Relationship Between the Second Trimester Maternal Serum AFP of Aneuploidy in Pregnancies and Placenta Accreta: A Cohort Study

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Research

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Abstract

Objectives

At present, placenta previa-accreta is a growing concern and is still a diagnostic challenge for obstetricians. This study aimed to investigated whether second trimester serum Alpha-fetoprotein (AFP) differed among pregnancies with placenta previa-accreta and placenta previa controls and healthy pregnant controls.

Methods

A retrospective chart review was performed. In 1 January 2016–30 February 2021, a total of 504 pregnant women were identified and included in our analysis as follows: 105 cases of placenta previa-accreta, 122 cases of placenta previa controls, and 277 cases of BMI-matched, healthy pregnant controls. AFP multiples of the median (MoM) were acquired from laboratory data files.

Results

AFP MoM of placenta previa-accreta group was significantly higher than those of the placenta previa controls and healthy pregnant controls group ($p < 0.001$, $p < 0.001$). Serum AFP was significantly positively associated with placenta accreta after adjusted age, BMI, and gestational week at time of blood sampling (β: 0.60; 95% CI: 0.52–0.68; $p < 0.001$). In addition, previous cesarean section history (β: 3.41; 95% CI: 2.18–5.34; $p < 0.001$) was also significantly associated with placenta accreta.

Conclusion

Increased second trimester serum AFP was significantly positively associated with placenta accreta. Such finding suggests the potential role of AFP in identifying pregnancies that are at high risk for placenta accreta. Second trimester biomarker of AFP can be used to raise a suspicion toward characterizing women into high-risk and low-risk groups for placenta accreta. In addition, previous cesarean section history may be a risk factor for accreta in placenta previa patients.

Background

Placenta accreta is characterized as the abnormal invasion of the placenta into, but not beyond, the myometrium. Placenta accreta, a life-threatening obstetric complication, carries significant risks, such as excessive hemorrhage, serious bleeding, shock, uterine perforation, secondary infection, and even death, for the mother and the offspring [1]. Its incidence tends to increase annually worldwide [2]. Invasive placenta affects approximately 2% of singleton deliveries [3]. Given the significant morbidity and adverse outcome associated with placenta accreta, accurate diagnosis is essential to diagnose placental accreta

in the prenatal period before the patients develop symptoms so that plans for the prevention of bleeding and related complications can be executed. Currently, the prenatal diagnosis of placenta accreta is mostly in accordance with resolution ultrasound and magnetic resonance imaging. Despite the improvements in imaging techniques, such as the use of high-resolution ultrasound and magnetic resonance imaging, placenta accreta is still a significant diagnostic challenge for physicians [4]. In addition, the accuracy of MRI diagnosis and other imaging tools of placenta accreta are still controversial as sensitivity and specificity range from 33–93% and 71–100%, respectively [4–7]. Still, many patients may not have the chance to receive an antenatal examination in a high-risk prenatal diagnosis center [8–10]. Therefore, improving the ability to identify pregnancies that are specifically at high risk for placenta accreta with a sensitive and convenient prenatal diagnostic mode is extremely urgent. Various studies investigated the possible risk factors and predictive markers of some adverse outcomes [11–13].

Maternal serum markers may help improve the prenatal diagnosis of placenta accreta. Furthermore, knowing the risks early may contribute to the accuracy of the interpretation of these imaging tools and improve the pregnancy outcomes. Alpha-fetoprotein (AFP), a major plasma protein produced during human fetal life, is a good marker for adverse pregnancy outcomes, such as pre-eclampsia, placental abruption, and preterm birth [14]. The relationship between the second serum AFP levels and placenta accreta is unclear. Therefore, we aimed to determine the relationship between the levels of the second trimester serum marker (AFP) and placenta accreta in this study.

