



Cesarean Section and Its Impact on Uterine Artery Resistance and the Risk of Pre-eclampsia in Subsequent Pregnancies

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Abstract

Background: The purpose of the current study was to compare the color Doppler findings of uterine arteries and perinatal outcomes in pregnant women with and without previous cesarean section (C/S).

Methods: This cohort study enrolled 308 pregnant women aged 20-35 without underlying diseases, with at least one previous pregnancy and childbirth. The participants were divided into two groups: 154 women without C/S and 154 women with C/S. Baseline data were collected, followed by uterine artery Doppler scans. Then, the perinatal outcomes, including pre-eclampsia, intrauterine growth restriction (IUGR), premature delivery, and birth weight were evaluated.

Results: The average age of patients in the C/S group was 30.46 ± 3.81 , which was significantly higher than the non-C/S group (28.86 ± 4.64). It was found that uterine artery resistance was higher in women with C/S history (1.11 ± 0.44 , $p < 0.001$) compared to those without (1.00 ± 0.37 , $p < 0.001$). Pre-eclampsia incidence was also higher in C/S group (16.1%, $p = 0.042$) compared to non-C/S group (9.1%, $p = 0.042$). The incidence of preterm birth in the C/S group ($p = 0.209$), the incidence of IUGR ($p = 0.791$), and the average birth weight ($p = 0.291$) in the two groups did not differ significantly. The average gestational age in the C/S group was 37.54 ± 1.4 , and in the non-C/S group was 38.01 ± 1.99 weeks. The results were not affected by potential confounders such as age, the time interval between pregnancies, and also body mass index.

Conclusion: Previous cesarean section can significantly increase the uterine artery resistance in subsequent pregnancy.

Keywords: Cesarean section, Color doppler ultrasonography, Pre-eclampsia, Uterine artery resistance, Uterine artery.

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Introduction

Developments in Color Doppler technology provided critical insights into maternal and fetal physiology during pregnancy, particularly in uteroplacental circulation and defective placentation (1). This technology allows for a

non-invasive assessment of blood flow in the uterine arteries, providing valuable information on the vascular resistance encountered within the utero-placental unit. Such assessments have traditionally focused on fetal vessels to monitor fetal health

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and detect potential complications (2). However, recent attention has shifted towards evaluating maternal vessels, offering enhanced predictive capabilities for adverse pregnancy outcomes (3-5). Changes in resistance indices such as the resistance index (RI) and pulsatility index (PI) play a key role in understanding blood flow dynamics and their impact on fetal well-being (6).

In a normal pregnancy, a shift is observed in uterine artery resistance, fostering increased blood flow to support optimal fetal development (7). This physiological adaptation ensures adequate delivery of oxygen and nutrients to the growing fetus. However, deviations from this norm, as indicated by abnormal uterine artery Doppler findings, are linked to heightened risks including small for gestational age births and increased neonatal intensive care unit (NICU) admissions. This predictive capacity extends to assessing the risk of conditions like premature birth, pre-eclampsia, and intrauterine growth restriction (3-5).

The rate of cesarean sections has been steadily increasing worldwide. In many countries, the cesarean section rate now exceeds the World Health Organization's recommended threshold of 10-15% (8). This rise can be attributed to various factors including increased maternal age, higher prevalence of obesity, preference for planned births, and improvements in surgical safety. While cesarean sections can be beneficial when medically required, their overuse poses significant risks for both mothers and infants in subsequent pregnancies. These include increased chances of uterine rupture, abnormal placentation, and other complications (9-11). As cesarean sections become more common, understanding their long-term impact on maternal and fetal health becomes increasingly important.

The importance of uterine artery Doppler studies is underscored by their ability to predict these adverse outcomes early in pregnancy, thereby facilitating timely interventions. Past studies reveal a compelling association suggesting that individuals with a cesarean delivery history exhibit increased arterial resistance which increases the risks of adverse outcomes such as premature birth, pre-eclampsia, and intrauterine growth restriction (12-14). This high resistance is thought to result from the surgical scarring and fibrosis that occur in the uterine tissue post-cesarean delivery, which may interfere with normal placentation and uteroplacental blood flow in subsequent pregnancies.

