

# First trimester mean arterial blood pressure is associated with placenta accreta: a retrospective study

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## Research article

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# Abstract

## Objective

The present study investigated whether first trimester mean arterial blood pressure (MAP) differed among pregnancies with placenta accreta and healthy pregnancies.

## Methods

We recruited 152 pregnant females from 1 January 2016 to 30 January 2020 in the Affiliated Hospital of Jining Medical University in this study, including 41 cases of placenta accreta pregnancies and 111 cases of BMI- and age-matched healthy pregnant controls. First trimester MAPs were acquired from laboratory data files of the Affiliated Hospital of Jining Medical University. Multiple logistic regression analysis was used to analyze the probable risk predictor of placenta accreta.

## Results

The performance of MAP was lower in healthy pregnancies. The MAP of the placenta accreta group was significantly higher than that of the control group ( $p = 0.001 < 0.05$ ). Our results also showed that MAP was significantly positively associated with placenta accreta after adjusting for age, BMI, fertilization type, gestational week at time of blood pressure measurement, and previous cesarean section history (odds ratio [OR]: 1.11; 95% confidence interval [CI]: 1.04–1.69;  $p = 0.0013 < 0.05$ ). In addition, smoking during pregnancy (OR: 7.57; 95% CI: 1.41–40.72;  $p = 0.018 < 0.05$ ) and previous cesarean section history (OR: 2.57; 95% CI: 1.19–5.54;  $p = 0.016 < 0.05$ ) were significantly positively associated with placenta accreta.

## Conclusions

Increased first trimester MAP was significantly positively associated with placenta accreta, suggesting the potential role of MAP in identifying high-risk pregnancies for placenta accreta. Smoking during pregnancy and previous cesarean section history may be risk factors for placenta accreta.

## Introduction

In the field of obstetrics, placenta accreta is a life-threatening complication that can lead to serious bleeding, secondary infection, uterine perforation, shock, and even death [1]. Placenta accreta affects approximately 3 out of 1000 pregnancies [2, 3]. In addition, the incidence of this condition is rising [4]. The prevalence of placenta accreta continues to rise internationally, placing a significant impact on health resources. Placenta accreta occurs by 10 weeks, and accreta cases have been diagnosed as early

as the first trimester [5]. Accurate antenatal diagnosis and prediction of placenta accreta are pivotal and important considering the gradually rising incidence and severe adverse outcomes of placenta accreta.

Evidence shows that accurate antenatal diagnosis of placenta accreta may reduce maternal peripartum hemorrhage and morbidity [6]. Ultrasound techniques such as ultrasound and magnetic resonance imaging (MRI) are mainly used in the current prenatal diagnosis of placenta accreta. However, the accuracy of MRI and ultrasound diagnosis of placenta accreta is controversial. In addition, many patients may not have access to a high-risk prenatal diagnosis center for antenatal examination [7–9]. The early accurate risk assessment of placenta accreta would identify high-risk women for targeted early prevention. In addition, the early accurate antenatal diagnosis of the risk of placenta accreta may allow for the improvement of the outcome by increasing patient surveillance or by initiating therapeutic interventions. Thus, developing an effective and convenient prediction strategy of placenta accreta at the first trimester is important to avoid adverse outcomes.

Extravillous trophoblast cells invade into the maternal decidua and play a critical role in the maintenance of a successful pregnancy [10]. Pre-eclampsia and gestational diabetes mellitus are pregnancy-associated diseases related to the invasion ability of trophoblasts [11–13]. By contrast, excessive trophoblast invasion, abnormal vascular remodeling, and decidual deficiency are the main pathophysiological mechanisms of placenta accreta [14]. These pregnancy-associated diseases are related to abnormal early trophoblastic invasion. First trimester mean arterial blood pressure (MAP) is closely related to some adverse pregnancy outcomes such as hypertensive disorders, pre-eclampsia, small for gestational age, and gestational diabetes mellitus [15–18]. In addition, first trimester MAP is typically used for assessing the risk of pre-eclampsia, small for gestational age, intrauterine growth restriction, and gestational diabetes mellitus during the trimesters of pregnancy [16–21]. The relationship between first trimester MAP and placenta accreta is still unclear. Thus, the present study aimed to determine the relationship between first trimester MAP and placenta accreta. First trimester MAP may help to improve the prenatal diagnosis of placenta accreta. In addition, knowing the risks of placenta accreta early may contribute to the accuracy of interpretation of MRI or sonogram findings and the customization of personalized diagnosis and treatment schemes.

