Early fluid aspiration among cesarean section scar deficiency reduces cancellation rate and increase the clinical pregnancy rate among patients undergoing frozen embryo transfer

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ABSTRACT
Background: Invitro fertility (IVF) has been set up in Vietnam since 1998. Upto now, all over Vietnam, we have 26 centers of IVF with more than 2000 babies per year. Almost all IVF pregnancies have been terminated by Cesarean sections (C section) in Vietnam. Deficient C section scars sometimes make it very difficult for frozen embryo transfer because of both endometrium development...
and the fluid inside the uterus cavity. This study aims to identify whether early fluid aspiration among C section scar deficiency reduces cancellation rate and increase the clinical pregnancy rate or not among patients undergoing frozen embryo transfer.

**Methods:** We analyzed thirty-six cases with C section scar impaired followed endometrium preparation before frozen embryo transfer at Hung Vuong hospital – Ho Chi Minh city- Vietnam, from January 2016 to January 2019. All participants have all the inclusive criteria of the study. **Results:** The average age of participants is 37± two years. 30.5% are residents of Ho Chi Minh City, others living in other provinces of Vietnam from North to South. 15/36 (41.7%) participants have had a C section before going through IVF. 15/36 (41.7%) have C section by obstetric in other provinces. All 36 cases were aspirated early from the 7th day of endometrial preparation, 22/36 (61.1%) were second-hand suction on day 14 of uterine endometriosis, and 5 / 36 (13.9%) smoke the third time on the 21st day of endometrial preparation. In 36 cases participating in the study, 05 cases did not meet the criteria of embryo transfer, so the cycle was canceled, with the rate of cancellation of 5/36 (13.8%) much lower than the previous intervention with Antibiotics and anti-inflammatory (40%). The pregnancy rate is 16/31 (51.6%), and the clinical pregnancy rate is 14/31 (45.2%), which is equivalent to the general pregnancy, and clinical pregnancy rate of embryo transfer at Infertility department of Hung Vuong Hospital. **Conclusion:** Early intrauterine fluid aspiration during endometrial preparation in frozen embryo transfer patients with C section scar failure reduced the cancellation rate and increased pregnancy and clinical pregnancy rates in this patient group but also need more research in the future.

**Keywords:** C section scar failure, intrauterine fluid aspiration, assisted reproduction

1. **BACKGROUND**

Recently in Vietnam, people faces not only a low fertility rate of 1.86, but also the infertility rate in the reproductive age population of 7.7% (Zegers-Hochschild et al., 2009). In vitro fertilization treatment in Vietnam, conducted in 1997 at Tu Du Hospital, Ho Chi Minh City, marked a new step in the field of Vietnamese obstetrics and gynecology. In vitro fertilization (IVF) has helped many infertile couples to become natural fathers and mothers, contributing to the happiness of many families while significantly reducing the divorce rate in society. Over 20 years, IVF technology in Vietnam has got many achievements to date, from significantly improving the success rate to implementing the most advanced techniques in the world. According to the report of the Ministry of Health, Vietnam currently has more than 25 reproductive assistance centers nationwide, including both public and private systems (Takashima et al., 2017). In Vietnam, most IVF pregnancies end with a cesarean section. As a result, the number of patients returning to the IVF centers for a second IVF pregnancy with the cesarean section scar is quite frequent.

Cesarean section scar deficiency has been still unclear. Theories are explaining the mechanism of Cesarean section scar deficiency, such as first of all, due to non-standardized sewing technique for uterine rehabilitation. It means that the surgeon does not take the layers of the uterine muscle fully. Secondary, the process of scar healing is not complete. Thirdly, the mechanism of sticking the wound into the abdominal wall causes the decrease of uterine muscle perfusion during the process of scar healing. Whatever the mechanism of Cesarean section scar deficiency, it leads to fluid retention inside the uterus. This directly affects the growth of the uterine lining favorably for implant embryos. Therefore, IVF cases with Cesarean section scar deficiency are usually very difficult, especially in endothelial preparation for embryos transfer. Cesarean section scar deficiency resulted in the developed uterine lining and retained fluid inside the uterus, contributing to increasing cycle cancellation and pregnancy failure rates after embryo transfer (Tower and Frishman, 2013).

Interventions dealing with the situation of Cesarean section scar deficiency are still controversial because the effectiveness of the treatments is not useful. Most often, the opening of a Cesarean section scar deficiency is mediated by reshaping the surgery with an abdomen laparotomy or laparoscopic surgery. However, the rate of proper wound healing after surgery only reaches 50-70% (Florio et al., 2012, Marotta et al., 2013). Some other points of view in the treatment of endothelial preparation in patients who have had a Cesarean section scar deficiency are to use exogenous estrogen to prepare the endometrium until the embryo transfer criteria are met, combined with antibiotics and inflammation. However, this method has a very high cancellation rate, resulting in an increase in treatment costs and increased psychological pressure for the patient. Therefore, we raise a research question: Does early uterine evacuation combined with endometrial preparation with exogenous estrogen affect embryo transfer in patients with Cesarean section scar deficiency? We carried out this study to evaluate the effectiveness of early uterine evacuation combined with endometrial preparation by exogenous estrogen in embryo transfer in patients with Cesarean section scar deficiency.

