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Local Endometrial Trauma (Endometrial Scratch): A Treatment Strategy to Improve Implantation Rates

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1. Background

Implantation continues to be a rate-limiting step in the success of assisted conception treatments. For implantation to occur, a blastocyst must attach to the endometrium under the influence of estrogen and progesterone. Many factors can affect an embryo's implantation potential, including sperm, oocyte and embryo quality, and iatrogenic factors, such as laboratory conditions and embryo transfer technique. In addition, many conditions of the uterine cavity may influence the ability of the embryo to implant, such as submucosal fibroids,[1] intrauterine adhesions[2] and endometrial polyps.[3]

Historical observations made in the guinea pig provided the first evidence that injury to the progestational endometrium resulted in decidualisation and subsequent improved uterine receptivity.[4] Subsequently, several studies[5-13] have examined the impact of endometrial injury in the luteal phase preceding an in vitro fertilisation (IVF) treatment cycle in women with recurrent implantation failure (RIF), which appear to provide convincing evidence of benefit of superficial endometrial injury (or scratch) in improving the implantation rate in this group of women. While there is, as yet, no universally accepted definition for RIF, it has been proposed as the failure to achieve a clinical pregnancy after transfer of at least four good quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years.[14] Thus far, the effect of endometrial trauma on pregnancy outcome in women who have experienced recurrent miscarriage (RM) has not been evaluated.

2. Evidence for endometrial trauma and improved implantation rates

In a prospective study[5] involving 134 women who had failed to conceive after one or more IVF treatment cycles, Barash et al. explored the possibility that local injury of the endometrium in the cycle preceding IVF treatment increased the success rate of implantation. Of these women, 45 were randomly selected to have repeated endometrial biopsy on days 8, 12, 21 and 26 of the cycle immediately preceding their IVF treatment cycle. The treatment resulted in significant improvements (approximately double) in the rates of implantation, clinical pregnancy and live births (27.7%, 66.7% and 48.9%, respectively) compared with control subjects who did not have an endometrial biopsy (14.2%, 30.3% and 22.5%, respectively). Similarly, a further prospective nonrandomised study[6] identified a favourable influence of local injury to the endometrium in intracytoplasmic sperm injection patients with high-order implantation failure. Two systematic reviews and meta-analyses[7,8] have shown a beneficial effect of local endometrial injury in RIF, but advised that further robust randomised trials are required.

Not all studies have identified a benefit from local endometrial trauma in advance of IVF cycles. A prospective randomised controlled trial[15] did not report any benefit from local injury to the endometrium in women with a high number of implantation failures, but this was a small study with a total of 36 women.

A further retrospective cohort analysis of 737 ovum donation cycles[16] concluded that there was no significant improvement in clinical pregnancy rates and live birth rates in cycles subjected to endometrial injury. A tendency toward improvement was observed when endometrial injury was performed after four implantation failures.

3. Mechanisms by which endometrial trauma may improve implantation

The mechanism by which endometrial trauma may lead to improvement in IVF outcome in women with RIF remains unclear. Successful implantation requires synchronous development of the endometrium and the embryo. It has been suggested that repeated IVF failure may be related to asynchrony of the

endometrium with the embryo stage[17–20] and, in particular, that endometrial development in IVF cycles may be more advanced than that of natural cycles by 2–4 days.[18,21]

It is postulated that local endometrial injury in stimulated cycles delays endometrial development due to the wound repair process and thereby corrects the asynchrony between the endometrial and embryo stages.[13] In natural cycles, embryo implantation occurs during the endometrial 'window of implantation', which is characterised by the expression of a number of factors by the endometrial epithelial cells, including adhesion molecules, cytokines, growth factors and enzymes.[22,23] Many investigators speculate that the repair process following local injury is associated with increased production of these various growth factors conducive to implantation.[5,8,17,24] Endometrial gene modulation following endometrial injury has also been hypothesised to increase endometrial receptivity.[25]

The process of repair after tissue injury is mediated in part by immunological factors, some of which are also involved in the embryo implantation process. A possible reason for improved embryo implantation after endometrial scratch is the production of these immunological factors brought about by the trauma. There are very few studies investigating this hypothesis, but one controlled clinical study[11] has shown increased expression of tumour necrosis factor alpha (TNF-α), interleukin (IL)-15 and other immune mediators in the endometrium of women who had undergone a previous biopsy during the proliferative phase of the same cycle.