Methods

Study design and population

A retrospective review was performed in the obstetrics of the affiliated hospital of Jining Medical University over a 5-year period (1 January 2016–30 February 2021). A total of 617 participants were enrolled in this study prior to being screened according to the inclusion and exclusion criteria. The inclusion criteria included: (1) placenta previa-accreta group: pregnant women were diagnosed as placenta previa prenatally by ultrasonography and later as placenta accreta histologically; (2) placenta previa controls (non-adherent placenta previa group): patients were diagnosed as placenta previa by ultrasonography but with no adhesion abnormalities later; (3) normal pregnant controls group: age and BMI matched pregnant controls (Fig. 1). The exclusion criteria included: (1) pregnant women with gestational diabetes, trophoblast tumor, acute and chronic infectious diseases, and other surgery and pregnancy complications; (2) twin or multiple pregnancy; (3) pregnant women whose delivery or clinical data were missing; and (4) miscarriage or stillbirths; (Fig. 1). Briefly, a total of 504 cases were finally included in our study (105 cases of placenta previa-accreta, 122 cases of placenta previa controls, and 277 cases of BMI-matched, normal pregnant controls). Pregnancy dating was compiled from the last menstrual period. All pregnant women in the study were tested for maternal serum AFP level during the second trimester according to the requirements of their attending doctors. Blood samples were collected at 17 weeks of gestation. Second serum AFP multiples of the median (MoM) values were acquired from laboratory data files of the Affiliated Hospital of Jining medical university. In addition, maternal

information, including maternal demographic, obstetrical, and medical histories, were retrieved from the information system of medical records. To protect patient privacy, our report did not include the participants' identifiable data. The study was approved by the Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China).

Statistical analysis

According to whether the continuous variables are normally distributed, we presented continuous variables in this study as mean ± standard deviation (normal distribution) or medium (Min–Max) (Skewed distribution). Categorical variables were expressed in frequency or percentage. We used $\chi 2$ (categorical variables), one-way ANOVA test (normal distribution), or Kruskal–Wallis H test (skewed distribution). All analyses were performed using the statistical software packages of R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). Categorical data were shown with n (number) and percentage (%). Binary logistic regression with single and multi-categorical predictor was used to determine the possible risk factors for placenta accreta. The data were examined at 95% confidence level, and a p-value of < 0.05 was considered significant.

Results

Baseline characteristics and maternal serum AFP of the three groups

A total of 504 gestational women were included in this study (105 cases of placenta previa-accreta, 122 cases of placenta previa controls, and 277 cases of BMI-matched, normal pregnant controls). Table 1 shows characteristics of all the study participants, lists the characteristics of clinical history, demography, and laboratory features, including the values of AFP MoM of the three groups. No statistically significant differences were detected in the age, height, BMI, gestational week at time of blood sampling, and cesarean hysterectomy at the time of delivery among the three groups. Delivery pregnancy week in the placenta previa-accreta group and placenta previa control group were significantly lower than those in the healthy pregnant control group ($p < 0.001$, $p < 0.001$) (Table 1).

Table 1
Baseline characteristics of subjects

Characteristic	placenta previa-accreta (n = 105)	placenta previa controls (n = 122)	healthy pregnant controls (n = 277)	p#-value	p*-value
Age (years) *	30.83 ± 4.75	30.13 ± 5.21	29.62 ± 4.12	P=(-) = 0.590 P=(-) = 0.036 P=(-) = 0.838	0.208
Height (cm) *	162.37 ± 4.41	162.75 ± 4.70	163.10 ± 4.32	P=(-) = 0.547 P=(-) = 0.242 P=(-) = 0.845	0.523
BMI (kg/m2) *	28.15 ± 4.33	28.08 ± 4.53	28.12 ± 3.38	P=(-) = 0.889 P=(-) = 0.976 P=(-) = 0.825	0.988
Gestational week at time of blood sampling (week)*	17.10 ± 1.07	17.11 ± 1.05	17.16 ± 0.76	P=(-) = 0.776 P=(-) = 0.032 P=(-) = 0.996	0.015
Delivery pregnancy week (week)*	37.63 ± 2.43	36.98 ± 3.25	38.88 ± 1.60	P=(-) = 0.137 P=(-) < 0.001 P=(-) < 0.001	< 0.001

: mean ± SD, normal distribution of data is presented as mean ± standard deviation; #: median, Min-Max, non-normal distribution of data is presented as median (Min-Max); categorical data were expressed by numbers and percentage (n, %). Results were analyzed by One-way ANOVA (Brown-Forsythe). p-value: between groups, p#-value: with in groups, $p < 0.05$ statistically significant. Statistically significant p values are marked as bold text.