## Methods

### Study settings and population

We conducted a retrospective study in the Department of Obstetrics of the Affiliated Hospital of Jining Medical University between 1 January 2016 and 30 January 2020. A total of 191 pregnancies were involved in our retrospective study prior to being screened according to the exclusion criteria. The inclusion criteria were as follows: (1) placenta accreta group: pregnant women were diagnosed as placenta accreta later histologically; (2) control group: age- and BMI-matched pregnant controls (shown in Fig. 1). The exclusion criteria were as follows: (1) pregnant women whose delivery or clinical data were missing; (2) twin or multiple pregnancies and miscarriage or stillbirths; (3) pregnant women with

trophoblast tumor, gestational diabetes, acute and chronic infectious diseases, and other pregnancy complications. Finally, a total of 152 cases were eligible in this study (111 for the control group and 41 for the placenta accreta group). Gestational age was compiled from last menstrual period (LMP) and confirmed by first trimester ultrasound where LMP was not known. The MAPs of all pregnant women in the study were measured and calculated during the first trimester according to the requirements of their attending doctors. Before systolic and diastolic blood pressure measurement, all pregnant women were required to rest for 15 min. All pregnant women were in the sitting position with their arms supported at the level of the heart, and a small (22 cm), normal (22–32 cm), or large (33–42 cm) adult cuff was used, depending on the mid-arm circumference. Two recordings of blood pressure were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements.[16] Additionally, maternal demographic characteristics, obstetrical and medical history, and other maternal information were collected from the maternity records of the Affiliated Hospital of Jining Medical University or the general medical practitioners of the women. To protect patient privacy, our report did not include participants' identifiable data. The study was approved by the Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China).

## Statistical analysis

Based on whether the continuous variables are normally distributed, we presented continuous variables in this study as medium (min–max, skewed distribution) or mean  $\pm$  standard deviation (normal distribution). Categorical variables were expressed in frequency or percentage. We used  $\chi^2$  (categorical variables), one-way ANOVA (normal distribution), or Kruskal–Wallis H test (skewed distribution). All analyses were performed with SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp. Armonk, NY, USA). Categorical data are 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 the 95% confidence level, and a p-value of  $< 0.05$  was considered significant.

## Results

### Baseline characteristics and first trimester MAP of the two groups

We recruited 191 gestational women, among which 152 were eligible. Two groups were included as follows: 111 age- and BMI-matched healthy controls and 41 placenta accreta patients. Table 1 lists the demographic characteristics, laboratory features, clinical history, and first trimester MAP of all groups. No statistical difference was observed in terms of age, BMI, height, gestational week at time of blood pressure measurement, cesarean hysterectomy incidence at the time of delivery, and mean birth weight in both groups. The incidence of smoking during pregnancy and previous cesarean section history in the placenta accreta group were significantly higher than those in the control group ( $p = 0.018 < 0.05$ ,  $p = 0.016 < 0.05$ ) (Table 1). Delivery pregnancy week in the placenta accreta group was significantly lower

than that in the control group ( $p < 0.05$ , Table 1). Blood transfusion incidence and vaginal bleeding incidence in the placenta accreta group were significantly higher than those in the control group ( $p < 0.05$ ,  $p < 0.05$ , Table 1). Delivery pregnancy week and neonatal weight in the placenta accreta group were significantly decreased than those in the control group ( $p < 0.05$ ,  $p < 0.05$ , Table 1). The normally distributed first trimester MAP is expressed as the median (min–max) in Table 1. The median first trimester MAP of placenta accreta cases was 89.74, which was significantly higher than that in the control group (84.79,  $p = 0.001 < 0.05$ ).

