**THE PREGNANCY OUTCOME OF SECONDARY INFERTILITY WOMEN WITH CAESAREAN SCAR DEFECT**

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**Abstract**

**Purpose:** This study was conducted to investigate pregnancy outcomes after infertility treatment in women with secondary infertility, with and without caesarean scar defects (CSD).

**Methods:** This retrospective cohort study was conducted at IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam. Women aged ≥18 years with at least one previous caesarean section (CS) were eligible for this study. Women who had uterine malformation, leiomyoma, adenomyosis, myometrial surgery except for CS, or previous CSD repair were excluded. The patients were followed up for 12 months. The primary outcome was the cumulative live birth rate.

**Results:** From October 2020 to March 2021, 340 women were included in this study. The cumulative live birth rate (CLBR) was not significantly different in both groups. However, the positive β-hCG and clinical pregnancy rate (CPR) were higher in the CSD group than in the control group. The prevalence of endometrial fluid in the CSD group was higher, which resulted in a higher treatment cancellation rate. Among those patients, there were only 6 patients with placenta previa, placenta accreta, and postpartum hemorrhage.

**Conclusions:** CSD did not have a detrimental effect on pregnancy outcome. Further studies focused on the correlation between endometrial fluid, pregnancy and complication outcome are needed to evaluate the impact of CSD.

**Key words:** caesarean scar defect, infertility, pregnancy outcome.

1. **Introduction**

Caesarean section (CS) has increased over 30 years to a frequency of more than 10–15% of births. It was estimated that 29.7 million births occurred through CS in 2015, which was almost double the number of CS births in 2000 (1). From 2000 to 2015, the prevalence of CS increased to 32.8% in the USA, 32.4% in Australia, and 36.2% in China (1). The incidence of caesarean delivery is higher in pregnancies conceived using assisted reproductive technology (ART) than in pregnancies of fertile women (2). Therefore, the prevalence of caesarean scar defect (CSD) is also higher in this population. Independent risk factors of having a CSD were smoking in the first trimester, higher parity, and previous CS (3). Using transvaginal ultrasound (TVS), the reported prevalence of a niche varied between 24% and 70%. Using contrast-enhanced sonohysterography in a random population of women with a history of CS, the prevalence was found to vary between 56% and 84% (4). For women with CS in Vietnam, the prevalence of CSD is 36.8% (5).

The correlation between infertility and CSD has been reported in many studies recently. The mechanism whereby CSD causes infertility was speculated as follows. Bleeding from the caesarean scar flows into the vagina, causing abnormal bleeding. If the blood flows into the uterine cavity, it may cause implantation failure. Blood retention in the uterine cavity may result in infertility via a mechanism similar to hydrosalpinx. The main focus is on the embryotoxic properties of the fluid, but endometrial receptivity may be reduced as a result of disturbed expression of the cytokine cascade, which is essential for implantation. The presence of excessive fluid in the uterine cavity may also be a mechanical hindrance to implantation. The cytotoxicity of iron in the blood may adversely affect implantation. However, the specific cause of infertility associated with bloody fluid retention in the uterine cavity is not clear (6). Moreover, women with residual myometrium at the site of the uterine scar measuring <50% of the adjacent myometrial thickness had postmenstrual spotting more often than women with a residual myometrial thickness of >50% of the adjacent myometrial thickness (OR 6.13, 95% CI 1.74-21.63), which can lead to fluid retention in the uterine cavity more often and resulted in implantation failure (7).

