistical significance.

tinuous variates), or the Kruskal-Wallis H test (skewedly distributed continuous variates) were performed for analysis, as applicable. Data analysis utilized R 4.0 (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA, USA). Binary logistic regression with single and multi-categorical predictors was utilized to identify potential risk factors for placenta accreta, determining 95% confidence intervals (95% CIs). $p < 0.05$ indicated statistical significance.

3. Results

3.1 Baseline Clinical Data and Maternal Serum AFP

A total of 504 pregnant women were examined, including 105 placenta previa-accreta, 122 placenta previa control, and 277 BMI-matched healthy pregnant control cases. Table 1 lists patient features, including clinical history, demography, and laboratory indexes, as well as MoM values for AFP, in all three study groups. Similar values were obtained for age, height, BMI, gestational week at blood collection, and the rate of cesarean hysterectomy at

Table 2. Categorical variable logistic linear regression of various variables for their associations with placenta accreta.

Covariate	β (95% CI)	OR	*p*-value
Age (years)	0.47 (–0.27, 1.22)	1.60	0.211
Weight (kg)	1.10 (–1.05, 3.25)	3.00	0.318
BMI	0.04 (–0.80, 0.87)	1.04	0.931
Gestational week at blood collection (week)	–0.04 (–0.23, 0.15)	0.96	0.6858
Pregnancy week at delivery (week)	–0.67 (–1.19, –0.15)	0.51	**0.0114**
Neonatal weight (kg)	–0.1 (–0.32, –0.06)	0.90	**0.0047**
Previous cesarean section	3.41 (2.18, 5.34)	30.26	**<0.001**
AFP MoM	0.59 (0.51, 0.67)	1.80	**<0.001**

$p < 0.05$ reflects statistical significance, bold marks significant*p*-values; BMI,body mass index; AFP, alpha-fetoprotein; MoM, multiple of the median; 95% CI, 95% confidence interval; OR, odds ratio.

Table 3. Associations of serum AFP with placenta accreta in multivariable linear regression.

Variable	Crude Model		Adjusted Model	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
AFP	0.59 (0.51, 0.67)	**<0.001**	0.60 (0.52, 0.68)	**<0.001**

Crude model: binary logistic regression with single- and multi-categorical predictive factors was utilized to assess potential risk factors for placenta accreta. Adjusted model: adjustment was made for maternal age, BMI, and gestational week at blood collection; $p < 0.05$ reflects statistical significance, bold marks significant *p*-values. AFP, alpha-fetoprotein.

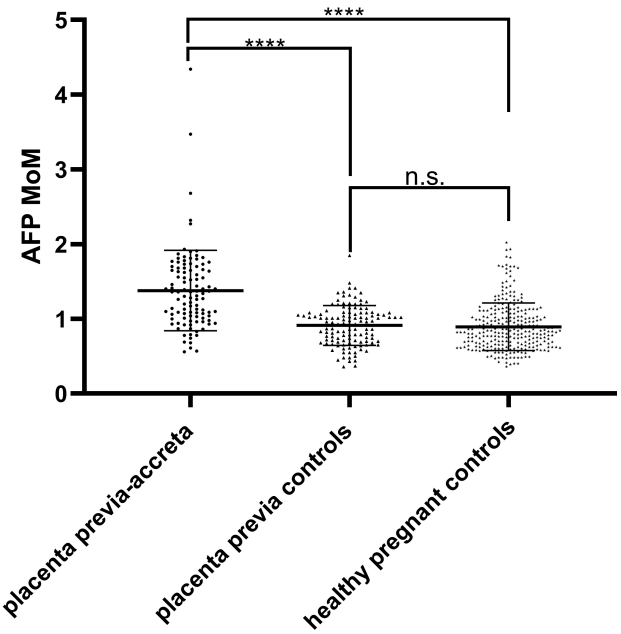

Fig. 2. Levels and distributions of second-trimester serum AFP in the three groups. Data are median and interquartile range. ****, $p < 0.0001$; AFP, alpha-fetoprotein; MoM, multiple of the median; n.s., not significant.

the time of delivery in the three groups. Pregnancy weeks at delivery were markedly reduced in placenta previa-accreta and placenta previa control cases compared with healthy pregnant controls (both $p < 0.001$, Table 1).

