RELATION OF GESTATIONAL SAC IMPLANTATION SITE TO PLACENTAL SITE IN WOMEN WITH OR WITHOUT A CESAREAN SCAR, A COHORT STUDY

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Abstract

Background: Implantation is the communication method between the embryo and the endometrium that allows the fetus receives nourishment and oxygen from the mother. We aimed to determine the relationship between the gestational sac implantation site and future placental site in women with or without a cesarean section (CS) scar, and whether this scar could affect the future placental location.
Methods: This prospective cohort study included 192 pregnant women with a singleton pregnancy (97 women with a CS scar and 95 without). Transvaginal ultrasound was done before ten weeks of gestation to assess the implantation site, distance from the lower edge of the gestational sac to the internal os, the relation of the gestational sac midpoint to the uterine midpoint, and retro-chorionic Doppler. At 34 weeks, the placental site was assessed using transabdominal ultrasound. Comparative analysis was performed between the two groups.
Results: There were no significant differences in the implantation site, the relationship of the gestational sac to the uterine midpoint, and the placental location between the two groups (P= 0.596, 0.692, and 0.536, respectively), with a high prevalence of posterior implantation, gestational sac above the uterine midpoint and posterior placentation. Correlation analysis showed a highly significant dependence between the placental site and implantation site (r=0.950, P<0.001).
Conclusions: The previous mode of delivery does not affect the gestational sac implantation site and future placental site. However, sonographic assessment of the gestational sac implantation site could be useful in predicting the placental location.

Keywords: Implantation; gestational sac; placenta; cesarean section scar

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1. Background

Implantation is a very complex process between the embryo and the endometrium that consists of apposition, adhesion, and invasion of the trophoblasts inside the endometrial tissue [1,2]. The blood flow at the implantation site is very crucial for embryo implantation and development. The high blood flow at the uterine fundus makes it a favorable site for embryo implantation [2]. During implantation, the majority of the embryos implant at the fundus owing to its high blood flow, whereas a minority (14%) implant at the transplacental site during migration [3].

The success of the implantation process is determined by direct interaction of three primary modules that are integral to the physiological process; endometrial competence with adequate progesterone priming, embryo viability, and immune regulatory mechanisms, some of which are controlled through genetic processes by the ovarian hormones [4].

The mechanism of placental localization is not fully known since placental development is a complicated process. The invading blastocyst interacts with the uterine wall tissue to form the placenta [5]. Women with a previous cesarean scar tend to have lower fundal placentae than women without a previous scar. The placentae in such women showed more preference for posterior location compared to women without previous cesarean deliveries. It is presumed that altered myometrial contractility and the disruption in the contraction wave resulting from the cesarean scar favor lower implantation of the embryos, increasing the incidence of the low-lying placenta and placenta previa [6]. Consequently, those placentas pose a significant obstetric risk as they are associated with increased bleeding during the third trimester and birth [7,8].

Few studies have evaluated the role of the cesarean scar on placentation [9–11]. Some have believed that defective decidualization is the cause of abnormal placentation [12]. Furthermore, it has been hypothesized that uterine scarring resulting from cesarean sections and other related procedures would impair the decidualization process [13].

The aim of the study is to assess the relationship between the implantation site, assessed as early as the 7th week of gestation, and the placental location assessed at the 34th week of gestation in women with or without cesarean section scar.

2. Methods:

A prospective cohort study, which included 192 pregnant women with a singleton pregnancy (97 women with a CS scar and 95 without), was conducted at the Obstetrics and Gynecology outpatient clinic of Kasr Al-Aini Teaching Hospital between May 2016 to March 2019. The study was approved by the Research Ethics Committee (REC) of the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University, and it was registered at ClinicalTrials.gov with the registration number NCT03208842. All women gave their consent before participating in the study.

Patients with or without a previous cesarean section were recruited for this study. Only those with a singleton pregnancy with a gestational age of less than ten weeks were included. Patients with previous myomectomy, known uterine cavity abnormalities, absence of fetal heart activity, or presence of any medical indication for pregnancy termination that interferes with the patient follow-up were excluded from the study. Enrolled patients underwent routine history taking, general examination, and an ultrasound scan to ensure that they met the inclusion criteria.