Table 1  
Baseline characteristics of subjects

Characteristic	Placenta accreta (n = 41)	healthy pregnant controls (n = 111)	p-value
Age (years)	31.07 ± 4.76	30.01 ± 4.35	0.07
BMI (kg/m <sup>2</sup> )	24.28 ± 3.03	23.46 ± 2.95	0.131
Weight (kg)	63.67 ± 7.19	62.14 ± 8.21	0.209
height (cm)	162.10 ± 4.71	162.69 ± 4.17	0.554
Previous cesarean section history	17 (41.46%)	24 (21.62%)	0.0161
Gestational week at time of pressure measurement (week)	12.29 ± 0.61	12.28 ± 0.58	0.940
Delivery pregnancy week(week)	36.30 ± 4.13	38.87 ± 1.30	<b>&lt; 0.001</b>
Neonatal weight (kg)	2.96 ± 0.73	3.31 ± 0.57	<b>0.033</b>
cesarean hysterectomy at the time of delivery	1 (2.44%)	0 (0.00%)	0.270
In-vitro fertilization	1 (2.44%)	7 (6.31%)	0.769
maternal weight before delivery	78.52 ± 11.05	75.20 ± 9.23	0.079
Smoking during pregnancy	5 (12.20%)	2 (1.80%)	<b>0.016</b>
Blood transfusion	31 (75.61%)	0 (0.00%)	<b>&lt; 0.001</b>
After the operation for hysteromyoma	1 (2.44%)	0 (0.00%)	0.272
MAP	89.74 ± 8.45	84.79 ± 8.27	<b>0.001</b>
mean ± SD, normal distribution of data is presented as mean ± standard deviation; categorical data were expressed by numbers and percentage (n, %). Results were analyzed by One-way ANOVA (Brown-Forsythe). $p < 0.05$ statistically significant. Statistically significant p values are marked as bold text.			
Abbreviations: BMI, body mass index; MAP (mean arterial blood pressure);			

## Logistic regression analysis of the possible risk factors for placenta accreta

Table 2 lists the median first trimester MAP and the results of univariate analyses of different parameters. Our results showed that age, BMI, height, gestational week at time of blood pressure measurement, in-vitro fertilization cesarean hysterectomy incidence at the time of delivery, and mean birth weight were not associated with placenta accreta ( $p > 0.05$ ). Previous cesarean section history (odds ratio [OR]: 2.57; 95% confidence interval [CI]: 1.19–5.54;  $p = 0.016$ ) and smoking during pregnancy (OR: 7.57; 95% CI: 1.41–40.72;  $p = 0.018$ ) were positively associated with placenta accreta. Delivery pregnancy week (OR: 0.56; 95% CI: 0.43–0.74;  $p < 0.0001$ ) and neonatal weight (OR: 0.41; 95% CI: 0.23–0.75;  $p = 0.004$ ) were negatively associated with placenta accreta. In addition, our results showed that the value of first trimester MAP was significantly positively associated placenta accreta.

Table 2  
Univariate analysis of different variables for placenta accreta

Covariate	OR (95%CI)	P-value
Age (years)	1.08 (0.99, 1.17)	0.0700
BMI	1.10 (0.97, 1.23)	0.1317
Weight (kg)	1.02 (0.98, 1.07)	0.2911
Smoking during pregnancy	7.57 (1.41, 40.72)	<b>0.0184</b>
Previous cesarean section history	2.57 (1.19, 5.54)	<b>0.0161</b>
Delivery pregnancy week (week)	0.56 (0.43, 0.74)	<b>&lt; 0.0001</b>
In-vitro fertilization	0.37 (0.04, 3.09)	0.3567
Maternal weight before delivery	1.04 (1.00, 1.07)	0.0669
Neonatal weight (kg)	0.41 (0.23, 0.75)	<b>0.0040</b>
MAP	1.07 (1.03, 1.12)	<b>0.0022</b>
* $p < 0.05$ statistically significant, NS; not significant, statistically significant p-values are marked as bold text.		