TNF-α is a key proinflammatory cytokine and increases the production of many other cytokines, including leukaemia inhibitory factor, IL-11, IL-6 and granulocyte-macrophage colony-stimulating factor, all of which are postulated to play a role in the implantation process.[22] A similar study in women undergoing IVF[26] also showed that endometrial trauma carried out in the proliferative phase of the cycle increased the uterine natural killer (uNK) cell numbers that had been reduced by ovarian stimulation. IL-15 plays a pivotal role in the control of uNK cells,[27] and changes in uNK cell numbers may be related to the changes seen following IL-15 administration in other studies.[11,28] uNK cells are also thought to play a role in implantation[29] and abnormal numbers have been seen in women with reproductive failure, including RM[30] and RIF after IVF.[31] In contrast to the study by Junovich et al.[26] where low uNK cell numbers were associated with adverse pregnancy outcome, studies of women with RM[30] and RIF after IVF[31] showed increased uNK cell numbers, and one nonrandomised study[32] showed that the reduction in 'high' uNK cell numbers was associated with improved pregnancy outcome in women with RM. Another, as yet unexplored, mechanism for the prolonged effect of tissue trauma on endometrial function may involve recruitment and activation of endometrial stem cells.[33,34]

4. Timing

The conclusion of studies to date[5–13] suggests that endometrial scratch should be carried out approximately 7 days prior to the onset of menstruation, immediately before the start of ovarian stimulation for IVF treatment. All couples should be advised of the importance of protected intercourse in the month of the endometrial scratch, since if carried out in the luteal phase of the cycle there is the risk of performing the procedure in the presence of an early pregnancy. The procedure should not be performed later during the IVF treatment cycle, as shown by a prospective controlled trial[35] where the procedure was performed at the time of oocyte recovery and led to a decreased pregnancy rate.

5. Technique of inducing endometrial injury

Endometrial injury or scratch is usually performed using an endometrial biopsy sampler. The sampler is introduced into the endometrial cavity and the inner shaft is then withdrawn to create a negative pressure, after which the sampler is gradually rotated as it is moved up and down the endometrial cavity several times to produce the 'scratching' action.

6. Who may benefit from endometrial trauma?

One randomised controlled study[36] that examined the effect of endometrial injury in an unselected group of women of whom 69.7% were embarking on their first cycle of IVF showed no significant improvement in pregnancy rate. However, this study was not powered towards women undergoing first-time IVF and included a mixture of protocols. Furthermore, there were no restrictions on the women's age or the day of embryo transfer, leaving the question of whether or not endometrial trauma may benefit women undergoing their first IVF cycle unanswered.

Current evidence suggests that endometrial trauma may benefit women with RIF. One published review[37] of endometrial injury in women undergoing assisted reproductive technology examined 14 trials, which included 1063 women in the intervention groups and 1065 women in the control groups. The authors concluded that the evidence was of moderate quality and indicated that endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer cycle was associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous failed embryo transfers.The quality of the evidence was considered moderate because insufficient participants were included and a large proportion of the studies had critical methodological limitations.

A further retrospective cohort analysis of 737 ovum donation cycles[16] identified a tendency toward improvement when local endometrial injury was performed after four implantation failures. Defining the optimal number of previously failed embryo transfer cycles for deciding on local endometrial injury needs, therefore, to be evaluated in large cohort randomised prospective clinical trials.[16]

7. Opinion

Further prospective randomised studies of sufficient power are required to confirm or rule out the clinical value of local endometrial trauma.The available evidence points towards a potential benefit of endometrial biopsy in women with RIF when performed in the cycle preceding the IVF treatment cycle. Current evidence on the value of the procedure in women undergoing their first IVF cycle is lacking.

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