A history of previous cesarean delivery had markedly elevated rate in the placenta previa-accreta group compared with healthy pregnant controls and placenta previa controls (both $p < 0.001$, Table 1). Vaginal bleeding had remarkably elevated incidence rates in placenta previa-accreta and placenta previa control cases compared with control cases (both $p < 0.001$). Blood transfusion showed significantly increase incidence in placenta previa-accreta cases compared with the healthy pregnant control and placenta previa control groups ($p = 0.001$ and $p < 0.001$, respectively). The normally distributed MoM for serum AFP was expressed as median (Min–Max) in Table 1. The MoM for median AFP in placenta previa-accreta cases was 1.49, which showed a significant elevation compared with 0.97 and 0.98 in placenta previa controls and in healthy pregnant controls, respectively (both $p < 0.001$; Table 1; Fig. 2).

3.2 Potential Risk Factors for Placenta Accreta

The univariate analysis of the abovementioned parameters and median MoM for AFP is summarized in Table 2. The results revealed that age, weight, BMI, and gestational week at blood collection were not associated with placenta accreta ($p > 0.05$). Univariate analysis also revealed that a history of cesarean delivery ($\beta = 3.41$; 95% CI: 2.18, 5.34; $p < 0.001$) had a positive association with placenta accreta, while neonatal weight ($\beta = –0.1$; 95% CI: –0.32, –0.06; 0.0047) and pregnancy week at delivery ($\beta = –0.67$; 95% CI: –1.19, –0.15; $p = 0.0114$) had negative associations with placenta accreta. The MoM for AFP had a positive association with placenta accreta. In addition, the number of prior

cesarean deliveries was positively correlated with placenta accreta (**Supplementary Table 1**). Our results also showed that the number of prior cesarean deliveries was not associated with serum AFP levels (**Supplementary Table 2**). The median MoM for AFP was further evaluated by multivariable logistic regression analysis (Table 3). The effect size (β) and 95% CI for each index are shown in Table 3. In an unadjusted model, multivariate logistic regression analysis revealed that elevated serum AFP levels had a significant positive association with placenta accreta (β = 0.59; 95% CI: 0.51, 0.67; $p < 0.001$). After adjustment for maternal age, BMI, and gestational week at blood collection, elevated serum AFP levels retained its significant positive association with placenta accreta (β = 0.60; 95% CI: 0.52, 0.68; $p < 0.001$) (Table 3). This indicates that increased AFP levels and a history of cesarean section are major parameters, positively associated with the underlying mechanism of placenta accreta.

4. Discussion

Low AFP is considered an abnormal finding because it increases the risk of pediatric down syndrome. Currently, with advances in prenatal screening tests for biochemical indexes, the association of elevated AFP with poor pregnancy outcomes began to be applied in clinical practice [18,19]. The current study investigated the association of second-trimester serum AFP levels with placenta accreta. The results indicated that generally, incremental AFP levels had a significant positive correlation with placenta accreta. In addition, a history of cesarean delivery was significantly and positively associated with placenta accreta. These findings also demonstrate such a positive association is independent of placenta previa.

Placenta accreta constitutes a serious obstetric disease with a high-risk of serious maternal complications, such as uterine perforation, bleeding, severe infection, and even death [20]. Currently, placenta accreta is diagnosed prenatally by MRI and high-resolution ultrasound. The diagnostic factors include the occurrence of placental lacunae, placenta previa with lost hypoechoic retroplacental interface, and hypervascularity of the interface between placenta and bladder or uterine wall [21,22]. However, the interpretation of the imaging of the above mentioned ultrasonic instrument s remains controversial. Similar to this work, previous studies have estimated the amounts of placental biomarkers in maternal serum might be altered in pregnant women with prior or high-risk of placental accreta [15,18]. AFP, an important tumor-related fetal protein, is utilized as a serum fetal defect/tumor biomarker for monitoring distress or disease progression [23,24], since it is associated with multiple birth defects, malformations, and congenital disorders, such as the neural-tube defects [23]. The MoM for AFP was markedly elevated in placenta previa-accreta cases, compared with placenta previa control and normal pregnant control cases, as shown above. In addition, our results also showed similar serum AFP amounts in placenta previa control and healthy pregnant control cases, suggesting placenta previa is not responsible for elevated serum AFP in pregnant women. Thus, elevated second-trimester serum AFP in pregnancies with placenta accreta can probably be explained by increased mother–fetus exchange, considering that a damaged endometrium may promote placenta accreta, and increased maternal–fetal exchange may release higher AFP amounts into the maternal blood [23,25,26]. Furthermore, a previous study showed that administration of heterologous antibodies against AFP in pregnant mice caused developmental arrest, congenital anomalies, and placental lesions [27–29]. Thus, AFP may be associated with abnormal placental development. In addition, AFP regulates growth in reproductive, placental, and lymphatic cells [30]. Elevated AFP levels may promote proliferation in placental cells, such as placental trophoblastic cells, and may induce abnormal placental invasion into the myometrium. Therefore, factoring serum AFP into risk assessment algorithms might help detect women prone to developing placenta accreta. Moreover, this would allow placenta accreta patients to receive closer and more refined monitoring and treatment. Additionally, race is known to be associated with variations in AFP levels [31]. In the present study, all the pregnant women examined were from China, and other races were not involved. As mentioned below, this is a limitation of this research. Thus, studies examining the relationship between AFP levels and different racial-ethnic populations are required.