Characteristic	placenta previa-accreta (n = 105)	placenta previa controls (n = 122)	healthy pregnant controls (n = 277)	p#-value	p*-value
Neonatal weight (kg) *	3.06 ± 0.60	3.02 ± 0.76	3.35 ± 0.49	P=(-) = 0.931 P=(-) < 0.001 P=(-) < 0.001	< 0.001
Previous cesarean section history*	67 (63.81%)	43 (35.25%)	93 (33.57%)	P=(-) < 0.001 P=(-) < 0.001 P=(-) = 0.975	< 0.001

: mean ± SD, normal distribution of data is presented as mean ± standard deviation; #: median, Min-Max, non-normal distribution of data is presented as median (Min-Max); categorical data were expressed by numbers and percentage (n, %). Results were analyzed by One-way ANOVA (Brown-Forsythe). p-value: between groups, $p^{\#}$-value: with in groups, $p < 0.05$ statistically significant. Statistically significant p values are marked as bold text.

Characteristic	placenta previa-accreta (n = 105)	placenta previa controls (n = 122)	healthy pregnant controls (n = 277)	p#-value	p*-value
AFP MoM#	1.49 ± 0.54	0.97 ± 0.52	0.98 ± 0.60	P=(-) < 0.001	< 0.001
Vaginal bleeding*	43 (40.95%)	52 (42.62%)	23 (8.30%)	P=(-) < 0.001	< 0.001
Blood transfusion*	34 (32.38%)	13 (10.66%)	3 (1.08%)	P=(-) = 0.909	< 0.001
Cesarean hysterectomy at the time of delivery*	2 (1.90%)	0 (0.00%)	0 (0.00%)	P=(-) = 0.799	0.043
				P=(-) < 0.001	
				P=(-) < 0.001	
				P=(-) < 0.001	
				P=(-) = 0.001	
				P=(-) = 0.909	
				P=(-) = 0.547	
				P=(-) = 0.075	
				P=(-) = 0.909	

: mean ± SD, normal distribution of data is presented as mean ± standard deviation; #: median, Min-Max, non-normal distribution of data is presented as median (Min-Max); categorical data were expressed by numbers and percentage (n, %). Results were analyzed by One-way ANOVA (Brown-Forsythe). p-value: between groups, p#-value: with in groups, $p < 0.05$ statistically significant. Statistically significant p values are marked as bold text.

Previous cesarean section history in placenta previa-accreta group was significantly higher than those in healthy pregnant control group and placenta previa control group ($p < 0.001$, $p < 0.001$) (Table 1). Vaginal bleeding incidence in the placenta previa-accreta group and placenta previa control group were significantly higher than that in the control group ($p < 0.001$, $p < 0.001$). Blood transfusion incidence in the placenta previa-accreta group was significantly higher than those in the healthy pregnant control group and placenta previa control group ($p < 0.001$, $p = 0.001$). The normally distributed serum AFP MoM is expressed as the median (Min–Max) in Table 1. The median AFP MoM of placenta previa-accreta cases

was 1.49, which was significantly higher than the median MoM of 0.97 observed in the placenta previa controls and 0.98 observed in healthy pregnant controls ($p < 0.001$, $p < 0.001$)(Fig. 2).

