

Reply: Endometrial scratching: the light at the end of the tunnel

Sir,

We would like to thank Dr Vitagliano (Vitagliano and Cicinella, 2024) and his colleagues for taking the time and effort to comment on our individual participant data meta-analysis (IPD) on endometrial scratching, and we encourage exchanging thoughts on both endometrial scratching and the undertaking of IPD's.

We agree that the enormous amount of research papers on endometrial scratching and the shifts in 'the answer on endometrial scratching' have asked for flexibility of mind from the readers and practitioners in this field. While we acknowledge that not one study or research undertaking can be flawless and provide *The Truth*, we indeed think that the current IPD is the best available evidence at this moment, and that it should lead to investigating subsequent questions such as the optimal timing and method of scratching, and its biological mechanism of action. We finally acknowledge the statement that science prevails, not only over opinions but also over personal beliefs.

Where endometrial scratching once started with the suggestion to be effective in women with *repeated endometrial failure* (RIF) (Gnainsky et al., 2015), it soon shifted to investigating its effectiveness in all women (Nastri et al., 2013; Yeung et al., 2014; Lensen et al., 2018; Mackens et al., 2020). Results of individual studies varied widely, and meta-analyses including different selections of studies also reported different results: a meta-analysis on RIF patients presented significant outcomes (Potdar et al., 2012), others reported (a trend of) increasing effectiveness (Nastri et al., 2015; Vitagliano et al., 2018, 2019), and another meta-analysis found no significant effect except for clinical pregnancy rate in women with one failed embryo transfer, but not in those with 0 or ≥ 2 failed transfers (van Hoogenhuijze et al., 2019). However, the hypothesis of increasing effectiveness with increasing number of failed transfers has remained vivid in many of us.

Our IPD could not identify such a correlation in a one-stage participant-level interaction analysis. The suggestion to dichotomize the population and test for different cut-offs of number of previous failed transfers is understandable but is generally advised against by expert IPD statisticians (Fisher et al., 2011; Riley et al., 2020). The reason is that categorization of continuous variables reduces power to detect a true interaction with an effect, because a lot of the information is lost when assembling it in groups. Also, logically speaking, it is hard to explain why someone with three failed transfers is more comparable to someone with two failed transfers than to someone with four failed transfers, in case of an arbitrary cut-off of ≤ 3 or >3 . We therefore believe that to detect a possible interaction between the number of

failed transfers and the effect of scratching, a continuous variable and interaction analysis is the best approach.

As Dr Vitagliano rightly mentions, we have used a linear model for the interaction analysis, while a potential effect modification could be non-linear. This can indeed be true, but we question whether from a biological perspective it is more likely to be a non-linear interaction than a linear interaction. As the number of previous failed transfers is both influenced by the endometrial receptivity and the number and quality of embryos a couple 'generates', it can also be argued that with an increasing number of failed embryo transfers, the more likely it is that a woman suffers from an endometrial factor—and thus that it may be a linear relation. Nevertheless, we did consider performing non-linear analysis but this appeared impossible due to the complexity of the model, resulting in convergence problems. Also, interpretation could have been problematic as the different studies all have different covariate means (mean number of previous failed transfers). We performed the interaction analysis using the centred study means of the covariate (in order to avoid aggregation bias), and therefore the change in treatment effect of a one-step increase from the covariate mean will have a different meaning for each study—making the summary outcome uninterpretable (Riley et al., 2020).

In our opinion, the underlying issue of the discussion on women with repeated implantation failure in relation to scratching, is the hypothesis that specifically women with an 'endometrial factor' may benefit from endometrial scratching. The problem is, however, that we do not know how to identify these women and that we have used the number of failed embryo transfers as a proxy—even though this number is influenced by other, non-endometrial, factors as well. We therefore suppose that further research should focus on unravelling the role of the endometrium in embryo implantation, such that we may be able to identify women with an endometrial factor and then investigate if it is indeed this group who benefits from endometrial scratching.

All in all, we agree with Dr Vitagliano that at this moment, the IPD provides the best available evidence on the effect of endometrial scratching. While the long-standing hypothesis of increasing benefit in women with repeated failed embryo transfers intuitively seems plausible, we have not been able to identify such an effect, with the caveat of not having performed a non-linear regression analysis. Nonetheless, in our opinion, further research should focus on whether an 'endometrial factor' exists and on how to identify these women, as well as on the biological mechanism of action of endometrial scratching and its optimal timing.

Conflict of interest

None.

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