Cases of placenta previa-accreta spectrum have been encountered more often because cesarean delivery has been increasingly applied in the last decades [32]. Inhibition of contractions, alleviation of anemia, prevention of infection, and timely termination of pregnancy are the major therapeutic principles of placenta previa-accreta [33–36]. Parallels have been observed between high placenta accreta rate, and elevated number of caesarean sections [37,38]. In agreement, the above data showed that the number of caesarean sections had a positive association with placenta accreta. Multiple trials have previously estimated the risk of placenta accreta considering the increased number of caesarean section cases, and reported findings that were similar to ours, suggesting that previous cesarean delivery is the main factor underlying placenta accreta [32,39,40]. Probable mechanisms may include the partial pressure of oxygen in the uterine scar, anomalous trophoblast differentiation, and altered angiogenesis [41,42].

The current work has several strengths that should be considered, including the fact that we evaluated the associations of age, BMI, and gestational week at blood collection with placenta accreta. Secondly, a placenta previa control group was included as an additional control group to exclude the effects of placenta previa on the identified associations. We could therefore show that the identified associations were not due to placenta previa. Thirdly, we excluded comorbidities that may influence the serum amounts of various angiogenic factors.

Nevertheless, there were several limitations in this study that must be acknowledged. First, selection bias may have been introduced because of the small sample size, which is explained by the rarity of placenta accreta. Secondly, fetal structural and chromosomal anomalies may affect AFP levels. Because of the small sample size of our study, we did not adjust confounders of fetal structural and chromosomal anomalies in this finding. Thirdly, all the pregnant women analyzed were from China; although this minimized the influence of confounding factors such as ethnic background, whether our results could be generalized to other ethnic groups remains to be confirmed. Furthermore, many additional parameters correlating with placenta accreta were unavailable for analysis because of the retrospective study design.

5. Conclusions

Taken together, increased second-trimester serum AFP has a significant positive correlation with placenta accreta. This finding suggests a potential role for second-trimester serum AFP in detecting pregnant women at high-risk of developing placenta accreta. Prior cesarean delivery might increase the risk of placenta accreta. Further studies involving larger cohorts of prospectively evaluated subjects, and investigating first- and second-trimester maternal biomarkers are warranted to validate this preliminary study.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

FW and DM designed the study. FW and SL performed the research. FW drafted the manuscript. FW analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Affiliated Hospital of Jining Medical University (approval number: 2023-08-C001).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5011232.

References

[1] O'Brien JM. Placenta previa, placenta accreta, and vasa previa. Obstetrics and Gynecology. 2007; 109: 203–204.

[2] Horgan R. Placenta previa, placenta accreta, and vasa previa. Obstetrics and Gynecology. 2006; 108: 693–694.

[3] Cui R, Li M, Lu J, Bai H, Zhang Z. Management strategies for patients with placenta accreta spectrum disorders who underwent pregnancy termination in the second trimester: a retrospective study. BMC Pregnancy and Childbirth. 2018; 18: 298.

[4] Belfort MA. Placenta accreta. American Journal of Obstetrics and Gynecology. 2010; 203: 430–439.