Logistic regression analysis of the possible risk factors for placenta accreta

The results in the univariate analyses for these abovementioned parameters and the median AFP MoM were listed (Table 2). By univariate linear regression, we found that age, weight, BMI, and gestational week at time of blood sampling were not associated with placenta accreta ($p > 0.05$). Univariate analysis also showed that previous cesarean section history (β: 3.41; 95% CI: 2.18–5.34; $p < 0.001$) was positively associated with placenta accreta; Neonatal weight (β: -0.1; 95% CI: -0.32, -0.06; 0.0047) and delivery pregnancy week (β: -0.67; 95%CI: -0.19, -0.15; $p = 0.0114$) were negitively associated with placenta accreta. AFP MoM was positively associated with placenta accreta. The median AFP MoM were further evaluated using multivariate logistic regression analysis (Table 3). The effect sizes (β) and 95% confidence intervals were listed in Table 3. In an unadjusted model, the multivariate logistic regression analysis showed that elevated serum AFP levels were significantly and positively associated with placenta accreta (β: 0.59; 95% CI: 0.51–0.67; $p < 0.001$). In the fully adjusted model (adjusted fβ maternal age, BMI, and gestational week at time of blood sampling), elevated serum AFP levels remained significantly and positively associated with placenta accreta (β: 0.60; 95% CI: 0.52–0.68; $p < 0.001$) (Table 3). Therefore, increased levels of AFP levels and previous cesarean section history are the most significant and positive factors related to the underlying mechanism of placenta accreta.

Table 2
Univariate analysis of different variables for placenta accreta

Covariate	β(95%CI)	*P*-value
Age (years)	0.47 (-0.27, 1.22)	0.211
Weight (kg)	1.10 (-1.05, 3.25)	0.318
BMI	0.04 (-0.80, 0.87)	0.931
Gestational week at time of blood sampling(week)	-0.04 (-0.23, 0.15)	0.6858
Delivery pregnancy week (week)	-0.67 (-1.19, -0.15)	**0.0114**
Neonatal weight (kg)	-0.1 (-0.32, -0.06)	**0.0047**
Previous cesarean section history	3.41 (2.18, 5.34)	**< 0.001**
AFP MoM	0.59 (0.51, 0.67)	**< 0.001**

*$p < 0.05$ statistically significant, NS; not significant, statistically significant p-values are marked as bold text

Table 3
Relationship between serum AFP and placenta accreta in different models using multivariate linear regression

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

** Logistic regression model (binary logistic regression with single- and multi-categorical predictors) was used to determine the possible risk factors for placenta accreta. Adjusted: adjusted for maternal age, BMI, and gestational week at time of blood sampling.

*p < 0.05 is statistically significant, NS; not significant. Statistically significant p-values are marked as bold text

Discussion

Generally, low AFP levels are regarded as an abnormal finding because they are associated with an increased risk of having an infant with down syndrome. Currently, with the development of prenatal biochemical screening test programs, studies about the relationship between increased AFP and adverse pregnancy outcomes began to be applied [15, 16]. In our study, we investigated the association between second trimester serum AFP level and placenta accreta. Our findings suggest that, in general, incremental AFP levels remained significantly and positively associated with placenta accreta. In addition, previous cesarean section history was significantly and positively associated with placenta accreta. Our findings also demonstrate that this positive association is not due to previa.

Placenta accreta is a life-threatening obstetrical disease that causes serious maternal morbidity, such as uterine perforation, hemorrhage, severe infection, and even death [17]. At present prenatal, the diagnosis of placenta accreta are based on MRI and resolution ultrasound. The diagnostic factors include the presence of placental lacunae, placenta previa with loss of the hypoechoic retroplacental interface, and a hypervascularity of the interface between the placenta and the bladder or uterine wall [18, 19]. However, the accuracy of these abovementioned ultrasonic instruments is still controversial. Previous studies estimated that levels of placental markers of maternal serum may change in pregnant women who have already developed or are destined to develop placental accreta, as we did and reported findings similar to ours [12, 15]. AFP, a tumor-associated fetal protein, has long been used as a serum fetal defect/tumor marker to monitor distress/disease progression [20, 21]. Currently, based on its association with many types of birth defects, malformations, and congenital anomalies[20]. AFP MoM of placenta previa-accreta group in the present study was significantly higher than those of the placenta previa controls and normal pregnant controls group. The elevated values of second trimester serum AFP of pregnancies with placenta accreta probably can be explained by the increased mother–fetus exchange. Considering that damaged endometrium may result in the occurrence of placenta accreta and increased maternal-fetal

