

# A pilot survey on obstetric complications in pregnant women with a history of repeated embryo implantation failure and those undergoing single local endometrial injury

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## Summary

**Purpose of Investigation:** To assess if a history of repeated implantation failure (RIF) or local endometrial injury (LEI) for RIF affects the pregnancy course in women who conceived in the subsequent *in vitro* fertilization (IVF)-embryo/blastocyst transfer (ET/BT) cycle. **Materials and Methods:** Of 42 pregnant women with a history of three consecutive failed ET/BT cycles with negative pregnancy tests, 11 patients had a clinical pregnancy in the immediate subsequent ET/BT cycle following (the RIF group), whereas 31 patients had a clinical pregnancy in the subsequent ET/BT cycle following single curettage LEI in the proliferative phase of the preceding spontaneous cycle (the RIF/LEI group). Information on the obstetric complications were retrieved from medical records and compared with that of women who had a live birth in the first ET/BT attempt (the control group). **Results:** The clinical pregnancy rate, ongoing pregnancy rate, and live birth rate were significantly higher in the RIF/LEI group than in the RIF group ( $p < 0.010$ ). There were no significant differences in the incidence of pregnancy of unknown location, ectopic pregnancy, miscarriage, stillbirth, preterm birth, premature rupture of the membranes, placenta previa, placental abruption, preeclampsia, pregnancy-induced hypertension, gestational diabetes, fetal growth restriction, caesarean section, and blood transfusion were similar between the three groups ( $p > 0.31$ ). **Conclusion:** In this pilot survey, neither a history of RIF nor LEI intervention for RIF increased the incidence of obstetric complications in the women who conceived in the subsequent ET/BT cycle.

**Key words:** Local endometrial injury; Repeated implantation failure; Obstetric complications.

## Introduction

Repeated implantation failure (RIF) is one of the major unanswered questions in infertility, which is recognized as serial failed conceptions following transfer of morphologically good embryos and/or blastocysts obtained in an *in vitro* fertilization-embryo transfer (IVF-ET) program. There is no consensus definition of RIF, but the literature recommends initiating the investigations following three failed cycles where good embryos/blastocysts were transferred [1].

The potential causes for RIF are subdivided into embryonic defects, diminished endometrial receptivity, and multiple factors. Recently, local endometrial injury (LEI) by curette biopsy is emerging as a promising tool to turn around the pregnancy outcome in infertile patients suffering from RIF [2-5]. The effect is thought to be mediated through the enhancement of endometrial receptivity by mechanical scratches, although its mechanism is not fully understood [4, 6, 7].

A growing body of evidence demonstrated that LEI not only improves embryo implantation rate but also live birth rate in the subsequent embryo/blastocysts transfer (ET/BT) cycle. Despite the beneficial reports of LEI, there

is a concern that LEI may cause damage such as scar formation or partial defect to the endometrium and myometrium, which potentially leads to onset of maternal and fetal problems including abnormal placentation, fetal growth restriction, and obstetric hemorrhage. Few studies, however, investigated the incidence of the obstetric complications in the pregnancy immediately following RIF or LEI for RIF. In this study, the authors aimed to survey the pregnancy course in the women who conceived in the subsequent IVF-ET/BT cycle following RIF and LEI.

## Materials and Methods

The pregnancy outcomes of infertile women undergoing IVF-ET/BT with controlled ovarian stimulation were followed up. The regimens for controlled ovarian stimulation using gonadotropin-releasing hormone agonist short or gonadotropin-releasing hormone antagonist protocol were described elsewhere [8]. Serum human chorionic gonadotropin concentration was measured on the 11<sup>th</sup> day following day-3 early cleavage ET or on the ninth day following day-5 BT using an automated enzyme immunoassay. According to the manufacturer's instructions, the values with two IU/l or more were regarded as a positive pregnancy test. Luteal support with

Table 1. — Pregnancy outcome and incidence of obstetric complications in ongoing pregnancy cases in RIF, RIF/LEI, and control group.

	RIF	RIF/LEI	Control	<i>p</i> value
Pregnancy outcome				
Clinical pregnancy	11/79 (13.9%)	31/92 (33.7%)	237/658 (36.0%)	< 0.0081
Ongoing pregnancy (>12 weeks)	8/79 (10.1%)	24/92 (26.1%)	207/658 (31.5%)	< 0.030
Live birth	8/79 (10.1%)	24/92 (26.1%)	186/642 (29.0%) *	< 0.030
Miscarriage/stillbirth	0/79 (0%)	0/92 (0%)	5/642 (0.8%) *	> 0.52
Obstetric complications in ongoing pregnancy cases				
Premature rupture of membranes	1/8 (12.5%)	2/24 (8.3%)	12/191 (6.3%)	> 0.58
Placenta previa	0/8 (0%)	1/24 (4.2%)	7/191 (3.7%)	> 0.56
Placental abruption	0/8 (0%)	1/24 (4.2%)	1/191 (0.5%)	> 0.20
Placental accreta	0/8 (0%)	1/24 (4.2%)	3/191 (1.6%)	> 0.36
Preeclampsia	0/8 (0%)	0/24 (0%)	3/191 (1.6%)	> 0.73
Pregnancy-induced hypertension	0/8 (0%)	1/24 (4.2%)	6/191 (3.1%)	> 0.62
Gestational diabetes mellitus	0/8 (0%)	0/24 (0%)	1/191 (0.5%)	> 0.90
Fetal growth restriction	1/8 (12.5%)	1/24 (4.2%)	17/191 (8.9%)	> 0.50
Stillbirth	0/8 (0%)	0/24 (0%)	3/191 (1.6%)	> 0.14
Preterm birth	1/8 (12.5%)	2/24 (8.3%)	12/191 (6.3%)	> 0.9
Caesarean section	3/8 (37.5%)	7/24 (29.2%)	65/191 (34.0%)	> 0.14
Blood transfusion	1/8 (12.5%)	1/24 (4.2%)	10/191 (5.2%)	> 0.34