[5] Soleymani majd H, Collins SL, Addley S, Weeks E, Chakravarti S, Halder S, *et al*. The modified radical peripartum cesarean hysterectomy (Soleymani-Alazzam-Collins technique): a systematic, safe procedure for the management of severe placenta accreta spectrum. American Journal of Obstetrics and Gynecology. 2021; 225: 175.e1–175.e10.

[6] He X, Cai H, Li D, Zhou J. Development of a Nomogram for Preoperative Prediction of Emergency Peripartum Hysterectomy with Postpartum Haemorrhage: A Chinese-Population-Based Study. Clinical and Experimental Obstetrics & Gynecology. 2022; 49: 174.

[7] Mégier P, Gorin V, Desroches A. Ultrasonography of placenta previa at the third trimester of pregnancy: research for signs of placenta accreta/percreta and vasa previa. Prospective color and pulsed Doppler ultrasonography study of 45 cases. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction. 1999; 28: 239–244.

[8] Oyelese Y, Smulian JC. Placenta Previa, Placenta Accreta, and Vasa Previa. Obstetrics and Gynecology. 2006; 107: 927–941.

[9] Lim PS, Greenberg M, Edelson MI, Bell KA, Edmonds PR, Mackey AM. Utility of Ultrasound and MRI in Prenatal Diagnosis of Placenta Accreta: a pilot study. American Journal of Roentgenology. 2011; 197: 1506–1513.

[10] Esakoff TF, Sparks TN, Kaimal AJ, Kim LH, Feldstein VA, Goldstein RB, *et al*. Diagnosis and morbidity of placenta accreta. Ultrasound in Obstetrics & Gynecology. 2011; 37: 324–327.

[11] Comstock CH, Love JJ, Jr, Bronsteen RA, Lee W, Vettraino IM, Huang RR, *et al*. Sonographic detection of placenta accreta in