exchange will release more AFPs into the maternal blood [20, 22, 23]. Furthermore, heterologous antibodies to AFP administered to pregnant mice resulted in developmental arrest, congenital abnormalities, and placental lesions [24–26]. Thus, AFP may be related to abnormal placenta. In addition, AFP can regulate growth in reproductive, placental, and lymphatic cells [27]. Elevated AFP levels may promote placental cell proliferation, such as placental trophoblastic cells, and may lead to the abnormal invasion of the placenta into the myometrium. Therefore, factoring serum AFP into the risk assessment could identify the patients who are at risk of developing placenta accreta better. Moreover, placenta accreta patients would be subject to closer and refined monitoring and treatment.

According to the increase in the rate of cesarean section over the last decades, cases with placenta previa accreta spectrum were encountered more often [28]. Parallels are observed between the increased incidence of placenta accreta and the increased number of caesarean section cases [29, 30]. In our study, we found a positively and significant association between previous cesarean section history and placenta accreta. Several studies estimated the risk of placenta accreta based on the increased number of caesarean section cases and the reported findings that were similar to ours, suggesting that previous cesarean section history might be the main factor of placenta accreta [28, 31, 32]. Probable mechanisms can be explained by the oxygen tension in the uterine scar, abnormal trophoblast differentiation, and abnormal angiogenesis [33, 34].

Several limitations in our study must be acknowledge. First, selection bias may be introduced because of the small amounts of cases. Second, all the pregnant women are from China, thereby fully minimizing the confounding effects of ethnic background. Thus, whether our results can be extended to other ethnic groups remains to be confirmed. Most of the other clinical factors associated with placenta accreta were not available in our databases because of their retrospective design.

Conclusion

Taken together, increased second trimester serum AFP were significantly and positively related with placenta accreta. Such finding suggests the potential role of second trimester serum AFP in identifying pregnancies that are at high risk for placenta accreta. Previous cesarean section history may increase the risk of placenta accreta. Furthermore, larger amounts of cases of prospective evaluation, including first-trimester and/or second-trimester maternal markers, are required to confirm these preliminary findings.

List Of Abbreviations

AFP: Alpha-fetoprotein

BMI: body mass index

MoM: multiples of the median

Declarations

Ethics approval and consent to participate: This study was approved by the Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China) (2019-zr-016).

Consent for publication

Not applicable

Availability of data and materials

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

Competing Interests: The authors declare no conflict of interest.

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Author's contributions: Fengge Wang, Shuxiong Chen, and Dongmei Man conceived and designed the study. Fengge Wang, and Chunlong Su, Ruixia Zhai, Miao Liu, and Fangxiang Dong participated in the design. Fengge Wang, Bin Zhang, and Chunlong Su drafted the manuscript. Fengge Wang, Xuemei Jin, Shuxiong Chen, and Ziheng Zhang performed the statistical analysis. Haiyan Zhang, Xueqin Feng, Tiantian Yu, and Ziheng Zhang participated in the design of the study and revised the manuscript. All authors have read and approved the final manuscript.

