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human reproduction EDITORIAL

A nod is as good as a wink to a blind horse: round 2

J.L.H. (Hans) Evers*, Editor-in-Chief

*Correspondence address. E-mail: jlh.evers@gmail.com

Not so long ago, in the November 2014 issue of this journal, I applauded Tracy Yeung's randomized controlled trial on endometrial *scratching* (Evers, 2014). She and her co-authors concluded from this study that among unselected subfertile women undergoing IVF endometrial injury did not result in a significant improvement of the ongoing pregnancy rate (Yeung *et al.*, 2014). Usually, after important studies have rejected the effectiveness of a theoretically attractive—and lucrative—new procedure, subsequent Letters-to-the-Editor will draw attention to a particular subgroup of patients who still might potentially benefit. So also here, Nastri *et al.* (2015a) cautioned that the results of the Yeung trial should not be extrapolated to women with what has been referred to as 'recurrent implantation failure' (RIF). They based this opinion on their meta-analysis (Nastri *et al.*, 2015b) that concluded that moderate-quality evidence exists to suggest that artificial endometrial injury is associated with an improvement in clinical pregnancy rates in IVF patients with more than two previous failed embryo transfers (please note that this includes more than 40% of all IVF patients). The authors continued to state that, 'although current evidence suggests some benefit of endometrial injury, we need evidence from well-designed trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage in the control group, stratify the results for women with and without recurrent implantation failure (RIF), and report live birth' (Nastri *et al.*, 2015b). That is a fair comment, further demarcating the categories of patients whom artificial endometrial injury might and might not benefit, and specifying the sort of evidence needed.

Meanwhile, people have continued to try and unravel the biological plausibility of the procedure, i.e. the mechanism by which endometrial injury might have a positive effect on the outcome of a subsequent IVF attempt (Liang *et al.*, 2015), and the clinical factors that affect it (Kitaya *et al.*, 2016), whereas others have continued testing the treatment in RCT's (Singh *et al.*, 2015).

In the current issue of the journal we publish a survey of the implementation of *scratching* in clinical practice (Lensen *et al.*, 2016). The survey reveals that the majority of the responding doctors offered this procedure in their clinic—usually at a cost to the patient; a whopping 83% are recommending endometrial *scratching* to women undergoing IVF, and 92% of these are recommending it to women with RIF. There were a small number of clinicians who strongly disagreed with the use of this procedure. Although the same meta-analysis shows that some studies also suggest a beneficial effect in women undergoing IUI, and even in those trying to conceive naturally, hardly any of the surveyed clinicians offered *scratching* to women in these two groups.

Apologies, esteemed Francis Bacon, we have made a mess again of the Scientific Method Circle: we (evidently but accidentally) have made an Observation, we formulated a (wobbly) Hypothesis, we developed (somehow) Testable Predictions, we have collected 'moderate-quality' Data to test these Predictions and we even have developed a kind of Theory, involving interleukins (IL) IL-1β, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), IL-13, Eotaxin CCL11, IP-10, RANTES, monocyte chemotactic protein-(MCP-)1, MMPs/TIMPs, and (why not) interferon-(IFN-)γ, and (of course) vascular endothelial growth factor (VEGF), *and* we have adjusted the Hypothesis in order to facilitate new Observations, this time limited to RIF patients. Sarah Lensen now furthermore has checked Implementation in daily practice. Data, beliefs, conjectures, presumptions, conclusions, shortcuts, premises and putative mechanisms have squared the circle. The question today however is: does anyone actually still know where in the Circle we are?

Human clinical research differs from animal experiments. The latter start with a theory, develop a relevant study design, formulate a hypothesis, do the research (test the hypothesis), and draw a conclusion. In Reproductive Medicine not infrequently a treatment forces itself upon us before we have even identified the corresponding disease. And long before a suitable theory of the mechanism of action has been developed. For *scratching* we can (and should) enter the Scientific Method Circle again however. If late-luteal *scratching* indeed will be shown to favorably modulate the local uterine immune response at the time of implantation, *and if* immune rejection of the embryo should turn out to be the corresponding 'disease', *and if* further clinical trials indeed will confirm a beneficial effect of endometrial injury in a RIF population, *then* this intervention might eventually turn out to become good clinical practice in this particular subgroup. But, if we wish to expose more than 40% of our patients to a potentially perilous procedure the first thing we need is robust evidence.

Seconds away! Next round!

References

Evers JL. A nod is as good as a wink to a blind horse. *Hum Reprod* 2014; **29**:2355.

Kitaya K, Matsubayashi H, Takaya Y, Nishiyama R, Yamaguchi K, Ishikawa T. Clinical background affecting pregnancy outcome following local

endometrial injury in infertile patients with repeated implantation failure. *Gynecol Endocrinol* 2016;**18**:1–4.

Lensen S, Sadler L, Farquhar CM. Endometrial scratching for subfertility: everyone's doing it. *Hum Reprod* 2016;**31**:1241–1244.

Liang Y, Han J, Jia C, Ma Y, Lan Y, Li Y, Wang S. Effect of endometrial injury on secretion of endometrial cytokines and IVF outcomes in women with unexplained subfertility. *Mediators Inflamm* 2015; article ID:757184.

Nastri CO, Lensen S, Polanski L, Raine-Fenning N, Farquhar CM, Martins WP. Endometrial injury and reproductive outcomes: there's more to this story than meets the horse's blind eye. *Hum Reprod* 2015a; **30**:749.

Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, Martins WP. Endometrial injury in women undergoing assisted reproductive techniques. *Cochrane Database Syst Rev* 2015b;**3**:CD009517.

Singh N, Toshyan V, Kumar S, Vanamail P, Madhu M. Does endometrial injury enhances implantation in recurrent in-vitro fertilization failures? A prospective randomized control study from tertiary care center. *J Hum Reprod Sci* 2015;**8**:218–223.

Yeung TW, Chai J, Li RH, Lee VC, Ho PC, Ng EH. The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. *Hum Reprod* 2014;**29**:2474–2481.