Ultrasound examination was done at 6-10 weeks of gestation using a "GE Voluson 730" machine (GE Healthcare Austria GmbH, Seoul, South Korea) equipped with a 5-7.5 MHz transvaginal probe. The site of the intrauterine gestational sac was assessed in relation to the endometrial cavity by relating the midpoint of the gestational sac to the midpoint of the uterine cavity. The uterine midpoint was identified as the midpoint of an imaginary line from the fundus to the internal os. Accordingly, the gestational sac site is classified as follows; above the midpoint, at the midpoint, and below the midpoint.

Furthermore, the implantation sites were classified as follows, fundal, anterior, low-lying anterior, posterior, and low-lying posterior [14]. The implantation site was identified by the visualization of a hyperdense ring located to one side of the sac and protruding inside the endometrial cavity. Retro-chorionic Doppler assessment was also done.

At 34 weeks of gestational age, an ultrasound examination was done during the routine antenatal care visits using a "GE Voluson 730" machine (GE Healthcare Austria GmbH, Seoul, South Korea) equipped with a 2-5 MHz abdominal transducer. The placental site was assessed and classified as fundal, anterior, low-lying anterior, posterior, and low-lying posterior.

Sample size: According to a previous study, the prevalence of low-lying placenta was 8.7%. Using Epi Info™ version 7 with a confidence level of 95% and power of 80%, the sample size was calculated to be 87 patients in each group. The sample size was increased by 5% to be 92 patients in each group for drop-out.

Statistical Analysis: The collected data was analyzed with IBM SPSS version 19 software. The quantitative variables were presented as mean ± standard deviation and range, whereas the qualitative variables were presented as frequencies and percentages. To detect a significant difference

between groups, the Student's t-test was used for quantitative variables, and the Chi-Square test was used for qualitative variables. Correlation between qualitative variables was conducted using Kendall's tau-b. The correlation coefficient (r) was presented from -1 (complete inverse relation) to +1 (complete concurrence relation), as the value (r = 0) indicates no correlation. P-value was used to determine the significance as a p-value < 0.05 indicates a significant result.

3. Results:

Two hundred eligible pregnant women were recruited for our study, of which 100 women had one more previous cesarean delivery, and the other 100 had not. However, only 192 women completed the study (97 women in the CS group and 95 in the non-CS group), as three patients had a first-trimester miscarriage, one had a preterm premature rupture of membranes at 29 weeks, and four patients were lost during follow up.

The demographic data and baseline clinical characteristics of both groups are shown in Table 1. There was no significant difference between CS and non-CS groups regarding age, gravidity, and body mass index (BMI). First-trimester ultrasound scan parameters demonstrate no significant difference between both groups regarding gestational age (in weeks), gestational sac diameter, distance from the lower edge of the sac to internal os, crown lump length (CRL), and retro chorionic resistive index (RI).

The implantation site at 6-10 weeks of gestation (whether fundal, anterior, low-lying anterior, posterior, or low-lying posterior), the relationship of the gestational sac to the uterine midpoint (whether above the uterine midpoint, at the uterine midpoint, or below the uterine midpoint), and the placental site at the 34 follow up visit (whether fundal, anterior, low lying anterior, posterior, or low lying posterior) showed no significant difference between both groups (P= 0.596, 0.692, and 0.536, respectively), as shown in Table 2. When correlation analysis was done, these parameters showed significant correlation to each other, particularly the implantation site and the placental site, which showed a strong correlation (r=0.950, P<0.001)

4. Discussion:

Despite some studies showing a link between increasing CS rates and worse outcomes, as well as the continuous debate about the impact of CS scars on early gestation processes, the CS rate has increased dramatically worldwide in recent decades, particularly in middle- and high-income countries [15].

Placental development is a complex process, and the mechanism of placental localization is not well understood. The placenta is formed as a result of interactions between the invading blastocyst and the uterine wall tissue [5]. Formation of the placenta involves several critical stages and processes; receptivity of the uterus, implantation, and placentation, i.e., the establishment of the final vascular arrangement in humans, a hemochorial placenta [16].

