

References

- Aleyamma TK, Singhal H, S Premkumar P, Acharya M, S Kamath M, George K. Local endometrial injury in women with failed IVF undergoing a repeat cycle: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* 2017; **214**:109–114.
- Baum M, Yerushalmi GM, Maman E, Kedem A, Machtinger R, Hourvitz A *et al*. Does local injury to the endometrium before IVF cycle really affect treatment outcome? Results of a randomized placebo controlled trial. *Gynecol Endocrinol* 2012; **28**:933–936.
- De Geyter C, Calhaz-Jorge C, Kupka MS, Wyns C, Mocanu E, Motrenko T, Scaravelli G, Smeenk J, Vidakovic S, Goossens V; European IVF-monitoring consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). ART in Europe, 2014: results generated from European registries by ESHRE: the European IVF-monitoring consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). *Hum Reprod* 2018; **33**:1586–1601.
- Gibreel A, El-Adawi N, Elgindy E, Al-Inany H, Allakany N, Tournaye H. Endometrial scratching for women with previous IVF failure undergoing IVF treatment. *Gynecol Endocrinol* 2015; **31**:313–316.
- Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011. Available from <http://handbook.cochrane.org>.
- Inal ZHO, Görkemli H, Inal HA. The effect of local injury to the endometrium for implantation and pregnancy rates in ICSI-ET cycles with implantation failure: a randomized controlled study. *Eur J Gen Med* 2012; **9**:223–229.
- Karimzadeh MA, Ayazi Rozbahani M, Tabibnejad N. Endometrial local injury improves the pregnancy rate among recurrent implantation failure patients undergoing in vitro fertilisation/intra cytoplasmic sperm injection: a randomized clinical trial. *Aust N Z J Obstet Gynaecol* 2009; **49**:677–80.
- Lensen S, Sadler L, Farquhar C. Endometrial scratching for subfertility: everyone's doing it. *Hum Reprod* 2016; **31**:1241–1244.
- Mak JSM, Chung CHS, Chung JPW, Kong GWS, Saravelos SH, Cheung LP, Li TC. The effect of endometrial scratch on natural-cycle cryopreserved embryo transfer outcomes: a randomized controlled study. *Reprod Biomed Online* 2017; **35**:28–36.
- Matsumoto Y, Kokeguchi S, Shiotani M. Effects of endometrial injury on frozen-thawed blastocyst transfer in hormone replacement cycles. *Reprod Med Biol* 2017; **16**:196–199.
- 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.
- Shahrokh-Tehranejad E, Dashti M, Hossein-Rashidi B, Azimi-Nekoo E, Haghollahi F, Kalantari V. A randomized trial to evaluate the effect of local endometrial injury on the clinical pregnancy rate of frozen embryo transfer cycles in patients with repeated implantation failure. *J Family Reprod Health* 2016; **10**:108–114.
- Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* 2012; **164**:176–179.
- Simón C, Bellver J. Scratching beneath 'The scratching Case': systematic reviews and meta-analyses, the back door for evidence-based medicine. *Hum Reprod* 2014; **29**:1618–1621.
- Singh N, Toshiyan 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.
- 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* 2018a; **110**:687–702.e2.
- Vitagliano A, Noventa M, Saccone G, Gizzo S, Vitale SG, Laganà AS, Litta PS, Saccardi C, Nardelli GB, Di Spiezio Sardo A. Endometrial scratch injury before intrauterine insemination: is it time to re-evaluate its value? Evidence from a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2018b; **109**:84–96.e4.
- Vitagliano A, Andrisani A, Alviggi C, Vitale SG, Valenti G, Sapia F, Favilli A, Martins WP, Raine-Ferring N, Polanski L, Ambrosini G. 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* 2019; **111**:734–746.

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

Sir,

In a recent review, Sar-Shalom Nahshon *et al.* (2019) argued the impact of intentional endometrial injury (scratching) on reproductive outcomes by systematic review and meta-analysis. However, we have found a discrepancy in the clinical pregnancy rate—two or more failed IVF cycles—between Fig. 5 in the study of Sar-Shalom Nahshon *et al.* (2019) and Fig. 2C (8.2.2) in the study of Vitagliano *et al.* (2018), notwithstanding the fact that both studies analyzed randomized controlled trials (RCTs) published between 2009 and 2017 for their meta-analyses. Figure 5 in the study of Sar-Shalom Nahshon *et al.* (2019) did not show the significant improvement of clinical pregnancy rate—two or more failed IVF cycles—(risk ratio, 1.53; [95% CI, 0.93–2.51]; $P = 0.09$) by endometrial injury (scratching) in the DerSimonian–

