

Endometrial scratching: the light at the end of the tunnel

Sir,

The sensation for readers of scientific literature on endometrial scratching is akin to immersing oneself in a novel full of plot twists. The surprising and, perhaps, conclusive final page is written by [van Hoogenhuijze et al. \(2023\)](#). It is not only astonishing in terms of its content but also the result of methodologically impeccable work. This is the first meta-analysis of randomized controlled trials (RCTs) with individual participant data, which was sorely needed to provide a breakthrough in the scratching story. Such an analysis was necessary because, despite several previous attempts to synthesize evidence on the effectiveness of scratching before IVF ([Vitagliano et al., 2018](#); [Sar-Shalom Nahshon et al., 2019](#); [van Hoogenhuijze et al., 2019](#); [Vitagliano et al., 2019a](#); [Lensen et al., 2021](#)), it was now possible to adjust for confounders. These types of meta-analyses represent the pinnacle of evidence-based medicine as they allow for active integration rather than passive aggregation of evidence from different clinical settings, geographic areas, and populations with diverse characteristics ([Wang et al., 2021](#)).

The meta-analysis by [Van Hoogenhuijze et al. \(2023\)](#) integrates data from 13 high-quality RCTs (12 published and 1 unpublished) after ensuring data integrity on 4112 patients (2059 allocated to scratching and 2053 to the control group). With intention-to-treat analyses, both two-stage and one-stage, adjusted and unadjusted (for age, BMI, duration of infertility, number of previous failed transfers, cause of infertility, and type of treatment), the authors demonstrate evidence in favour of a positive effect of the intervention. This evidence remains robust even after conducting a sensitivity analysis that excludes studies at higher risk of bias.

The beneficial effect of the intervention appears modest but not negligible, with an odds ratio of 1.29 (95% CI 1.02–1.64). Assuming a 25% baseline chance of live birth (i.e. without scratching), this corresponds to a relative risk of 1.20 (95% CI 1.02–1.41) and an estimated chance of live birth of 30.1% (95% CI 25.5–36.3%). This translates to approximately five additional children per 100 treatments performed after scratching compared to routine care, which aligns with our estimate published in 2021 ([Vitagliano et al., 2021](#)).

The two-stage scratch-timing analysis suggests that luteal phase, natural cycle scratching may be superior to other timed and/or contraceptive cycle scratching. This finding is consistent with some previous observations ([Vitagliano et al., 2019a](#)). What substantially changes with this study is that the subgroup analysis for age and number of previous failed embryo transfers could not identify subgroups in which endometrial scratching performed better or worse. This finding contradicts previous studies that had highlighted a more favourable effect with increasing female age ([Sar-Shalom Nahshon et al., 2019](#)) or after the second/third transfer ([Potdar et al., 2012](#); [Nastri et al., 2015](#); [Vitagliano et al., 2019a](#)). While the age finding is not surprising (due to a

highly contested meta-analysis ([Sar-Shalom Nahshon et al., 2019](#); [Vitagliano et al., 2019b](#))), what is striking is the lack of effect in relation to the number of previous failures. In this regard, a statistical observation worthy of attention is that the participant-level interaction of previous failed transfers with the scratch-effect on live birth is assessed considering previous failed transfers as a continuous variable. There is an incremental trend of effect in the analysis by [van Hoogenhuijze et al. \(2023\)](#), but it is not statistically significant. In this regard, it would be interesting to consider previous failed transfers as a binary variable, arbitrarily testing various cut-offs (at least one failed transfer, two, three, or four). This approach would probably address numerical issues (reducing the dispersion of the effect among smaller subgroups with an increasing number of failed transfers) and biological considerations (a linear relationship between the number of failures and the benefit of the intervention seems unlikely).

Although the robustness of the analysis by [van Hoogenhuijze et al. \(2023\)](#) is unquestionable, as rightly emphasized by the authors, the limitations of each individual study cannot be overcome, and adjustment for confounders is a strategy to mitigate biases rather than abolish them. In essence, the authors have made the most of the available evidence, and it is an exceptional achievement given the resources at hand.

Therefore, the results of this study surprise the reader for different reasons. Firstly, because after the pragmatic, multicentre, RCT published by [Lensen et al. \(2019a\)](#) and the subsequent Cochrane review ([Lensen et al., 2021](#)), almost every scientist and reproductive specialist had become convinced that the era of scratching had ended ([Lensen et al., 2019b](#); [Mol and Barnhart, 2019](#)). More deeply, because the demonstration of the lack of effect of this type of intervention had balanced the scientific data with our consciousness, which is not free from biases towards what we cannot understand or explain with rational biological logic. Indeed, today, almost 20 years after Barash et al.'s ([Barash et al., 2003](#)) initial chance observation of the potential beneficial effects of scratching before IVF, after 37 published RCTs on pre-IVF scratching and over 300 studies published on the topic overall, we still have not fully understood why this add-on should improve IVF outcomes ([Palomba et al., 2023](#)). Thus, at the first sign supporting its futility, most of us were immediately ready to set scratching aside and include it in the endless list of 'fake news' in reproductive medicine. On the contrary, we should have and will certainly need to dedicate more efforts to understanding why this intervention yields positive results.