In our study, we found no significant difference in the gestational sac implantation site between the non-CS and the CS group. About 178 cases (92.7%) had their gestational sac implanted above the uterine midpoint, with 91 cases belonging to the CS group and 87 cases belonging to the non-CS group. Six cases (3.1%) had their gestational sac implanted below the uterine midpoint, 4 cases in the non-CS group, and 2 cases in the CS group. There was a significant direct relationship between the implantation site and gestational sac in relation to the uterine midpoint.

Few studies were found to address the effect of the previous cesarean on the implantation site and the placental location. Naji et al. conducted a similar study on 380 women; 170 had one or more previous CS, and 210 with no history of previous CS. Their main outcome was the effect of the CS scar on the implantation site and the pregnancy outcome. Patients were only followed up till the age of 12 weeks. Their study found that the CS group had more posterior implantation than fundal implantation (54 % vs. 23%), whereas the non-CS group had more fundal implantation than posterior implantation (42% vs. 31%). This difference was found to be significant. However, the low implantation rate was the same among both groups and was the lowest in frequency.

Those results contradict ours, in which the implantation site was not significantly different among the two groups. Several factors could explain the discrepancy in the results between the two studies. In the study of Naji et al. (2013), women in the CS group were older and had higher parity and BMI compared to the non-CS group [9]. In addition, the mean age of our studied population was younger (28 vs. 33). Moreover, the CS group in Naji et al. study had more smokers compared to the non-CS group [9]. None of the studied women in our study was a smoker; this could explain that smoking could be another variable that could have affected their results.

In our study, there was no significant difference in the distance of the lower end of the gestational sac from the internal os between the non-CS and CS groups (30.55 vs. 30.72 mm). Our results were contradictory to that of Naji's study, in which the gestational sac in the CS group was lower than that of the non-CS group by 8.7 mm (35.3 vs. 26.6 mm). In agreement with other studies [9,10], it was

hypothesized that maternal age could play a role in placental location. The age difference between the two studies could explain the discrepancy in the results.

In another study by Naji et al. (2012), a total number of 2594 patients were recruited; of which 738 had one more previous cesarean, and the remaining 1856 had no previous cesarean deliveries. This study found that women with previous cesarean had more posterior placentation than fundal placentae [10]. In our study, the posterior placentae were the highest among the studied population (51%), followed by anterior placentation (33%), then fundal placentation (16%). The CS group had more posterior placentation compared to the non-CS group (55% vs. 47%); however, this was not statistically significant. So our study results contradict those of Naji that a previous cesarean sac affects placentation in subsequent pregnancies.

Mohamedsalih et al. (2018) conducted a prospective case-control study to characterize placental position during the first trimester of pregnancy and, later, placental migration in women with and without a history of prior CS. They found the distance between the gestational sac and the internal os among women with a history of previous CS is less than those with no CS [17].

Pirjani et al. (2017) evaluated the effect of cesarean section scar on implantation and placentation in 370 women [11]. It was found that placental implantation at 11-14 weeks favored an anterior location in the CS group, whereas in the non-CS group, it favored a posterior location. At 34 weeks, the posterior location of the placenta was less likely in the CS group (29.7 %) compared to the non-CS group (37.7%). However, this study did not find any significant difference in the prevalence of low-lying placenta or placental migration between the two groups. The placenta implantation and location were shown to be affected by the cesarean scar, which agrees with that of Naji. However, Naji's study showed a higher prevalence of posterior placentation in the CS group. Pirjani's study differs from ours and that of Naji, in the inclusion of second gravidas only, thus having one previous vaginal delivery or cesarean section. It has therefore eliminated the effect of higher order parity and cesarean section which was found in our study. As both groups were comparable regarding gravidity, this should not affect the reliability of our results.

The strength of this study is that it addresses a debatable subject in which no solid conclusion has been reached. This could affect future research primarily related to assisted reproduction, implantation, and embryo transfer. The smaller number of patients in our study could be a limitation, so we recommend a larger scale of patients in subsequent studies.

