# Endometrial scratch

## A tale with a happy ending?

**A recent survey found that 92% of physicians questioned support the concept of endometrial 'injury' before IVF in women with recurrent implantation failure. Ying Cheong and Nick Macklon explore the science behind the technique and ask if the magic wand will yield a fairy story.**

The tale of the rapid introduction into clinical IVF of endometrial injury (or, euphemistically, 'scratch') is a salutary one. It tells us much about the challenges and frustrations felt by clinicians and patients alike when faced with implantation failure after IVF. It reflects the lack of other effective clinical interventions, and it reveals many of the drivers for implementing innovative practices into modern fertility medicine. The frustrations are real and well founded. Despite spectacular advances in embryology, ongoing pregnancy rates after IVF appear to have plateau'd, and in recent years the endometrium has increasingly become the focus of efforts to identify new ways to improve outcomes.

Up to now, however, the story has not been very encouraging. Complex and expensive medical therapies, based largely on the two premises that thrombophilia and disrupted immune responses to the presence of an embryo can be successfully modulated, have failed to deliver any real benefits. New insights into human endometrial biology and embryo-endometrial signalling offer promising new avenues for research, but sometimes serendipity is as important to advancing care as fundamental research. And there begins the story of the endometrial scratch.

At the end of the last millennium an Isreali group was investigating endometrial protein markers in 12 women who had previously suffered failed IVF treatment.[1] However, observing that 11 of these women who had had endometrial biopsy went on to conceive in the following cycle, the group moved quickly to investigate the possible therapeutic benefit of endometrial trauma, and in 2003 published the first case series, reporting an apparent doubling of IVF pregnancy rates in those having a biopsy in the previous cycle.[2] So here was a simple clinical intervention, already within the skills and practice of trained clinicians, that promised to revolutionise IVF outcomes.

Initial clinical reports were very promising, and, with a frustrating lack of therapeutic options for improving endometrial receptivity and patient-driven pressure to 'try something', the scratch seemed to offer clinicians a magic wand. No wonder it was rapidly adopted. In a recent survey, 83% of clinicians were found to recommend a scratch prior to IVF and 92% to endorse the technique in women with recurrent implantation failure.[3] Yet we still await confirmation of its efficacy from large randomised studies.

So is the tale of the endometrial scratch a fairy story destined to disappoint? Or will it after all have a happy ending?

### Does it work?

The endometrial scratch distinguishes itself from other receptivity interventions in at least two ways. Firstly, it has been a wholly empirical intervention searching for a biological explanation for its efficacy. Even the more creative branches of reproductive immunotherapy can refer to some degree of mechanistic plausibility to justify their interventions. Secondly, it is counter-intuitive and even anti-Hippocratic. 'First do no harm' is exactly the opposite of what the scratch requires. So, if we are to justify

'harming' the patient, we need to be well assured that it works, and preferably that we know why.

Since Barash et al described in 2003 the 'doubling' of pregnancy rate in their retrospective case-control study, there have been 15 randomised controlled trials and five meta-analyses evaluating the impact of endometrial scratching on reproduction. The conclusions from these studies are conflicting. While there is support for the beneficial effects of the procedure, other studies and authors have suggested the opposite.[4,5,6] This has led to a lively controversy played out in our journals and conference halls, particularly as personal experience conflicts with data from more recent well designed but conflicting studies.[7,8]

As clinicians, we are frequently challenged to devise sound treatment strategies in the face of inconsistent findings from studies and systematic reviews, and often the patients will try to guide us with information from the lay press. This is reflected in the ongoing uncertainty over the efficacy of acupuncture to improve pregnancy rates after IVF.[9] Such non-consensus may often arise because the reviewers differed in their choice of methods, their assessment of the quality of studies for inclusion, and their summing-up evidence.

Analysis of the studies included in the major meta-analyses of endometrial scratch shows them to be heterogeneous in design - with pooled studies of participants having first-time IVF, or with one or more failures or 'recurrent' implantation failure, itself a condition characterised by various causes and definitions.

The studies included in these reviews also vary considerably in the timing of the scratch. Some involved intervention in the preceding month, some within the month of ovarian stimulation, some during oocyte retrieval and others during hysteroscopy. The method of scratch also varies, from not being specified to more than one scratch; from using the Pipelle to the Novak curette. Furthermore, the control groups were non-standardised. For example, some used a sham-type intervention. while others continued with routine care, simply omitting a scratch procedure.

