



## Article

## The effect of endometrial scratch on natural-cycle cryopreserved embryo transfer outcomes: a randomized controlled study

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### KEY MESSAGE

This prospective, double-blind, randomized controlled study on the evaluation of the implantation and pregnancy rate after endometrial scratch prior to natural-cycle cryopreserved embryo transfer found no beneficial effect in an unselected group of women. Further studies on its effect in women with recurrent implantation failure after IVF are warranted.

### ABSTRACT

The benefit of endometrial scratch (ES) prior to embryo transfer is controversial. Systemic analysis has confirmed its potential benefit, especially in women with repeated IVF failures, yet most studies have focused on fresh embryo transfer, and its effect on vitrified-warmed embryo transfer (FET) cycles is yet to be explored. We hereby present our prospective, double-blind, randomized controlled study on the evaluation of the implantation and pregnancy rate after ES prior to natural-cycle FET. A total of 299 patients underwent natural-cycle FET and were randomized to receive ES ( $n = 115$ ) or endocervical manipulation as control ( $n = 114$ ) prior to FET cycle, and a total of 196 patients had embryo transfer (93 patients in each group). Our study showed no significant difference in the implantation and pregnancy rate, as well as the clinical and ongoing pregnancy or live birth rates between the two groups. It appears that ES does not have any beneficial effect on an unselected group of women undergoing FET in natural cycles. Further studies on its effect in women with recurrent implantation failure after IVF are warranted.

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## Introduction

Despite medical advances in assisted reproductive technologies in the last decade, including selecting the best embryo to transfer at blastocyst stage or reducing chromosomally abnormal embryos by pre-implantation genetic screening, the success rate of IVF remains modest, with clinical pregnancy rate per embryo transfer at 33.8% [European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) et al., 2016].

Implantation is the rate-limiting step for the success of IVF [Paulson et al., 1990]. Successful implantation requires a receptive endometrium, a functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues [Simon et al., 2000]. Generally, the probability of an embryo successfully implanting is approximately 30%, while its failures can be multifactorial. Recurrent implantation failures (RIF) may occur in 5–10% of women undergoing IVF cycles, and a significant proportion of this is related to endometrial receptivity. Endometrial scratch (ES) is one of several strategies proposed to improve endometrial receptivity.

The use of ES to improve implantation rates in women undergoing IVF was first described in 2003 [Barash et al., 2003], which showed that ES doubles the rates of implantation, clinical pregnancy and live birth in women with RIF. Since then, the procedure has been further studied in women with previous IVF failures [Almog et al., 2010; Baum et al., 2012; El-Toukhy et al., 2012; Gibreel et al., 2015; Gnainsky et al., 2010; Karimzadeh et al., 2009; Narvekar et al., 2010; Potdar et al., 2012; Raziel et al., 2007; Singh et al., 2015]. To date, the majority of studies have found beneficial effect of ES in women undergoing embryo transfer [Barash et al., 2003; Guven et al., 2014; Inal et al., 2012; Karimzadeh et al., 2009; Narvekar et al., 2010; Nastri et al., 2013; Raziel et al., 2007; Shohayeb and El-Khayat, 2012; Singh et al., 2015], whereas a few others could not confirm the benefit [Baum et al., 2012; Yeung et al., 2014].

Three systematic reviews and a meta-analysis all concluded that there appeared to be a general beneficial effect of ES in IVF [El-Toukhy et al., 2012; Potdar et al., 2012]. Among the 14 trials included in a recent updated Cochrane Review, 13 randomized controlled trials (RCT) studied endometrial injury during the menstrual cycle before embryo transfer, in which seven studies included women with previous IVF failures, five included women regardless of the number of previous IVF cycles and one included only women undergoing their first IVF cycle; the study found a favourable effect of ES with an increased clinical pregnancy rate based on pooled results from 13 RCT including 1972 women [relative risk (RR) 1.34, 95% confidence interval (CI) 1.21–1.61,  $P = 0.002$ ] and an increase in live birth or ongoing pregnancy rate from nine RCT including 1496 women [RR 1.42, 95% CI 1.08–1.85,  $P = 0.01$ ] [Nastri et al., 2015]. Since the Cochrane Review was published, two additional RCT have been reported [Mahran et al., 2016; Singh et al., 2015]. Singh et al. [2015] examined women with previous failed IVF-embryo transfer and found a significant increase in implantation rate after ES in patients while Mahran et al. [2016] studied patients undergoing their first IVF cycle and observed significant improvement in both implantation and live birth rate. The findings of these two studies were consistent with the conclusion reached in the Cochrane Review. However, it is noteworthy that all the studies analysed in the Cochrane Review and the two recent, additional RCT were all related to fresh embryo transfer cycles.

There are several important confounding variables affecting the outcomes of ES, including the numbers of previous IVF failures and the type of embryo transfer cycles, i.e. fresh embryo transfer in stimulated cycle, FET in natural or artificial cycle using hormone replacement therapy (HRT). Whilst studies have been performed in fresh embryo transfer cycles [Barash et al., 2003; Baum et al., 2012; Gibreel et al., 2015; Guven et al., 2014; Inal et al., 2012; Karimzadeh et al., 2009; Mahran et al., 2016; Narvekar et al., 2010; Nastri et al., 2013; Raziel et al., 2007; Shohayeb and El-Khayat, 2012; Singh et al., 2015; Yeung et al., 2014] and FET in HRT cycles [Aflatoonian et al., 2016; Dunne and Taylor, 2014], the possible impact of ES in natural-cycle FET has not been previously examined.

Consequently, we conducted a prospective, double-blind, randomized controlled trial to evaluate the impact of local endometrial injury in the mid-luteal phase of the cycle immediately preceding natural-cycle FET.

## Materials and methods

### Study design

This was a prospective, double-blind, randomized controlled study conducted in the Assisted Reproductive Unit of the Prince of Wales Hospital, Department of Obstetrics and Gynaecology of The Chinese University of Hong Kong, during the period of March 2013 to April 2016.

### Study population

All patients scheduled for FET cycles using non-donor oocytes were assessed for eligibility. Women who had normal ovulation and were deemed suitable for natural-cycle FET were recruited to the trial. The exclusion criteria included those who had any uterine anomaly or pathology such as endometrial polyps, endometriomas larger than 4 cm or hydrosalpinx.

### Randomization

After informed consent, patients were randomly allocated to either study group who would receive ES or a control group in which endocervical manipulation would be performed using computer-generated random numbers concealed in opaque envelopes. A research nurse coordinated the randomization process. The doctors who performed the ETs, the embryologists and the patients involved in the study were blinded to the treatment allocation.

### Intervention

ES (study group) or endocervical manipulation (control group) were performed at the mid-luteal phase of the preceding menstrual cycle before FET, which was scheduled to take place  $7 \pm 1$  days after the surge of LH, according to the LH surge identified by daily urine LH monitoring from day 8 of the cycle. Serum progesterone level was checked at the same time to confirm spontaneous ovulation.

### Endometrial biopsy

Endometrial samples were obtained using a biopsy catheter (Pipette; MedGyn, USA) by inserting the pipette through the cervical os and

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