Letters to the Editor

Reply: Adherence to review protocol and rigorous methodology are the pre-requisites of a well-conducted systematic review

Sir,

Endometrial injury (EI), a proposed treatment for repeated implantation failure (RIF), has been gaining popularity among clinicians. However, the procedure is controversial and subject to discussions.

Following our published meta-analysis (Sar-Shalom Nahshon et al., 2019), we would like to address the issues raised by Vitagliano et al. and Taguchi et al. in their letters.

Our protocol, registered in PROSPERO (CRD42018092773), described our objective to investigate the influence of confounders, specifically maternal age, on EI efficacy. We also studied the influence of other possible confounders (hysteroscopy and RIF). The difference between our published meta-analysis and the protocol is not fundamental, and our main objective to investigate EI remains the same. This change enabled a more focused meta-analysis, concentrating on women with at least one previous failed cycle.

EI is a common meta-analysis subject and browsing in PROSPERO shows several protocols exploring it. The issue of overlapping meta-analyses is hardly new, and it has been shown that for about two third of published meta-analyses at least one other overlapping meta-analysis can be found (Siontis et al., 2013).

Our meta-analysis included the study published by Matsumoto et al. (Matsumoto et al., 2017), which allocated patients into two groups according to the clinical case record number. The Cochrane collaboration tool defines this way of randomization as one with ‘high risk for bias’. Thus, the note made by Vitagliano et al. that the above study is not a randomized controlled trial (RCT) is inaccurate. In fact, this study was not included in the ‘low risk of bias’ group in our meta-analysis, and the degree of bias is clearly noted in Figure 2.

Vitagliano et al. (Vitagliano et al., 2018), included in their meta-analysis the study published by Mak et al. (Mak et al., 2017). Due to the inclusion criteria which has no information of past implantation failure, this study was not included in our meta-analysis. In this study, all patients were assigned to embryo transfer (ET) cycles using non-donor oocytes for eligibility. We note that ET cycles are not necessarily performed in RIF patients. In the entire ‘Materials and methods’ chapter, previous failed cycles are not mentioned once. It is discussed only as a subgroup analysis and mentioned only in the results. We considered this a possible source of bias, as the objective of investigating EI in women with previous failed cycles was not required for inclusion. Furthermore, examination of this specific subgroup might compromise the randomization for potential confounders. Moreover, their conclusion refers to an unselected group of women and does not include any statement on women with previous failed cycles.

As opposed to Mak et al., all papers included in our meta-analysis required previous failed cycles as an inclusion criterion.

The analysis in our paper included women in whom EI was eventually performed and did not include patients who had fallen out of each study. Each study analysed the results according to the patients that were followed throughout the whole study, and these results were analysed in our meta-analysis for maximal accuracy.

Vitagliano et al. obtained additional data from the authors of several studies regarding patients with two or more implantation failures. Similarly, Taguchi et al. combined our results with those of Vitagliano et al. (2018) and found a significant improvement in clinical pregnancy rates (CPR) in the subgroup of women with two or more implantation failures. Nevertheless, as we aimed to find several confounding factors in addition to the number of previous failed cycles (age and hysteroscopy), we did not focus exclusively on one parameter. Therefore, we did not approach the authors, and a difference in the results of the subgroup of patients with two or more implantation failures is noted, as referred to by Taguchi et al. That said, the overall analysis including patients with one or more implantation failures is consistent in both studies (Vitagliano et al., 2018, Sar-Shalom Nahshon et al., 2019).

The heterogeneity between the studies, partly due to different studied populations, makes the assessment of EI difficult. We tried to find an association between EI efficacy and maternal age. Therefore, we divided the studies into two groups according to the mean maternal age (below and above 30 years). The results showed a beneficial EI effect only in the younger subgroup. Our results strongly suggest that age is indeed a confounder, and as the age rises, even above 30 years, the beneficial EI effect might decrease.

Moreover, we defined hysteroscopy as a possible confounder, as it may have an independent EI effect, and created a subgroup of studies in which hysteroscopy was not performed. In the most recent RCT, in line with our approach, only patients with no recent exposure to disruptive intrauterine instrumentation (e.g. hysteroscopy) were included (Lensen et al., 2019).

We also wish to raise a few points after reading the published paper by Vitagliano et al., (2018).

Vitagliano et al. (2018) note that ET cycles, rather than fresh cycles, provide a more accurate endometrial preparation, making the embryo-endometrium synchronization effect of EI irrelevant. Many basic science studies have shown that the mechanism for improved implantation rates is by an inflammation process (Barash et al., 2003; Dekel et al., 2014; Gnainsky et al., 2010, 2015; Kalma et al., 2009).

The ‘synchronization’ mechanism, a proposed hypothesis (Zhou et al., 2008), has not been studied yet.

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doi:10.1093/humupd/dmu023

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The ‘synchronization’ mechanism, a proposed hypothesis (Zhou et al., 2008), has not been studied yet.
Moreover, Vitagliano et al. (2018) cited a retracted article (Aflatoonian et al., 2013). According to the retraction note, this article was retracted at the request of the Editor and the ASRM Publications Committee, based on the results of an investigation which found serious methodological flaws in the study.

Vitagliano et al. (2018) states that the FET cycles transferred lower quality embryos as the higher quality embryos were previously transferred as fresh embryos. This statement lacks evidence as it was not mentioned in the included studies (Mak et al., 2017; Shahrokh-Tehraninejad et al., 2016) and is not relevant if all embryos were frozen.

To our knowledge, our study is one of the most comprehensive papers on EI.

Finally, our conclusion is very much supported by the final conclusion of Vitagliano et al.

The most recent RCT, published in the New England Journal of Medicine (Lensen et al., 2019), was not included either in the meta-analyses. Lensen et al. found no beneficial EI effect; nevertheless, we believe that the last word has not been said.

Interestingly, Taguchi et al. notes the need for RCTs studying the EI effect when performed in the follicular phase, however Vitagliano et al. showed that that greatest beneficial EI effect was achieved when performed twice during the luteal phase (Vitagliano et al., 2018).

In our opinion, before concluding that EI has no beneficial effect and that it is ‘Time to Stop’ (Mol and Barnhart, 2019), an RCT on ovum donation cycles in RIF patients should be conducted. Such a study has not been published yet.

**Conflict of interest**

All authors declared no competing interests.

**References**


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doi:10.1093/humupd/dmz022