In this cohort study, the impact of the history of cesarean section, regardless of the cause, was investigated on uterine artery resistance and its consequences for subsequent singleton pregnancies were evaluated in healthy women. Understanding these dynamics is crucial as cesarean sections are becoming increasingly common worldwide, making it imperative to discern their long-term effects on maternal and fetal health.

Methods

Study design and population: In this prospective cohort study conducted from April 2021 to April 2023, pregnant women aged 20-35 with a history of at least one prior pregnancy and childbirth were included. Women with multiple pregnancy, a history of underlying diseases, pregnancy hypertension, severe pre-eclampsia, and the use of anticoagulant medications (such as aspirin and heparin) were excluded from the study. A total of 308 women, divided into two groups based on the presence or absence of a previous history of cesarean section (154 in each group), were followed to assess prenatal outcomes. The study received approval from the ethical committee of Iran University of Medical Sciences, under the reference number IR.IUMS.FMD.REC.1400.360.

Data collection: Basic information, including age, BMI, gestational age, and cesarean section history, was obtained during the initial clinical visit. All women underwent transabdominal ultrasound, anomaly scans, and color Doppler ultrasound of the uterine artery. Uterine artery Doppler assessments were conducted transabdominally at 18-20 weeks of gestation using the Philips Affiniti 70 ultrasound. To ensure uniform Doppler results, a dedicated perinatologist performed all sonographies. The resistance of the uterine artery was defined if the average pulsatility index of the right and left uterine arteries exceeded 1.45, as per the established threshold (15).

Outcomes: Patients were continuously monitored until the termination of pregnancy in the clinic, and the data was collected concurrently. Then, the incidence rates of severe pre-eclampsia, intrauterine growth restriction, preterm labor, and birth weight were assessed.

Pre-eclampsia is diagnosed by a combination of blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) on two separate readings taken at least four to six hr apart after 20 weeks of gestation, along with the presence of proteinuria (≥ 0.3

gr or 300 mg in a 24-hr urine sample). IUGR is diagnosed based on fetal weight estimated to be below the 10th percentile for gestational age, abdominal circumference below the 2.5th percentile, fundal height lagging more than 3 cm behind gestational age, amniotic fluid index less than the 2.5th percentile, and presence of maternal conditions that restrict fetal growth.

Statistical analysis: The study's sample size was determined using Pass software version 2021 (NCSS LLC, Utah U.S.), with a type 1 error of 0.05, a study power of 0.8, and a standard deviation of 0.35. The effect size for the pulsatility index (PI), identified as the main outcome, was set at 0.11 based on the findings from the Işıkalın et al.'s study (16). The statistical analysis was performed using SPSS version 18 (IBM, USA), employing a confidence interval of 0.95%. The comparison of quantitative variables was done using independent sample t-test and Mann-Whitney U-test. For hypothesis testing in categorical variables, Chi-square and Fisher exact tests were applied. Logistic and linear regression were employed to adjust for potential confounding effects of age, BMI, interval between last pregnancies, and gestational age concerning the impact of cesarean section on the pulsatility index outcome.

Results

From March 2021 to April 2023, a total of 308 mothers, comprising 154 with a history of cesarean section and 154 without, were included in the study and underwent evaluation for uterine artery color Doppler ultrasound indices. The mean age and 95% confidence interval for mothers with and without a previous cesarean section were 30.47 (29.86-31.08) and 28.86 (28.12-29.6), respectively. In the cesarean section group, 133 patients

(87%) had a history of one prior cesarean section, 19 patients (12.3%) had a history of two prior cesarean sections, and 2 patients (1.3%) had a history of three prior cesarean sections. The previous cesarean sections were indicated by maternal request in 96 cases (62.3%), repeat cesarean section in 21 cases (13.63%), and emergent cesarean section due to premature rupture of membranes, labor arrest, or other medical situations in the remaining cases. The characteristics of the mothers were compared between the two study groups, as presented in table 1.

The analysis of ultrasound outcomes between the two study groups revealed a notable elevation in uterine artery resistance among mothers with a history of cesarean section. The occurrence of increased uterine artery resistance was significantly higher in mothers with a cesarean section history, affecting 34 cases (22.1%), compared to only 11 cases (7.1%) without such a history. This difference was statistically significant (OR=3.68, 95%CI: 1.79-7.58) (Table 2).