Multivariate logistic regression analysis was further performed to evaluate the median first trimester MAP (Table 3). Table 3 lists the effect sizes (OR) and 95% CIs. In the unadjusted model, multivariate logistic regression analysis showed that elevated values of first trimester MAP were significantly positively associated with placenta accreta (OR: 1.07; 95% CI: 1.51–4.95;  $p = 0.009 < 0.05$ ). After adjusting for maternal age, BMI, smoking during pregnancy, gestational week at time of blood pressure measurement, and previous cesarean section history, elevated values of first trimester MAP remained significantly positively associated with placenta accreta (OR: 1.11; 95% CI: 1.03–1.12;  $p = 0.0022 < 0.05$ ) (Table 3). Thus, increased values of first trimester MAP, previous cesarean section history, and smoking during

pregnancy may be the most significant and positive risk factors related to the underlying mechanism of placenta accreta.

Table 3

Relationship between MAP and placenta accreta in different models using multivariate linear regression

Variable	Crude Model		Adjusted	
	OR (95%CI)	P-value	OR (95%CI)	P-value
PIGF	4.68 (1.90, 11.54)	0.0008	4.83 (1.91, 12.24)	<b>0.0009</b>
** 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

### Main findings

MAP, a feasible tool and part of antenatal surveillance, has remained the target of scientific research in the prediction of pregnancy-related diseases [17, 22]. The association between first trimester MAP and placenta accreta is still unclear. In our retrospective case–control study, we investigated the association between first trimester MAP and placenta accreta. Our results showed that elevated first trimester MAP remained significantly positively associated with placenta accreta. Furthermore, first trimester MAP, smoking during pregnancy, and previous cesarean section history were significantly positively associated with placenta accreta, indicating that they may be probable risk predictors of placenta accreta.

### Strengths and Limitations

The strength pertains to the availability of data on a wide range of maternal characteristics on an individual level. In addition, the early accurate risk assessment of placenta accreta would identify high-risk women for targeted early prevention. Despite our findings, our study has several limitations. One limitation is the small number of cases, which possibly introduces selection bias. Another limitation is that all pregnant women were from China, which fully minimized the confounding effects of ethnic background. Whether our results can be extended to other ethnic groups remains to be confirmed.

### Interpretation

Placenta accreta refers to abnormal placental invasion to the uterine wall, which is characterized by invasion of trophoblasts into the myometrium, but not beyond [23, 24]. Placenta accreta is a life-

threatening obstetrical disease and has a high maternal morbidity and mortality rate, presenting specific intrapartum challenges [25, 26]. Placenta accreta affects about 2% of singleton deliveries, and its incidence is gradually increasing [27]. Considering the rising incidence and associated severe adverse outcomes of placenta accreta, methods that can accurately diagnose placenta accreta in the prenatal period before patients develop symptoms need to be developed so that plans for the prevention of bleeding and related complications and individualized treatment can be made. Currently, ultrasound and MRI are the methods used to diagnose placenta accreta. The diagnostic factors include the presence of placental lacunae, loss of the hypoechoic retroplacental interface, and hypervascularity of the interface between the placenta and the bladder or uterine wall. However, the effectiveness and accuracy of the above mentioned methods are controversial. Recently, an increasing number of studies showed that first trimester MAP is associated with adverse pregnancy outcomes [28, 29].

In the present study, we observed that elevated first trimester MAP remained significantly positively associated with placenta accreta. Previous studies showed that first trimester MAP values may change in pregnant women who have already developed or are destined to develop placenta accreta. First trimester MAP may be helpful to improve the antenatal diagnosis of placenta accreta. Furthermore, knowing the risks early may contribute to explain the MRI or sonogram findings more accurately.