Footnote. \*The pregnancy course of 16 women in the control group was unavailable.

progestogens was continued until nine weeks of gestation. RIF was defined as a history of three consecutive negative pregnancy tests following transfer of high-grade early cleavage embryos and/or blastocysts [9, 10]. Based upon the treatment preferences of the patients, hysteroscopy and single LEI was or was not performed once between the sixth and 12<sup>th</sup> day in the spontaneous cycle as previously described [11]. The patients with endometrial micropolyps, submucosal fibroids, and intrauterine septa/adhesion were excluded from the study. The patients with normal hysteroscopic findings proceeded subsequent ET/BT cycle. Information on pregnancy course was retrieved from medical records.

The continuous variables were analyzed using Tukey-Kramer test for multiple comparisons or Dunnett's test for comparisons with the control group. The proportional data sets were compared using Pearson's chi-square test, Fisher's exact test, or Ryan's multiple comparison method. A *p* value less than 0.05 was considered significantly different.

## Results

From January 2010 to March 2012, a total of 789 infertile women underwent IVF-ET with short or gonadotropin-releasing hormone antagonist flexible protocol. Of them, 207 (26.2%) had a clinical pregnancy in the first transfer cycle of morphologically good embryo/blastocyst and live birth (the control group). One hundred and eighty-five patients (23.4%) had RIF despite three transfer cycles of morphologically good embryos/blastocysts. Of them, 171 patients preferred further infertility treatment. While 79 patients continued ET/BT cycle (the RIF group), 92 patients opted for single curettage LEI in the proliferative phase of the subsequent spontaneous cycle (the RIF/LEI group).

There were no significant differences in age and body mass index between the RIF group ( $36.9 \pm 3.3$  years,  $20.6 \pm 1.7$  kg/m<sup>2</sup>), RIF/LEI group ( $37.8 \pm 3.8$  years,  $20.8 \pm 2.5$  kg/m<sup>2</sup>), and the control group ( $36.1 \pm 4.2$  years,  $20.5 \pm 2.3$  kg/m<sup>2</sup>) (*p* > 0.41). Information on the pregnancy course was available in all patients in the RIF/LEI group and RIF group, and 191 out of 207 (92.3%) patients in the control group (Table 1). There were no reports on fatal obstetric complications in the patients in each group. The clinical pregnancy rate and ongoing pregnancy rate and live birth rate were significantly higher in the RIF/LEI group and control group than in the RIF group (*p* < 0.010). Meanwhile, the incidence of pregnancy of unknown location, ectopic pregnancy, miscarriage, stillbirth, premature rupture of the membranes, placenta previa, placental abruption, preeclampsia, pregnancy-induced hypertension, gestational diabetes, fetal growth restriction, preterm birth, caesarean section, and blood transfusion were similar among the three groups (*p* > 0.31).

## Discussion

Studies demonstrated that IVF-ET pregnancy is a risk factor of obstetric complications [12]. Several researchers hypothesized that defective blastocyst implantation may be the initial step that lead to some obstetric complications such as preeclampsia or gestational hypertension [13]. In this pilot survey, the authors found that past history of RIF does not increase the onset of obstetric complications in the subsequent IVF-ET pregnancy. Moreover, LEI for infertile women suffering from RIF did not have a negative impact on the gestational course and outcome of these patients.

LEI was shown to upregulate the local expression of the embryo implantation-associated molecules including chemokines (CCL4 and CXCL1), cytokines (tumor necrosis factor- $\alpha$  and interleukin-15), adhesion molecules (transmembrane mucin-1, laminin 4, and integrin 6), and membrane-bound proteins (uroplakin 1b, adipose differentiation-related protein, and lysosomal associated membrane protein-2). These findings support the idea that LEI is capable of inducing mucosal inflammatory responses required for migration, attachment, and invasion of blastocysts [4, 6, 7, 14, 15]. The current findings implicate that these local inflammatory responses induced by mechanical scratches do not negatively influence intrauterine environment during the pregnancy course.

Early studies adopted multiple LEI in the preceding cycle [2-6]. However, considering the pains of the patients and the onset of the complications, it is conceivable that less invasive approach is more acceptable in the clinical practice. In this regard, the present authors previously demonstrated that the ongoing pregnancy rate following single-time LEI by curettage biopsy in the proliferative phase of the preceding spontaneous cycle is comparable to that following multiple LEI [8]. In combination with the results of the current study, the present authors suggest single LEI by curettage biopsy in the proliferative phase of the preceding spontaneous cycle as a safe and effective medical intervention to treat unexplained RIF.

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