The evaluation of clinical prenatal outcomes in the two groups revealed a significantly higher incidence of pre-eclampsia in the cesarean group (OR=2.03, 95% confidence interval: 1.02-4.06). Severe pre-eclampsia was observed in 12 (7.8%) and 5 (3.2%) cases with and without history of cesarean section. There were no statistically significant differences in birth weight, preterm labor, and intrauterine growth restriction between the two groups. In the group with caesarean section history, 36 (23.38%) pregnancies were terminated by cesarean section urgently due to pre-eclampsia, IUGR, and premature rupture of membrane (PROM). The remaining 122 patients underwent elective repeat cesarean section. The rate of urgent cesarean delivery in the group without a history of

Table 1. Baseline comparison between two study groups

	Without previous history of cesarean section				With previous history of cesarean section				p-value
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age (year)	28.86	4.65	20.00	35.00	30.47	3.82	20.00	35.00	<0.001
BMI (kg/m^2)	23.23	3.68	18.0	34.07	22.88	2.89	19.04	37.1	0.014
Gravidity	1.12	1.0000	1.00	3.00	1.16	0.419	1	3.00	0.376
Interval between last pregnancies (years)	4.90	1.46	2	7	5.32	1.91	3	11	0.033
Section number	-	-	-	-	1.15	0.39	1.00	3.00	

p-value of Mann-Whitney U-test

Table 2. Color Doppler ultrasound assessment of uterine artery resistance in two study groups

Groups	Without previous history of cesarean section					With previous history of cesarean section					p-value
	Mean	Median	SD	Min	Max	Mean	Median	SD	Min	Max	
RUA PI	0.97	0.85	0.35	0.38	2.75	1.09	0.97	0.42	0.41	3.55	<0.001*
LUA PI	1.02	0.86	0.50	0.49	3.94	1.13	0.97	0.54	0.42	3.49	0.042*
Mean PI	1.00	0.89	0.37	0.44	3.18	1.11	0.99	0.44	0.60	3.41	0.005*
BW (gr)	3060.2	3200	515	950	4285	3052.8	3100	416.03	1250	3670	0.291**

RUA: Right uterine artery, LUA: Left uterine artery. * p-value of Mann Whitney U-test. ** p-value of independent t test

Table 3. Distribution of clinical prenatal outcomes in the two study groups

	Without previous history of cesarean section	With previous history of cesarean section	Chi ² p-value
Pre-eclampsia	14 (9.1%)	26 (16.9%)	0.042
Preterm labor	28 (18.2%)	37 (24%)	0.209
IUGR	7 (4.5%)	8 (5.2%)	0.791
Total adverse events	45 (29.2%)	69 (44.8%)	0.005

Data are represented as frequency (%)

cesarean section was 24 (15.58%). The mean $\pm$ standard deviation of gestational age at the time of delivery was 37.5 ± 1.41 weeks in the group with a history of cesarean section, which was slightly lower than the 38.01 ± 1.99 weeks in the group without a cesarean history ($p=0.066$). The sensitivity of increased pulsatility index (PI) for predicting pre-eclampsia, preterm labor, and IUGR was 42.5%, 18.5%, and 33.3%, respectively. Meanwhile, the specificity for these predictions was 89.6%, 86.4%, and 86.3%, respectively (Table 3).

Data are represented as frequency (%): Taking into account the basic differences in age, BMI, and gestational age at Doppler examination between the two groups, an additional analysis of increased uterine artery resistance was conducted in both study groups. This evaluation involved adjusting for potential confounders, including maternal age, BMI, gravidity, time of Doppler ultrasound, number of cesarean sections, and also the interval between cesarean sections and the current pregnancy through logistic regression. The association between a previous history of cesarean section and increased uterine artery resistance persisted even after adjustment for potential confounders. The adjusted odds ratio was 3.13 (95%CI: 1.42-6.37) in the enter method of regression model, and 3.31

(95%CI: 1.61-6.88) in the backward regression model (Table 4). No correlation was identified between uterine artery resistance and the number of cesarean sections. Additional adjustment for confounders through linear regression was performed to quantitatively compare uterine artery resistance between the two study groups, confirming the categorical analysis of the data (Table supplementary 1). A multivariate analysis was conducted to adjust for the impact of potential confounders on the incidence of any adverse events during pregnancies (Table supplementary 2).