the second and third trimesters of pregnancy. American Journal of Obstetrics and Gynecology. 2004; 190: 1135–1140.
[12] Brown BP, Meyers ML. Placental magnetic resonance imaging Part II: placenta accreta spectrum. Pediatric Radiology. 2020; 50: 275–284.
[13] Miernik A, Gratzke C. Current Treatment for Benign Prostatic Hyperplasia. Deutsches Arzteblatt International. 2020; 117: 843–854.
[14] Androutsopoulos G, Gkogkos P, Decavalas G. Mid-trimester maternal serum HCG and alpha fetal protein levels: clinical significance and prediction of adverse pregnancy outcome. International Journal of Endocrinology and Metabolism. 2013; 11: 102–106.
[15] Wang F, Zhang L, Zhang F, Wang J, Wang Y, Man D. First trimester serum PIGF is associated with placenta accreta. Placenta. 2020; 101: 39–44.
[16] Oztas E, Ozler S, Ersoy AO, Ersoy E, Caglar AT, Uygur D, *et al*. Decreased placental and maternal serum TRAIL-R2 levels are associated with placenta accreta. Placenta. 2016; 39: 1–6.
[17] Duc-Goiran P, Mignot TM, Robert B, Machavoine F, Mondon F, Hagneré AM, *et al*. Expression and localization of alpha-fetoprotein mRNA and protein in human early villous trophoblasts. Placenta. 2006; 27: 812–821.
[18] Waller DK, Lustig LS, Cunningham GC, Feuchtbaum LB, Hook EB. The association between maternal serum alpha-fetoprotein and preterm birth, small for gestational age infants, preeclampsia, and placental complications. Obstetrics and Gynecology. 1996; 88: 816–822.
[19] Öztürk H, Erkaya S, Altınbaş S, Karadağ B, Tonyalı NV, Özkan D. The role of unexplained high serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) levels in the second trimester to determine poor obstetric outcomes. Journal of Turkish Society of Obstetrics and Gynecology. 2014; 11: 142–147.
[20] Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study. PLoS ONE. 2012; 7: e52893.
[21] Wong HS, Cheung YK, Zuccollo J, Tait J, Pringle KC. Evaluation of sonographic diagnostic criteria for placenta accreta. Journal of Clinical Ultrasound. 2008; 36: 551–559.
[22] Pongrojpaw D, Chanthasenanont A, Nanthakomon T, Suwannarurk K. Prenatal diagnosis of placenta accreta by colour Doppler ultrasonography: 5-year review. Journal of the Medical Association of Thailand. 2014; 97 Suppl 8: S171–S174.
[23] Mizejewski GJ. Biological roles of alpha-fetoprotein during pregnancy and perinatal development. Experimental Biology and Medicine. 2004; 229: 439–463.
[24] Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, *et al*. Presence of fetal DNA in maternal plasma and serum. Lancet. 1997; 350: 485–487.
[25] Tikkanen M. Etiology, clinical manifestations, and prediction of placental abruption. Acta Obstetricia Et Gynecologica Scandinavica. 2010; 89: 732–740.
[26] Mol BW. Fetal heart-rate monitoring. The Lancet. 2002; 359: 261.
[27] Mizejewski GJ, Vonnegut M. Mechanisms of fetal demise in pregnant mice immunized to murine alpha-fetoprotein. American Journal of Reproductive Immunology. 1984; 5: 32–38.
[28] Mizejewski GJ, Grimley PM. Abortogenic activity of antiserum to alpha-foetoprotein. Nature. 1976; 259: 222–224.
[29] Mizejewski GJ, Phillips L, Stoll W. *In vitro* studies of the abortogenic potential of antiserum to alpha-fetoprotein. International Journal of Immunopharmacology. 1981; 3: 87–95.
[30] Dauphinée MJ, Mizejewski GJ. Human alpha-fetoprotein contains potential heterodimerization motifs capable of interaction with nuclear receptors and transcription/growth factors. Medical Hypotheses. 2002; 58: 453–461.
[31] Burns NR, Kolarova T, Katz R, Ma K, Delaney S. Reconsidering race adjustment in prenatal alpha-fetoprotein screening. Obstetrics and Gynecology. 2023; 141: 438–444.
[32] Silver RM, Barbour KD. Placenta accreta spectrum: accreta, increta, and percreta. Obstetrics and Gynecology Clinics of North America. 2015; 42: 381–402.
[33] Wang Y, Zhou Y, Zeng L, Chen L, Zhao Y. Analysis of risk factors for massive intraoperative bleeding in patients with placenta accreta spectrum. BMC Pregnancy and Childbirth. 2022; 22: 116.
[34] Capriglione S, Ettore C, Terranova C, Plotti F, Angioli R, Ettore G, *et al.* Analysis of ultrasonographic and hystopathologic features of placental invasiveness *in Vitro* Fertilization (IVF) pregnancies: a prospective study. The Journal of Maternal-Fetal & Neonatal Medicine. 2022; 35: 5631-5638.
[35] Gulino FA, Guardo FD, Zambrotta E, Di Gregorio LM, Miranda A, Capriglione S, *et al*. Placenta accreta and balloon catheterization: the experience of a single center and an update of latest evidence of literature. Archives of Gynecology and Obstetrics. 2018; 298: 83–88.
[36] Hong L, Chen A, Chen J, Li X, Zhuang W, Shen Y, *et al*. The clinical evaluation of IIA balloon occlusion in caesarean delivery for patients with PAS: a retrospective study. BMC Pregnancy and Childbirth. 2022; 22: 103.
[37] Vyshka G, Çapari N, Shaqiri E. Placenta increta causing hemoperitoneum in the 26th week of pregnancy: a case report. Journal of Medical Case Reports. 2010; 4: 412.
[38] Shellhaas CS, Gilbert S, Landon MB, Varner MW, Leveno KJ, Hauth JC, *et al*. The Frequency and Complication Rates of Hysterectomy Accompanying Cesarean Delivery. Obstetrics and Gynecology. 2009; 114: 224–229.
[39] Dreux S, Salomon LJ, Muller F, Goffinet F, Oury J, ABA Study Group, *et al*. Second-trimester maternal serum markers and placenta accreta. Prenatal Diagnosis. 2012; 32: 1010–1012.
[40] Luo L, Sun Q, Ying D, Wu X, Yan P, Yang Y, *et al*. Scoring system for the prediction of the severity of placenta accrete spectrum in women with placenta previa: a prospective observational study. Archives of Gynecology and Obstetrics. 2019; 300: 783–791.
[41] Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development by oxygen tension. Science. 1997; 277: 1669–1672.
[42] Tantbirojn P, Crum CP, Parast MM. Pathophysiology of placenta creta: the role of decidua and extravillous trophoblast. Placenta. 2008; 29: 639–645.