MAP, the mean value of arterial pressure in one cardiac cycle, is a part of antenatal surveillance. In addition, higher levels of MAP are related to the increased risk of developing hypertension during pregnancy, pre-eclampsia, and gestational diabetes [15, 16, 19]. All these pregnant outcomes and placenta accreta belong to the disorders of placental development. Placenta accreta starts to develop in the first trimester [10].

In women with pre-eclampsia, the values of uterine artery pulsatility index and mean arterial pressure are increased. Interestingly, our findings showed that first trimester MAP is significantly increased in the placenta accreta group compared with that in the healthy control group. However, all the values are within normal range. Uteroplacental vasculature circulation undergoes significant structural and functional modifications to ensure an adequate blood supply to the developing placenta and the fetus in the first trimester [30]. In early stages of pregnancy, trophoblasts invade the uterine spiral arteries, replacing muscular and endothelial cells of the arterial wall and transforming them in low resistance vessels with an increased blood flow [31]. As mentioned above, placenta accreta starts to develop in the first trimester [10]. Thus, the probable mechanisms underlying this phenomenon may be that increased MAP within normal limits may provide more blood supply to the placental circulation and other organs of placenta accreta patients [32].

Considering the excessive trophoblast invasion and abnormal vascular remodeling of placenta accreta patients, these patients need more blood supply. Hence, factoring first trimester MAP into the risk assessment could better identify patients who are at risk of developing placenta accreta, and placenta accreta patients would be subjected to closer and refined monitoring and treatment.

In addition, we found that the incidence of smoking during pregnancy was significantly positively associated with placenta accreta in our study, suggesting that smoking during pregnancy may be related to the occurrence and development of placenta accreta. A potential mechanism is that cigarette smoke increases placental adrenomedullin expression and aggravates trophoblast invasion via the adrenomedullin pathway [26]. Excessive invasion of trophoblast cells leads to the occurrence and development of placenta accreta eventually.

The incidence of placenta accreta is increasing every year [33]. There are parallels between the increasing number of caesarean section cases and the increasing incidence of placenta accreta [34, 35]. Evidence shows that women with a history of caesarean delivery have the highest risk of developing placenta accreta [36-38]. In the present study, we found a significant positive association between previous cesarean section history and the incidence of placenta accreta. Our results also echo those of previous studies, suggesting that previous cesarean section history may be an important factor of placenta accreta [33, 39, 40]. The probable mechanisms underlying this phenomenon may include abnormal angiogenesis, abnormal trophoblast differentiation, and oxygen tension in the uterine scar [41, 42].

## Conclusion

Taken together, increased values of first trimester MAP were significantly positively related to placenta accreta, suggesting the potential role of first trimester MAP in identifying high-risk pregnancies for placenta accreta. Smoking during pregnancy and previous cesarean section history may increase the risk of placenta accreta. Future large-scale studies investigating the association between placenta accreta and first trimester MAP need to be conducted.

## Abbreviations

MAP  
mean arterial blood pressure

BMI  
body mass index

## Declarations

**Ethics approval and consent to participate:** The 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.

Competing interests: The authors declare that they have no competing interests.

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**Availability of data and materials:** The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

**Code availability:** Not applicable

**Authors' contributions:** Fengge Wang, Shuxiong Chen, and Dongmei Man conceived and designed the study. Fengge Wang and Shuxiong Chen designed the study. Fengge Wang drafted the manuscript. Shuxiong Chen, Fengge Wang, Miaomiao Qu, and Miao Liu performed the statistical analysis. Fangxiang Dong, Chunlong Su, Tiantian Yu, and Liangxi Zhu created the charts of the manuscript. All authors have read and approved the final version of the manuscript.