2. **MATERIALS AND METHODS**

**Study population**

**Target population:** all patients preparing to frozen embryo transfer with Cesarean section scar deficiency during the study period.
Study population: all patients making to frozen embryo transfer with Cesarean section scar deficiency at Hung Vuong Hospital during the study period.

Sampling population all patients preparing to frozen embryo transfer with Cesarean section scar deficiency at Hung Vuong Hospital during the study period and meet the sampling criteria

Inclusion criteria were: 1) The patient performed IVF with frozen embryo transfer; 2) Having had a pregnancy before; 3) Have been diagnosed Cesarean section scar deficiency by a vaginal probe ultrasound. This ultrasonography was conducted by two independent ultrasound doctors to identify Cesarean section scar deficiency (Figure 1); 4) There are specific and complete contact information.

Exclusion criteria were: 1) Change treatment methods; 2) Severe side effects of the medication; 3) Insufficient information during analysis

Data collection
Recorded variables: age of the patient, place of residence, occupation, education level, area of previous cesarean section, time of uterine evacuation procedure in endothelial preparation, duration Endometrial preparation with exogenous estrogen, side effects, endometrium characteristics when deciding on embryo transfer such as thickness, endometrium classification, time of embryo transfer, number of transferred embryos, pregnancy outcome, Biochemical pregnancy or clinical pregnancy, number of cases canceling cycles, reasons for canceling cycles.

Statistical methods
The variables and data entered into Microsoft Excel 2010 and processed statistical analysis using R software. The qualitative variables estimated by n (%) and the quantitative variables are equal to ± standard deviation (SD).

3. RESULTS
Between January 2016 to January 2019, we collected 36 cases of Cesarean section scar deficiency to prepare for frozen embryos transfer at Hung Vuong hospital that met the criteria to receive samples. All participants in the study were diagnosed Cesarean section scar deficiency with a vaginal transducer ultrasound carried out by two doctors who read the results independently (Table 1).

All patients enrolled in the study were prepared with endogenous estrogen with exogenous estrogen (Progynova 2 mg) starting on day 2 of the menstrual cycle. Patients are instructed to take the medicines regularly every day with a maximum dose of 8mg, depending on the endometrial response to the drug. The endometrium is called getting the standard of embryo transfer when the thickness of the endometrium measured on the ultrasound is over 8mm (outside-outside measurement), there is a leaf image classification, and there is no chamber fluid retention bow. In order to minimize bias during the study, we controlled it by identification only one doctor for endometrium measurement and embryos transfer in all participants. The median endometrial preparation time in this study group was 20 ± 2 days. All post-embryo transfer patients used the same luteal support regimen with intra-vaginal progesterone transfer (Crimson 8%: 2 ampoules/day).
During the monitoring of the uterine endometrium development, we proactively use intrauterine insertion (IUI) catheter to draw fluid early on the 7th of the endometrium preparation process, then depending on whether there is fluid retention or not will decide whether or not to aspirate on days 14 and 21 of the preparation process (Figure 2).

Table 1 Epidemiological characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=36</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean, y</td>
<td>37± 2</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban of Ho Chi Minh city</td>
<td>11</td>
<td>30.5</td>
</tr>
<tr>
<td>Suburban</td>
<td>25</td>
<td>69.5</td>
</tr>
<tr>
<td>Career</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employees</td>
<td>15</td>
<td>41.7</td>
</tr>
<tr>
<td>Housekeeper</td>
<td>8</td>
<td>22.2</td>
</tr>
<tr>
<td>Business</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>19.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior high school</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>High school</td>
<td>18</td>
<td>49.9</td>
</tr>
<tr>
<td>College and postgraduate</td>
<td>12</td>
<td>33.4</td>
</tr>
<tr>
<td>Place of previous C section carrying out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ho Chi Minh city</td>
<td>15</td>
<td>41.7</td>
</tr>
<tr>
<td>Other provinces</td>
<td>21</td>
<td>58.3</td>
</tr>
<tr>
<td>Previous C section after IVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>91.7</td>
</tr>
<tr>
<td>No</td>
<td>03</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Figure 2 intrauterine insertion (IUI) catheters to draw early the fluid inside the uterus cavity