Therefore, some studies show the correlation between CSD and infertility and pregnancy outcomes. A study reported on 1,317 women showed live birth rates were significantly lower in women with a previous CS than in women with a previous vaginal delivery (VD), 15.9% (51/320) versus 23.3% (219/941) (OR 0.63 95% CI 0.45-0.87) (8). In 2021, a study by Jurong et al. suggested that the existence of a CS without a defect does not have negative impact on the live birth rate after IVF or ICSI compared with a previous VD. However, the presence of a CSD in women, especially in women ≤ 35 years old, significantly affects the outcomes of a subsequent pregnancy (9). Sardo et al. provided strong evidence that there is little or no effect of CS on future fertility; the clinical and social circumstances leading to the CS have a greater effect on future fertility than the CS itself (10). However, these studies did not directly compare patients with and without CSD. The data about the effect of CSD, especially for women with secondary infertility, is still limited. Therefore, this study was conducted to investigate the pregnancy outcome after infertility treatment in women with secondary infertility, with and without CSD.

1. **Materials and Method**
   1. **Study design**

This multicenter retrospective cohort study was performed at IVFMD, My Duc Hospital, and Ngoc Lan Clinic in Vietnam. The study was approved by the Medical Ethics Committee at My Duc Hospital, Ho Chi Minh City, Vietnam (18/21/DD-BVMD)

* 1. **Study population**

Women aged ≥18 years with at least one previous CS and diagnosed with infertility from October 2020 to March 2021 were eligible for this study. Women with uterine malformation, leiomyoma, adenomyosis, myometrial surgery except for CS, or previous CSD repair were excluded.

All eligible women were evaluated for CSD by TVS and then were divided into two groups: the CSD group and the non-CSD group. All participants were interviewed by telephone to collect information on infertility treatment such as expectant management, ovarian induction or ovarian stimulation, and pregnancy information. Data were also extracted from the database of each center. All patients were followed up for 12 months until March 2022.

* 1. **Transvaginal ultrasound evaluation**

The diagnosis of niche was established with TVS performed using a 7.5-MHz transvaginal transducer (Samsung Medison HS30 ultrasound machine) 7 to 9 days after last menstruation. All measurements of the CSD were evaluated following the modified Delphi procedure (11). The physicians performed the scans were trained professionally.

* 1. **Expectant management**

Expectant management was defined as a couple having regular unprotected intercourse during the fertile phase of the menstrual cycle.

* 1. **Ovarian induction**

Ovarian induction was performed using human menopausal gonadotrophins (hMG) (IVF-M, LG Life science, Korea), and follicular development was monitored by transvaginal ultrasound every 3-5 days. An injection of hCG (IVF-C 5000 IU, LG Life Science, Korea) was given to trigger ovulation when the mean diameter of the dominant follicle reached ≥18 mm. Those with more than 7 follicles ≥14 mm were counseled to cancel or convert to IVM or IVF. IUI or natural intercourse was scheduled 36-38 hours after hCG injection.

* 1. **Ovarian stimulation**

All patients were treated with a gonadotropin-releasing hormone (GnRH) antagonist protocol (12). Recombinant follicle-stimulating hormone (FSH) was given on day 2 or day 3 of the menstrual cycle for 5 days. The starting dose was individualized for each patient based on the anti-Müllerian hormone level, with subsequent dosage titration based on the treating physician's clinical judgment. Follicular development was monitored by ultrasound scanning and by the measurement of estradiol and progesterone levels, starting on day 5 of stimulation. Scanning and hormonal measurements were repeated every 2–3 days, depending on follicle size. A GnRH antagonist was routinely used on day 5 until the day of triggering. Criteria for human chorionic gonadotropin (hCG) triggering included the presence of at least three leading follicles with a diameter of 17 mm. In women with an excessive follicular response (≥15 follicles of ≥12 mm in diameter), 0.2 mg of a gonadotropin-releasing hormone agonist was used when there were at least two leading follicles of 17 mm in diameter. Oocyte retrieval was performed 36 hours after triggering (12).

* 1. **Outcome**

The primary outcome was the cumulative live birth rate after 12 months. Live birth is defined as the complete expulsion or extraction of a product of fertilization from a woman after 24 completed weeks of gestational age, which breathes or shows any other evidence of life after separation. These include heartbeat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A birth weight of 350 grams or more can be used if gestational age is unknown (twins are a single count). Cumulative live birth rate is total live birth per number of patients.