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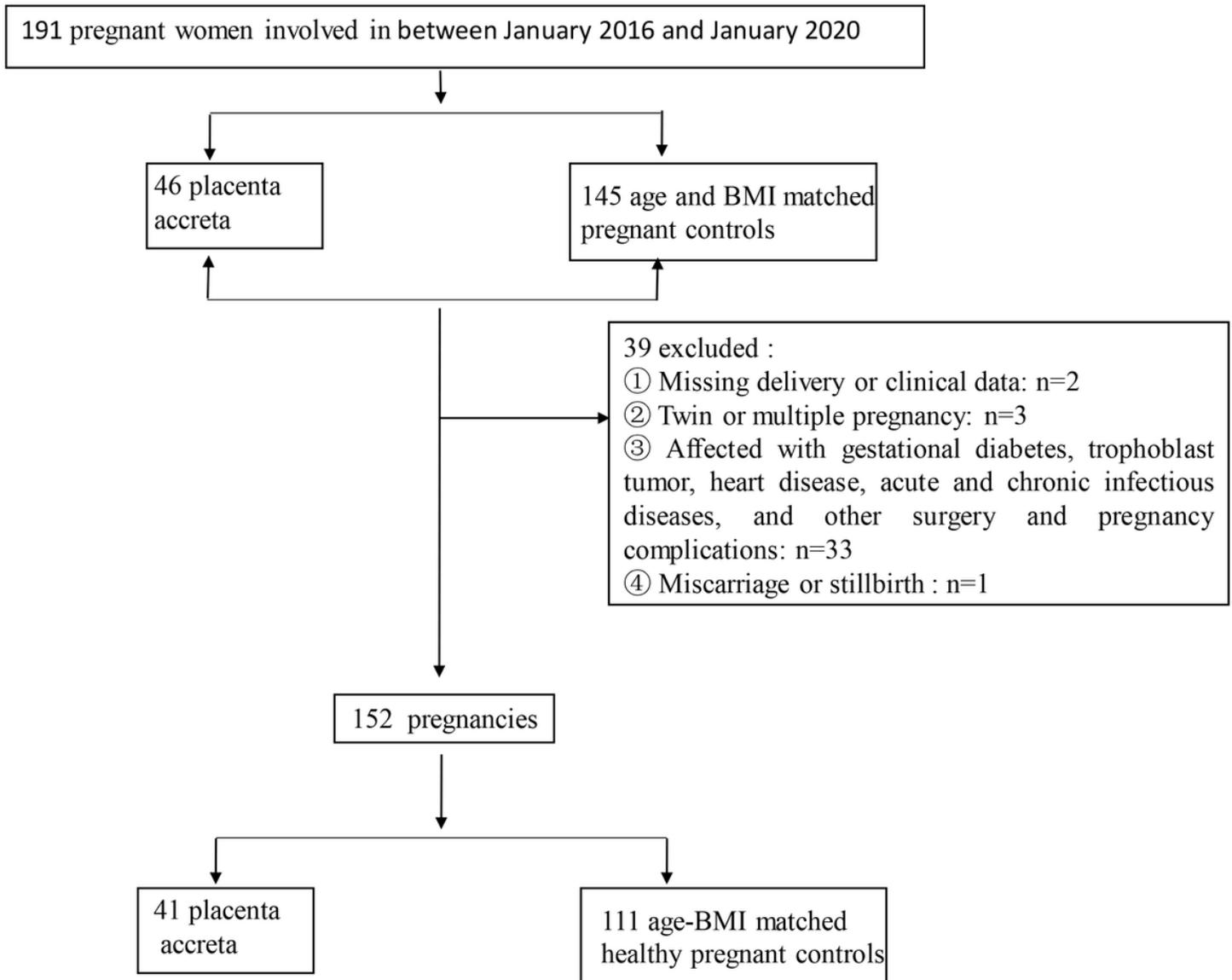
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## Figures



**Figure 1**

Flowchart of the study population In total, 152 patients from the Department of Obstetrics of the Affiliated Hospital of Jining Medical University, Shandong Province, China, between 1 January 2016 and 30 January 2020 were included in the study. Among them, 41 placenta accreta cases and 111 cases of age- and BMI-matched, healthy pregnant controls were further selected in accordance with the inclusion and exclusion criteria.