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Not applicable

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Figures

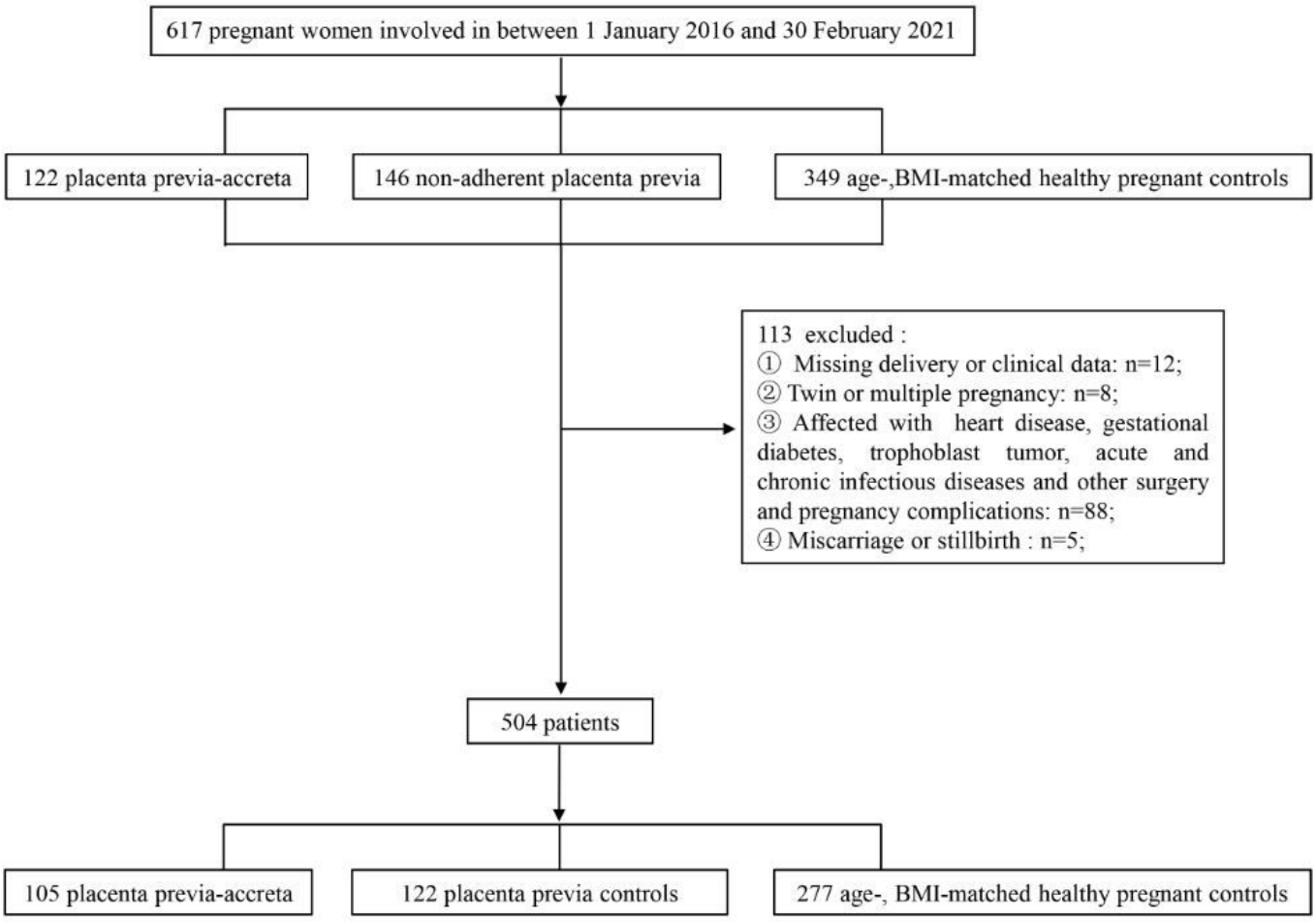

Figure 1

Flowchart of the study population In total, 504 patients from the department of obstetrics, affiliated hospital of Jining medical university in Shandong province of China between 1 January 2016 and 30 February 2021 were included in the study. Among these patients, 105 were placenta previa-accreta cases, 122 were cases of placenta previa controls, and 277 were cases of age and BMI-matched healthy pregnant controls. Healthy pregnant controls were further selected in accordance with the inclusion and exclusion criteria.