* 1. **Statistical analysis**

Baseline data was presented using descriptive statistics (mean and standard deviation for normally distributed variables, or median and interquartile range for skewed variables). Categorical data was presented as numbers (%). All analyses were performed using the R statistical program (R version 4.1.0; ©2021 The R Foundation for Statistical Computing). Statistical significance was defined as p<0.05.

1. **Results**
   1. **Study population**

From a total of 340 infertile patients with previous CS between October 2020 and March 2021, this analysis included 320 women (117 patients with CSD and 203 patients without CSD) (Figure 1). Patient characteristics, including age, body mass index (BMI), anti-Müllerian hormone (AMH) level, and indication for infertility treatment were comparable between both groups (Table 1). For the history of CS, the indication for CS was similar but the wound infection was significantly higher in the CSD group compared to the non-CSD group (Table 2). In regards to caesarean scar dehiscence, we surveyed all measurements following Delphi modified procedure such as: niche length, depth, width, residual myometrial thickness (RMT), adjacent myometrial thickness (AMT), distance between niche and vesicovaginal (VV) fold, distance between niche and external os, and branches. The median niche length, depth, width was 5 mm, 4.5 mm, and 5.3 mm, respectively, the median RMT was 4 mm, and the median AMT was 9.1 mm (Figure 2).

* 1. **Infetility treatment**

There were no significant differences between the CSD and the non-CSD group for the treatment method (Table 3). The prevalence of endometrial fluid in the CSD group was higher than in the non-CSD group (36 (30.8%) vs. 9 (4.4%) , p<0.001), which results in higher treatment cancellation rate in the CSD group (8 (6.8%) vs. 3 (1.5%) p=0.021) (Table 4). There was just one case with operative CSD repair.

* 1. **Pregnancy outcome**

For the pregnancy outcome, our results showed that of the 320 patients with follow-up, there were 113 patients with live births, including 46 patients with CSD (one patient after IUI, 45 patients after IVF) and 67 patients without CSD (one patient after expectant management, one patient after IUI, 65 patients after IVF) (Figure 3).

The cumulative live birth rate (CLBR) was not significantly different in both groups (39.3% vs. 33.0%, p=0.31). The positive ß-hCG and clinical pregnancy rate (CPR) were higher in the CSD group versus the control group (53.0% vs. 47.3% and 48.8% vs. 41.9%, p=0.045). The cumulative ectopic pregnancy, miscarriage, multiple pregnancy and live birth weight was comparable between both groups (Table 5).

* 1. **Pregnancy complication**

In our study, there are 4 cases with placenta previa (one patient with CSD and 3 patients without CSD), one case with placenta accreta (CSD group), one case with postpartum hemorrhage (CSD group), and no cases with uterine rupture (Table 6).

1. **Discussion**

For infertility treatment outcomes, our study reported a higher cumulative positive β-hCG and clinical pregnancy rate in the CSD group compared to the non-CSD group (53% vs. 47.3% and 48.8% vs 41.9%, respectively, p=0.041 and 0.045). In 2021, Friedenthal et al. also reported that the biochemical pregnancy rate after in vitro fertilization treatment was higher with caesarean delivery than with vaginal delivery, but it was not significant (20.1 vs. 16.9, p=0.42) (13). However, in a subanalysis in patients with a niche compared to patients with a history of vaginal delivery, Friedenthal did not report this finding. Yangping Li et al. also showed caesarean section leads to significantly decreased clinical pregnancy rate (CPR) (risk ratio (RR) 0.86; 95% confidence interval (CI), 0.81, 0.92; p<0.00001) (14). However, these studies did not directly compare between CSD and non-CSD groups. There are limitations to our study, including the possibility of leading to bias on the infertility treatment. Therefore, we cannot conclude the effect of infertility treatment in either group. The number and quality of embryos were not consistent, and patients with preimplantation genetic testing (PGT) and donor cycles were not excluded, but there were no cases of PGT and only three cases of donor cycles. The second limitation was that detailed treatment data was not collected, such as intrauterine fluid reduction treatment.