In conclusion, the meta-analysis by [van Hoogenhuijze et al. \(2023\)](#) shows us again that evidence ultimately prevails over opinions. This study brings us back down to earth, humbles our intellectual ego, and reminds us that 'science replace private prejudice with public, verifiable evidence' ([Dawkins, 2007](#)).

Conflict of interest

None.

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References

- Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, Granot I. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. *Fertil Steril* 2003;**79**:1317–1322.
- Dawkins R. *The Enemies of Reason*. London, UK: Penguin Books, 2007.
- Lensen S, Osavlyuk D, Armstrong S, Stadelmann C, Hennes A, Napier E, Wilkinson J, Sadler L, Gupta D, Strandell A et al. A randomized trial of endometrial scratching before in vitro fertilization. *N Engl J Med* 2019a;**380**:325–334.
- Lensen S, Venetis C, Ng EHY, Young SL, Vitagliano A, Macklon NS, Farquhar C. Should we stop offering endometrial scratching prior to in vitro fertilization? *Fertil Steril* 2019b;**111**:1094–1101.
- Lensen SF, Armstrong S, Gibreel A, Nastri CO, Raine-Fenning N, Martins WP. Endometrial injury in women undergoing in vitro fertilisation (IVF). *Cochrane Database Syst Rev* 2021;**6**:CD009517.
- Mol BW, Barnhart KT. Scratching the endometrium in in vitro fertilization—time to stop. *N Engl J Med* 2019;**380**:391–392.
- 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* 2015;**6**:CD009517.
- Palomba S, Vitagliano A, Marci R, Caserta D. Endometrial scratching for improving endometrial receptivity: a critical review of old and new clinical evidence. *Reprod Sci* 2023;**30**:1701–1711.
- Potdar N, Gelbaya T, Nardo LG. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis. *Reprod Biomed Online* 2012;**25**:561–571.
- Sar-Shalom Nahshon C, Sagi-Dain L, Wiener-Megnazi Z, Dirnfeld M. The impact of intentional endometrial injury on reproductive outcomes: a systematic review and meta-analysis. *Hum Reprod Update* 2019;**25**:95–113.
- van Hoogenhuijze NE, Kasius JC, Broekmans FJM, Bosteels J, Torrance HL. Endometrial scratching prior to IVF; does it help and for whom? A systematic review and meta-analysis. *Hum Reprod Open* 2019;**2019**:hoy025.
- van Hoogenhuijze NE, Lahoz Casarramona G, Lensen S, Farquhar C, Kamath MS, Kunjummen AT, Raine-Fenning N, Berntsen S, Pinborg A, Mackens S et al. Endometrial scratching in women undergoing IVF/ICSI: an individual participant data meta-analysis. *Hum Reprod Update* 2023;**29**:721–740.
- Vitagliano A, Ambrosini G, Andrisani A, Kamath MS, Sardo ADS. Adherence to review protocol and rigorous methodology are the pre-requisites of a well-conducted systematic review. *Hum Reprod Update* 2019b;**25**:802–803.
- Vitagliano A, Andrisani A, Alviggi C, Vitale SG, Valenti G, Sapia F, Favilli A, Martins WP, Raine-Fenning N, Polanski L et al. Endometrial scratching for infertile women undergoing a first embryo transfer: a systematic review and meta-analysis of published and unpublished data from randomized controlled trials. *Fertil Steril* 2019a;**111**:734–746.e2.
- Vitagliano A, Di Spiezio Sardo A, Noventa M, Carugno J, Cicinelli E, Pacheco LA, Vitale SG, Campo R, Laganà AS, Haimovich S et al. Endometrial scratching can be offered outside clinical research setting: let us show you why. *Hum Reprod* 2021;**36**:1447–1449.
- Vitagliano A, Di Spiezio Sardo A, Saccone G, Valenti G, Sapia F, Kamath MS, Blaganje M, Andrisani A, Ambrosini G. Endometrial scratch injury for women with one or more previous failed embryo transfers: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2018;**110**:687–702.e2.
- Wang H, Chen Y, Lin Y, Abesig J, Wu IX, Tam W. The methodological quality of individual participant data meta-analysis on intervention effects: systematic review. *BMJ* 2021;**373**:n736.