5. Conclusions:

As long as the mode of delivery does not affect the implantation site in subsequent pregnancies, it does not consequently affect the placental site. However, sonographic assessment of the gestational sac implantation site could be used as a useful predictor of the placental location in the second and third trimesters. It could be used to early detect cesarean scar pregnancy and predict abnormally adherent placentae.

List of abbreviations:
BMI: body mass index
CRL: crown lump length
CS: cesarean section
REC: Research Ethics Committee
RI: resistive index

DECLARATIONS

Ethics approval and consent to participate: The study was approved by the Research Ethics Committee (REC) of the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University, and it was registered at ClinicalTrials.gov with the registration number NCT03208842. All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

Consent for publication: Not applicable.

Availability of data: Data is available from the corresponding author upon request.

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Table 1: Demographic and baseline clinical characteristics of all participants

	Non-CS group (n=95)	**CS group (n=97)**	**p-value**
Age (years)	27.49 ± 4.82 (18 - 41)	28.43 ± 4.45 (20 - 41)	0.163
Gravidity	2.64 ± 1.74 (1 - 8)	3.02 ± 1.09 (2 - 8)	0.073
BMI (kg/m^2)	27.89 ± 3.20 (23 - 38)	28.16 ± 3.10 (23 - 38)	0.553
Gestational age at first ultrasound scan (weeks)	7.08 ± 0.94 (6 - 10)	7.00 ± 0.80 (6 - 9)	0.506
Gestational sac diameter (ml)	24.51 ± 6.31 (14.4 - 54.1)	24.20 ± 5.45 (14.1 - 34.5)	0.715
CRL (ml)	11.79 ± 5.49 (4.5 - 38.9)	11.49 ± 4.54 (4.2 - 22.1)	0.677
Distance from lower edge of sac to	30.55 ± 3.85	30.72 ± 4.08	0.778

internal os (ml)	(10 - 35.9)	(10 - 35.8)	
Retro chorionic RI	0.51 ± 0.03 (0.44 - 0.58)	0.51 ± 0.03 (0.38 - 0.61)	0.610

Table 2: Implantation site, relation to the uterine midpoint, and placental site

	Non-CS group (n=95)	**CS group (n=97)**	**p-value**
Implantation Site			
- Fundal	17 (17.9%)	13 (13.4%)	
- Anterior	31 (32.6%)	30 (30.9%)	
- Posterior	45 (47.4%)	52 (53.6%)	0.596
- Low Lying Anterior	1 (1.1%)	1 (1.0%)	
- Low lying Posterior	1 (1.1%)	1 (1.0%)	
Gestational sac relation to uterine midpoint			
- Above uterine midpoint	87 (91.6%)	91 (93.8%)	
- At uterine midpoint	4 (4.2%)	4 (4.1%)	0.692
- Below uterine midpoint	4 (4.2%)	2 (2.1%)	
Placental Site (34 weeks)			
- Fundal	17 (17.9%)	13 (13.4%)	
- Anterior	32 (33.7%)	31 (32.0%)	
- Posterior	45 (47.4%)	53 (54.6%)	0.536
- Low Lying Anterior	0 (0.0%)	0 (0.0%)	
- Low lying Posterior	1 (1.1%)	0 (0.0%)	

Table 3: Correlation analysis of the implantation site, relation to the uterine midpoint, and placental site

	Gravidity	**Mode of delivery**	**Implantation site**	**Relation to the uterine midpoint**	**Placental site**
Gravidity	1	0.130 (0.072)	-0.113 (0.118)	-0.052 (0.478)	-0.105 (0.148)
Mode of delivery	0.130 (0.072)	1	0.067 (0.359)	-0.056 (0.444)	0.057 (0.435)
Implantation site	-0.113 (0.118)	0.067 (0.359)	1	**0.264 (<0.001*)**	**0.950 (<0.001*)**
Relation to the uterine midpoint	-0.052 (0.478)	-0.056 (0.444)	**0.264 (<0.001*)**	1	**0.149 (0.039*)**
Placental site	-0.105 (0.148)	0.057 (0.435)	**0.950 (<0.001*)**	**0.149 (0.039*)**	1