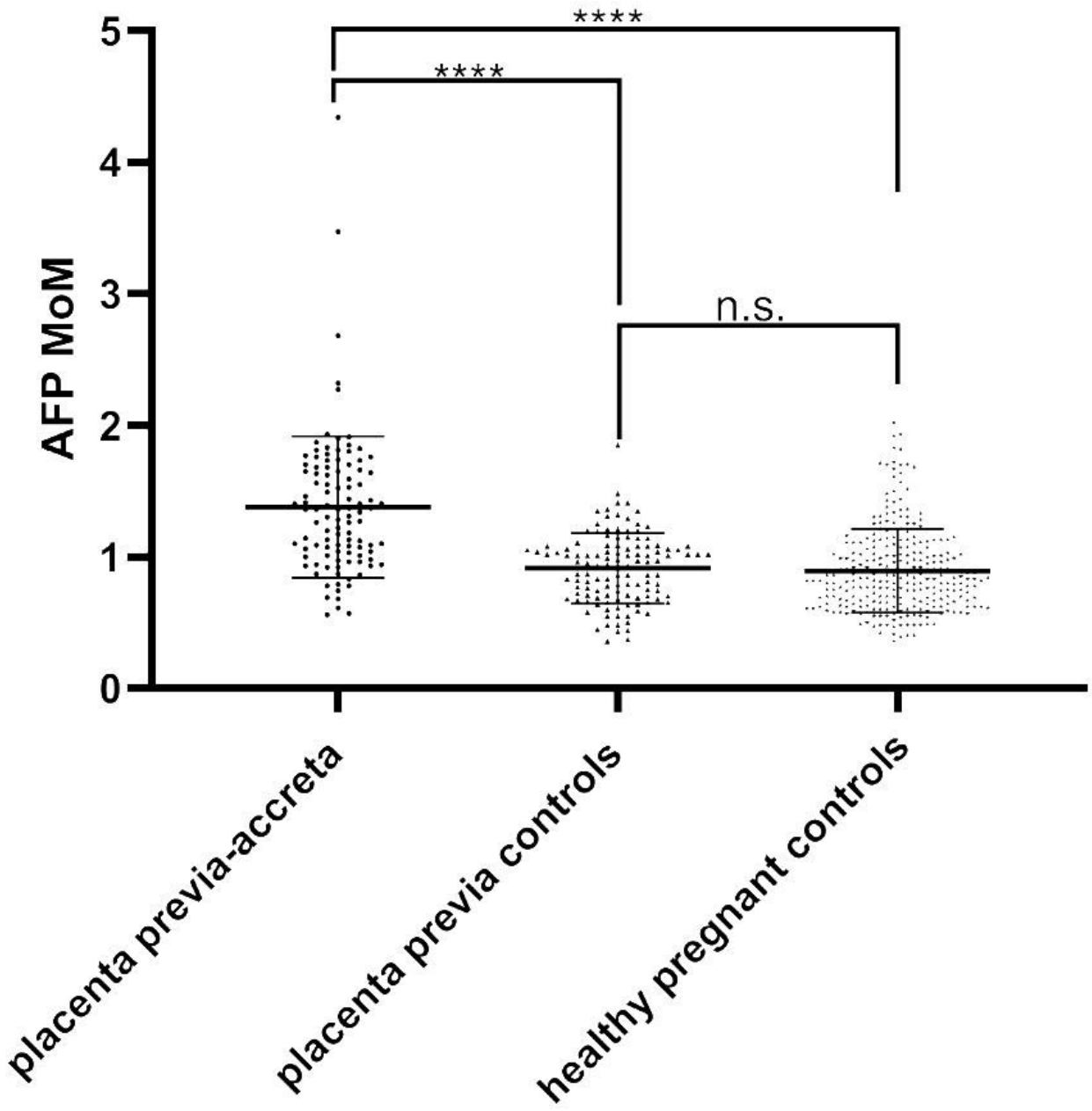

Figure 2

Levels and distribution of second trimester serum AFP in three groups. Data are shown as Median with interquartile range. *p < 0.05; **p < 0.01; ***p < 0.001; n.s., not significant.