Most studies, therefore, while concluding that there is a clinical benefit of endometrial scratch in improving pregnancy rates, were judged to suffer from a high risk of bias, As a result, almost all the authors of the reviews have concluded that more evidence is required to make their conclusions robust. Conversely, some reviewers who adopted a strategy which limits heterogeneity within the meta-analysis concluded that there is no clinical benefit of endometrial scratch, or that it is possibly only useful in a subgroup of women with recurrent implantation failure.[7,8]

The interpretation of conflicting results to help inform and implement clinical practice requires a common sense approach. The field is still uncertain, and this equipoise provides the opportunity to carry out definitive, well powered randomised controlled studies. It is reassuring to report that these are now under way.

### How does it work?

From the molecular perspective, the over-arching belief is that endometrial scratching induces an inflammatory response which encourages implantation. Pro-inflammatory factors are implicated in eliciting a receptive endometrial phenotype and the increase of pro-inflammatory cytokines, chemokines, and immune cells after endometrial scratching has been observed.[10] Our own group has reported increased implantation rates when a pro-inflammatory cytokine profile is identified in endometrial secretions aspirated immediately prior to embryo transfer.[11] However, the ability for endometrial scratch to simply invoke inflammation and thereby result in better implantation could be deemed overly simplistic and unconvincing.

As mentioned earlier, extensive research in reproductive immunology has not yet yielded any significant therapeutic leads for improved implantation rates. The accurate prediction of endometrial receptivity and prediction is an ongoing challenge in the field of reproductive medicine, and the most promising strategies are only on the cusp of clinical validation.[12] An endometrial biopsy is a prerequisite part of 'receptivity testing' using gene array tests but surprisingly this has not been associated with better pregnancy outcomes in this cohort of patients.[13]

In recent years the importance of endometrial decidualisation as a determinant of successful implantation has become increasingly apparent.[14] It has been hypothesised that endometrial injury may induce or enhance endometrial decidualisation, and thus could assist implantation. Those seeking experimental evidence to support this concept can point to the induction of decidualisation by embryo implantation and the efficacy

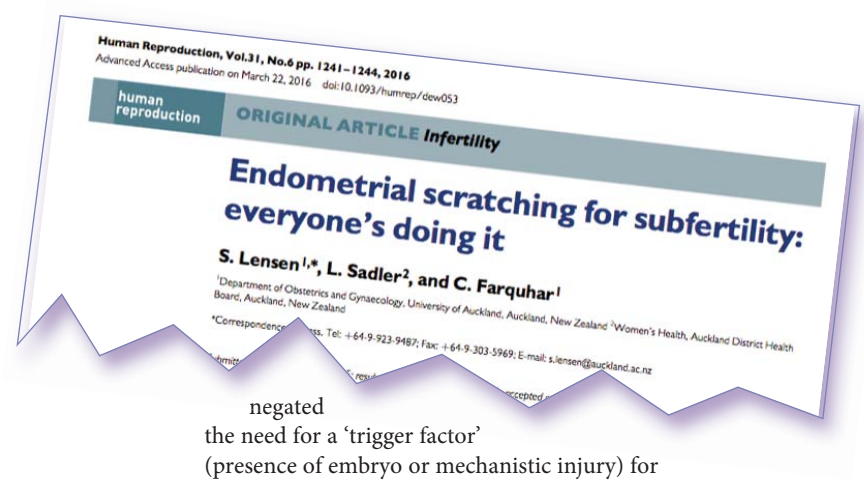
*Ying Cheong and Nick Macklon: 'Robust trials to possibly undo the introduction of an "unproven" procedure rather than vice versa.'*

of mechanical and irritant stimuli in inducing decidualisation in laboratory animals.

Mechanistically, however, there are distinct differences in the way endometrial stromal cells differentiate between commonly employed animal models and higher primates. In the latter group, which includes humans and apes, decidualisation is not triggered by the implanting embryos but is hormonally regulated. In humans, decidualisation occurs in every ovulatory cycle irrespective of conception or implantation. So, while a mechanical stimulus (taken here to be synonymous to a 'scratch') has long been known to provoke rapid growth of decidua cells in guinea pigs and rodents (and there may be an element of evolutionary conservation of this mechanism in humans), the story is likely to be more complex. For instance, the clinical effect relies on decidualisation being modulated in the cycle following the intervention rather than in the scratch itself.