Finally, the clinical prenatal adverse outcomes were compared between patients with and without uterine artery (UA) resistance. The results demonstrated that patients with UA resistance had significantly higher rates of pre-eclampsia and IUGR, with odds ratios (OR) of 6.35 and 4.43, respectively. Notably, the findings indicated that patients with high UA resistance experienced at least one prenatal adverse event (Table 5).

Discussion

The primary objective of this study was to determine the association between history of previous cesarean section and increased resistance in uterine arteries and the potential impact on preg-

Table 4. Logistic regression for assessment of the effect of cesarean section on elevated uterine artery resistance adjusted for potential confounders

	Un-adjusted				Adjusted (enter method)				Adjusted (backward method)			
	p-value	OR	95%CI for OR		p-value	OR	95%CI for OR		p-value	OR	95%CI for OR	
			Lower	Upper			Lower	Upper			Lower	Upper
Study group	0.00	3.68	1.79	7.58	0.004	3.01	1.42	6.37	0.001	3.317	1.600	6.88
Age	0.013	1.11	1.02	1.21	0.047	1.1	1.001	1.20	0.046	1.09	1.00	1.19
BMI	0.886	1.00	0.91	1.11	0.770	0.98	0.87	1.10	-	-	-	-
Gravidity	0.811	1.10	0.50	2.43	0.586	1.27	0.53	3.04	-	-	-	-
Time interval between last pregnancies (years)	0.269	1.10	0.92	1.32	0.485	1.07	0.89	1.28	-	-	-	-
Gestational age at the time of doppler assessment (weeks)	0.086	0.87	0.74	1.01	0.272	0.90	0.75	1.08	-	-	-	-
Number of cesarean sections	0.65	1.24	0.493	3.11	N/A	N/A	N/A	N/A	-	-	-	-

Beta: regression coefficient, SE: standard error, Exp (B): beta exponential, CI: confidence interval

Table 5. Comparison of clinical prenatal outcomes in patients with and without uterine artery (UA) resistance

	Without UA resistance	With UA resistance	Chi ² p-value
Pre-eclampsia	23 (8.7%)	17 (37.8%)	<0.001
Preterm labor	53 (20.2%)	12 (26.7%)	0.32
IUGR	10 (3.8%)	5 (11.1%)	0.035
Total adverse events	69 (26.2%)	45 (100%)	<0.001

nancy outcomes. Following a meticulous adjustment for confounding factors, our study revealed a significantly high incidence of uterine artery resistance in the cesarean section group compared to the natural delivery group. Moreover, a significant increase in the incidence of pre-eclampsia was observed within the cesarean section group. Conversely, no statistically significant differences were found in the incidence of preterm labor, intrauterine growth restriction, or the mean of birth weight between the cesarean section and the group without the history of cesarean section. These findings contribute valuable insights into the complex relationship between uterine artery resistance, cesarean section history, and pregnancy outcomes.

The increased perinatal adverse events following a previous cesarean section can be attributed to several factors related to impaired uteroplacental circulation and placental function. A cesarean sec-

tion can cause scarring and fibrosis in the uterine tissue, which may disrupt normal placental implantation and development in subsequent pregnancies. This disruption can lead to increased uterine artery resistance, as observed in Doppler studies, thereby reducing blood flow to the placenta and fetus (17, 18).

In a study conducted in 2017 by Torabi et al., it was found that women with a history of previous cesarean section experienced significantly higher rates of adverse pregnancy outcomes compared to those who had undergone natural delivery. Furthermore, the incidence of all measured adverse pregnancy outcomes was notably elevated in women exhibiting abnormal uterine artery Doppler index (12). Their results are aligned with our study findings.

Also, Barati et al. demonstrated that the Doppler evaluation of uterine arteries during the 16-22 weeks of pregnancy could serve as an effective

tool for identifying pregnancies at increased risk of developing pre-eclampsia and small-for-gestational-age (15). The results of the aforementioned studies were consistent with our findings, although minor differences can be attributed to the patients' inclusion criteria; Torabi's study included elective cesarean sections, while our study included cesarean sections performed for any reason in healthy women which resulted in enhanced external validity.