For pregnancy outcomes, our results showed that in 320 patients with follow-up, there were 113 patients with live births, including 46 patients with CSD (one patient after IUI, 45 patients after IVF) and 67 patients without CSD (one patient after expectant management, one patient after IUI, 65 patients after IVF). Our study showed that the rate of cumulative live birth, ongoing pregnancy and live birth weight was similar between both groups. There are several differences that distinguish the aforementioned studies from our study. Friedenthal et al. showed that the live birth rate was significantly lower in patients with a previous caesarean delivery than those in the vaginal delivery cohort (49.0% vs 59.1%, p=0.02). In a subgroup analysis of women with a documented isthmocele, the authors found a notable difference in the live birth rate between the groups. The presence of an isthmocele was associated with a 49% reduction in the odds of ongoing pregnancy and live birth (aOR, 0.51; 95% CI, 0.30-0.89; P=0.02) (13). However, the authors did not clearly define the criteria for diagnosis of CSD and the decision for TVS. Moreover, the live birth rate in Friedenthal’s study is higher than ours because the author combined the ongoing pregnancy and live birth rates, and the study focused on the patients undergoing IVF treatment and elective single-embryo transfer procedure. Other outcomes such as miscarriage rate was similar between both groups, and is similar to the one in our study. In 2021, Yangping Li et al. conducted a meta-analysis study and reported that the live birth rate was lower in the patients with a previous caesarean delivery than those in the vaginal delivery cohort, with an I2 value of 18%. The fixed-effects model combined RR was 0.80 (95% CI 0.73, 0.86; p<0.00001) and Yangping Li reported the miscarriage rate was higher in patients with caesarean delivery (14). Our study reported the miscarrage and ectopic pregnancy rates were similar between both groups.

For pregnancy outcomes, the number of complications was very low. In our study, there were 4 cases with placenta previa (one patient with CSD and 3 patients without CSD), one case with placenta accreta (CSD group), one case with postpartum hemorrhage (CSD group), and no cases with uterine rupture. In other studies, the authors did not report complications. In 2004, Guise et al. showed that the risk of caesearean section pregnancy, placenta previa, placenta accreta and uterine rupture were increased (15); and in 2022, a study concluded CS scar myometrial thickness changes throughout pregnancy and that the appearance of the CS scar niche was associated with a significant decrease in LUS myometrial thickness between the second and third trimesters (16).

Many studies have investigated the influence of CSD on infertility treatment and pregnancy outcome, but the results are conflicting; and most lack direct comparison between CSD and non-CSD groups. Despite the limitations inherent in the retrospective cohort design of our study, we included comprehensive baseline and treatment cycle characteristics for all included patients. In addition, we analyzed the time to live birth of all patients to confirm the same follow-up period. Another limitation of our study is that did not collect details on infertility treatment, such as intrauterine fluid reduction. Future trials should be prospectively designed to determine the effect of endometrial fluid on infertility treatment and pregnancy outcome. This will provide robust data to support the findings of our analysis.

In conclusion, CSD did not have a detrimental effect on CLBR, but slightly increased β-hCG levels and CPR. Further studies focused on the correlation between endometrial fluid, pregnancy and complication outcomes are needed to evaluate the impact of CSD.

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**CONFLICT OF INTEREST**

LNV has received speaker and conference fees from Merck; and grant, speaker, and conference fees from Merck Sharpe & Dohme and Ferring. TMH has received speaker fees from Merck, Merck Sharp & Dohme, and Ferring. VTTT, VNAH, TDP, NTN, HTLH and DLN have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

**APPROVAL BY THE ETHICS COMMITTEE**

The study was approved by the Medical Ethics Committee at My Duc Hospital, Ho Chi Minh City, Vietnam (18/21/DD-BVMD) on 09th December 2021.

**CLINICAL TRIAL REGISTRY**

This was not a clinical trial.

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