Despite this rather unpromising landscape, recent work by the Brosens group points to a possible plausible mechanism by which endometrial injury might increase stem cell numbers in the endometrium, and encourage the removal of excessive senescent cells by stimulating NK cell activity.[15]

In addition, clinical evidence for the propensity of implantation to occur in uterine fibrosis or a scar niche, resulting in the ongoing challenges in the management of 'scar' pregnancies, would support an element of decidual enhancement distant in time to the episode of trauma. Indeed, in humans, the process of menstruation can be viewed as a hormonally orchestrated monthly 'injury' necessary for recruitment of the endometrial stem cell system and subsequent implantation.[16] This development of an endogenous control through the hypothalamic pituitary axis for menstruation may have evolutionarily



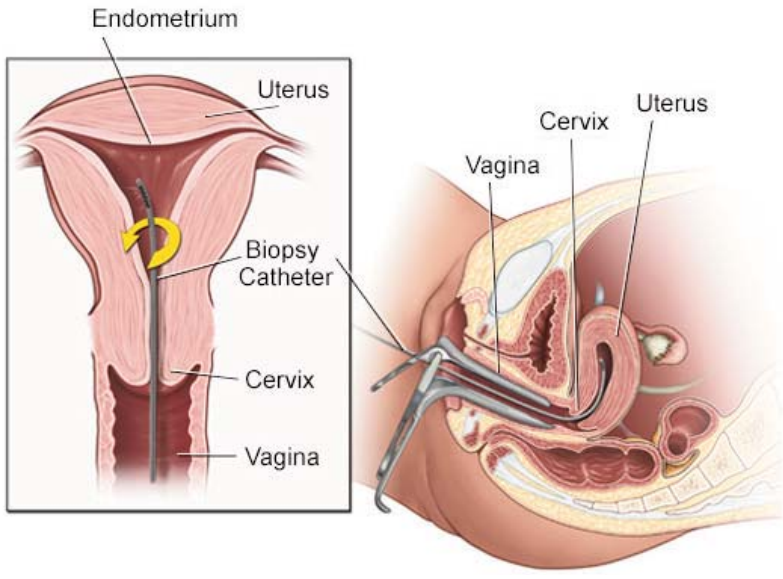

negated the need for a 'trigger factor' (presence of embryo or mechanistic injury) for decidualisation.

From an evolutionary perspective, the notion of reproductive tract injury and its association with conception is a familiar concept. Lost in human lineage due to the deletion of an otherwise highly conserved sequence, but preserved in many animals (eg, chimpanzees, cats and mice), is the presence of penile spines. These appendages are crucial for effective mating, probably through the generation of reproductive tract injury, induction of spontaneous ovulation, or via the removal of 'mating plugs' that may prohibit effective fertilisation. Hence, the proposed mechanistic hypotheses around how the scratch works should be expanded to include the processes involved in conducting a scratch rather than focusing on the endometrium alone. However, development secondary to evolution need not necessarily always confer reproductive advantages, and it could be that in a selected population a mechanical stimulus by way of endometrial injury reconstitutes a missing evolutionary link. In seeking mechanistic explanations as to how the scratch works, it is therefore important to adopt a systems approach in conjunction with investigating local factors.

## Conclusion

*Primum non nocere* dictates that clinicians be honest with patients. At this juncture, endometrial scratch remains an unproven procedure, without full knowledge of its potential implications (or risks). This should be clearly explained to patients to ensure they are fully informed and consented for treatment. Last but not least, clinicians should audit outcomes of the scratch procedure when used in clinical practice, as this could inform us of the 'unintended' but practical advantages of the procedure.

To scratch or not to scratch, that is still the question. There are no quick answers, other than to pursue good-quality clinical trials. These are happily ongoing and we find ourselves in the scientifically unorthodox, yet not uncommon, situation of engaging in robust trials to possibly undo the introduction of an 'unproven' procedure rather than vice versa. As Lensen et al tell us, 'everyone is doing it' and it is now being offered well beyond the initial indication to women having IUI and even trying to conceive spontaneously.[3] Will we look back at this phenomenon as a well meaning but misguided fairy




*Endometrial biopsy procedure.*

tale or will the story of the endometrial scratch have a happy ending? The answer will become apparent 'all in good time' (Horace, 65-8 B.C).

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## Freeze-all oocytes

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### 7. Task force needed

Freezing oocytes instead of embryos for the prevention of OHSS presents undeniable advantages. However, this strategy still needs careful evaluation to rule out potential disadvantages before extending its application to other situations, such as increased progesterone level on the day of triggering. Therefore, prospective studies are required to assess the efficiency this approach.

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