In a meta-analysis conducted by Velauthar et al., it was revealed that the sensitivity of abnormal uterine artery Doppler in predicting pre-eclampsia and fetal growth restriction was 26.4% and 15.4%, respectively. The specificity for these conditions was reported to be 93.4% and 93.3%, respectively. These findings closely align with the results of our study, emphasizing the significance of high specificity of normal Doppler indices (19). Toal et al. conducted an assessment of adverse perinatal outcomes in high-risk women with abnormal uterine artery Doppler images. Their study investigated the prognostic value of abnormal uterine artery Doppler result obtained at 19-23 weeks of gestation, concurrently examining the shape and tissue abnormalities of the placenta during this period of pregnancy. The results highlighted that the combination of abnormal uterine artery Doppler findings and placental abnormalities served as indicators of increased risk for adverse outcomes, including intrauterine fetal death, delivery before the 32nd week of pregnancy, and intrauterine growth restriction (20).

The combined results of the above-mentioned studies emphasize the need for additional investigation and increased attention to pregnant women with a history of previous cesarean sections, a significant finding that is also well illustrated in the present study. Identifying these disorders is crucial, as uterine contractions can cause intermittent reductions in uterine placental perfusion which threaten the health of fetuses with undetected placental insufficiency during pregnancy (38).

In contrast, another study reported that uterine artery Doppler screening during the second trimester in primiparous women did not sufficiently predict small-for-gestational-age (SGA) or pre-eclampsia/gestational hypertension, and therefore was not considered clinically useful. In fact, future studies should focus on the use of uterine artery Doppler studies in high-risk populations. One of the most important high-risk populations are

mothers with a history of cesarean section or pregnancy disorders in previous pregnancies (21). Prenatal interventions for managing complications associated with this condition encompass the administration of anti-platelet drugs for pre-eclampsia, balanced energy protein supplements, and multiple micronutrient supplements during pregnancy (22, 23).

The strengths of our study included the prospective enrollment of a substantial patient population and the strict inclusion criteria applied to pregnant women. These attributes enable the extrapolation of our findings to women sharing similar demographic characteristics. Conversely, the limitation of a single-center study design must be acknowledged, as it could introduce bias and limit the generalizability of our study results.

Conclusion

Increased uterine artery resistance is significantly observed in women with a history of cesarean section and can lead to adverse outcomes such as pre-eclampsia, intrauterine growth restriction, and other pregnancy complications. This underscores the importance of careful monitoring and management of pregnancies following a cesarean section.

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Conflict of Interest

The authors declared that there is no conflict of interest.

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Supplementary table 1. Linear regression for mean pulsatility index to adjust the confounding effect of age and BMI

	Adjusted (enter method)				Adjusted (backward method)			
	Coefficients (beta)	95.0%CI for beta		p-value	Coefficients (beta)	95.0%CI for beta		p-value
		Lower bound	Upper bound			Lower bound	Upper bound	
Group (ref)=1	0.089	-0.006	0.184	0.067	0.093	0.002	0.185	0.046
Age	0.012	0.001	0.024	0.038	0.014	0.004	0.025	0.008
BMI	0.001	-0.014	0.016	0.880	-	-	-	-
Gravidity	-0.034	-0.159	0.091	0.588	-	-	-	-
Time interval between last pregnancies (years)	0.002	-0.024	0.029	0.863	-	-	-	-
Gestational age at the time of Doppler assessment (weeks)	-0.018	-0.045	0.009	0.191	-	-	-	-
Constant	0.581	0.268	0.893	0.000	-	-	-	-

Supplementary table 2. Logistic regression for assessment of the effect of cesarean section on total perinatal adverse events, adjusted for potential confounders

	Adjusted (enter method)				Adjusted (backward method)			
	OR	95%CI for OR		p-value	OR	95%CI for OR		p-value
		Lower	Upper			Lower	Upper	
Group (ref)=1	1.883	1.140	3.110	0.013	1.887	1.148	3.103	0.012
Age	1.052	.989	1.120	0.109	1.052	0.991	1.116	0.098
BMI	1.108	1.022	1.202	0.013	-	-	-	-
Gravidity	1.024	0.518	2.026	0.946	1.108	1.022	1.202	0.013
Time interval between last pregnancies (years)	1.159	1.005	1.336	0.043	1.159	1.005	1.336	0.043
Constant	0.004	-	-	0.000	-	-	-	-