Table 2 Features of early uterine fluid evacuation during endometrial preparation for frozen embryos transfer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=36</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first time of fluid draw: on the 7th day of the endometrium preparation process</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>The second time of fluid draw: on the 14th day of the endometrium preparation process</td>
<td>22/36</td>
<td>61.1</td>
</tr>
<tr>
<td>The third time of fluid draw: on the 21st day of the endometrium preparation process</td>
<td>5/36</td>
<td>13.9</td>
</tr>
<tr>
<td>Cycle cancellation</td>
<td>5/36</td>
<td>13.9</td>
</tr>
</tbody>
</table>
Thus, we carried out embryo transfer for 31 cases out of a total of 36 study cases (Table 2). The pregnancy rate was 16/31 (51.6%). There were 05 (13.9%) cases that had to be canceled due to ineligibility to embryo transfer, of which 3 cases (60%) were due to excessive fluid retention in the uterine cavity and 02 cases (40%) without the eligible endometrium development for frozen embryos transfer: either the endometrium is too thin or layered even after taking the drug for 21 days. In 16 pregnancies in 14 days post-embryo transfer with beta HCG (+) results, we monitored follow-up convalescence, with 2/16 (12.5%) biochemical pregnancies and 14/16 cases with clinical pregnancy progression.

5. DISCUSSION

The diagnosis of Cesarean section scar deficiency is relatively easy via ultrasound with the vaginal probe. Most ultrasound authors agree to diagnose the Cesarean section scar deficiency when the patient has a history of cesarean section, and the ultrasound of the incision site shows a V-shaped defect arch with a V-shaped base rotating into the uterine muscle and V’s mouth swings into the uterine (Tower et al., 2013). This diagnosis made more accessible when the leak has fluid, the V appears clear with a hypoechoic image (Roberge et al., 2016). In this study, we also used a vaginal probe ultrasound to diagnose and detect Cesarean section scar deficiency, but we only confirmed the diagnosis when there were two ultrasound results with two independent ultrasound doctors giving the same conclusions.

Among frozen embryos transfer cases with Cesarean section scar deficiency, early uterine evacuation during endometrial preparation with exogenous estrogens frozen embryos transfer significantly reduces cycle cancellation. Indeed, we previously handled Cesarean section scar deficiency cases with antibiotics, anti-inflammatory cycle cancellation rates up to 40-50%. Early intrauterine fluid evacuation and endometrium preparation until meeting the eligible embryo transfer criteria (Florio et al., 2012, van der Voet et al., 2014) including: 1) Endometrium thickness on ultrasound reaches over 8mm; 2) The endometrium has leaf image layering; 3) No uterine fluid retention.

The doctor will then determine the delivery date. Embryos are unfrozen on the day of embryo transfer. The majority of embryos transferred were day three embryos (28/31 cases) and few days 5 (3/31) embryos. The embryo transfer was also carried out by one doctor to all cases (31/36) to reduce bias. The pregnancy rate is similar to the general pregnancy rate in the embryo transfer group in the infertility department of Hung Vuong Hospital, which is 45-52%. Besides, the clinical pregnancy rate is also encouraging, which is 14/31 (45.16%) is equivalent to the group of embryo transfer with Cesarean section scar deficiency at Hung Vuong Hospital. In the case of the canceling cycle, 05 cases all fell into the group with the highest number of suction times (3 times). In 5 cases of 3 times aspiration, we recorded 3 cases of reconstituted and active fluid in the uterus quite quickly and much more. Besides, there were 2 out of 5 cases of canceling the cycle because the endometrium was poorly developed in terms of thickness and stratification; 3) No uterine fluid retention.

The study conducted with the method of reporting series cases, so the reliability level is not high, and there is no control group to compare. The results in this study compared with the general data of the Infertility department of Hung Vuong Hospital, so the persuasion of the research has been not high yet. But the research results also open up a new direction in the intervention of patients with Cesarean section scar deficiency who have frozen embryos transfer, but more and more strong studies needed in the future.

5. CONCLUSION

Frozen embryo transfer in IVF patients with Cesarean section scar deficiency is genuinely a clinical challenge for both physicians and patients because the current intervention options have a low success rate. At the same time, the rate of canceling the treatment cycle is very high, causing economic and social costs for the patient and creating considerable pressure on the patient and positively affecting the treatment results. The study still has some limitations, but the results show that intervention by early intrauterine evacuation during the endometrial preparation contributes to a significant reduction in the cancellation rate of treatment cycles and a significant improvement, including pregnancy and clinical pregnancy rates.

Author’s contribution
All authors contributed equally to this work.
Funding:
This research received no external funding.

Conflict of Interest
The authors declare that they have no conflict of interest.

Informed consent
Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for study protocol
The study was approved by the Ethics Committee of Tu Du Hospital (ethical approval code: 051/2016-TDH).

REFERENCE