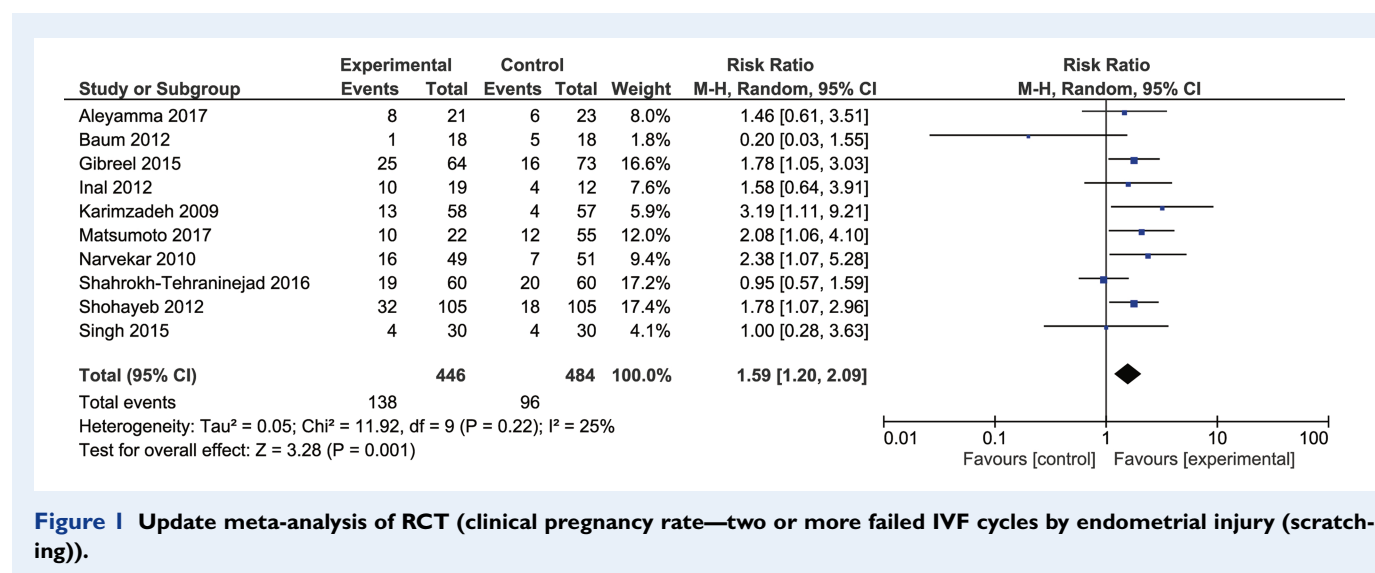


Figure 1 Update meta-analysis of RCT (clinical pregnancy rate—two or more failed IVF cycles by endometrial injury (scratching)).

Laird random effects model. However, Fig. 2 C (8.2.2) in the study of Vitagliano *et al.* (2018) showed significant improvement of clinical pregnancy rate—two or more failed IVF cycles—(risk ratio, 1.44; [95% CI, 1.14–1.84]; $P = 0.006$) by endometrial injury (scratching) in the DerSimonian–Laird random effects model. Although this discrepancy may be caused by the differences of selected RCTs in these two meta-analyses, we have updated the meta-analysis for the impact of endometrial injury (scratching) on clinical pregnancy rate—two or more failed IVF cycles—by using published data for the both studies (Vitagliano *et al.*, 2018; Sar-Shalom Nahshon *et al.*, 2019) and RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Then, the clinical pregnancy rate—two or more failed IVF cycles—was analyzed on an intention-to-treat basis in our meta-analysis, in contrast to Sar-Shalom Nahshon *et al.* (2019) who did not always analyze on an intention-to-treat basis in their meta-analysis. As a result, unlike the contention of Sar-Shalom Nahshon *et al.* (2019), we have found a significant improvement of clinical pregnancy rate—two or more failed IVF cycles by endometrial injury (scratching)—($n = 930$; risk ratio, 1.59; [95% CI, 1.20–2.09]; $P = 0.001$) in the DerSimonian–Laird random effects model (Fig. 1). Furthermore, according to Cochrane Handbook for Systematic Reviews of Interventions (<https://training.cochrane.org/handbook>), 0–40% in an I-squared statistic might not be important and was considered as a low level of heterogeneity. Therefore, our meta-analysis would be considered as a low level of heterogeneity and could show a significant improvement of clinical pregnancy rate in women who had had two or more failed IVF cycles by endometrial injury (scratching) (Fig. 1), while current evidence did not support performing endometrial injury (scratching) with the purpose of improving the success of the first and second embryo transfer attempt (Frantz *et al.*, 2019; Vitagliano *et al.*, 2019). However, in most RCTs for endometrial injury (scratching) among infertile women, endometrial injury (scratching) was conducted in luteal phase, including recent RCTs (Frantz *et al.*, 2019; Lensen *et al.*, 2019). The only randomized controlled study (Shohayeb and El-Khayat, 2012) for endometrial injury (scratching) included in the meta-analyses of RCTs (Vitagliano *et al.*, 2018; Sar-Shalom Nahshon *et al.*, 2019; Vitagliano *et al.*, 2019) was conducted in follicular phase. The endometrial injury (scratching) in follicular phase in the study of Shohayeb and El-Khayat (2012) did result

in a higher rate of live birth than no intervention (risk ratio, 2.00; [95% CI, 1.12–3.58]; $P = 0.02$) in the DerSimonian–Laird random effects model (Vitagliano *et al.*, 2018). Furthermore, the study of Shohayeb and El-Khayat included 200 infertile women with repeated implantation failures (two or more failed IVF cycles) (Shohayeb and El-Khayat, 2012; Vitagliano *et al.*, 2018).

Considering the above-mentioned matters, the study for endometrial injury (scratching) is not ‘Time to Stop’ (Mol and Barnhart, 2019) but ‘Time to Try in Follicular Phase’ among the infertile women with repeated implantation failures.

Conflict of interest


None.


References

- Frantz S, Parinaud J, Kret M, Rocher-Escriva G, Papaxanthos-Roche A, Creux H, Chansel-Debordeaux L, Bénard A, Hocké C. Decrease in pregnancy rate after endometrial scratch in women undergoing a first or second in vitro fertilization. A multicenter randomized controlled trial. *Hum Reprod* 2019;**34**:92–99.
- 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* 2019;**380**:325–334.
- Mol BW, Barnhart KT. Scratching the endometrium in in vitro fertilization—time to stop. *N Engl J Med* 2019;**380**:391–392.
- 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.
- Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomised controlled trial. *Eur J Obstet Gynecol Reprod Biol* 2012;**164**:176–179.
- Vitagliano A, Andrisani A, Alviggi C, Vitale SG, Valenti G, Sapia F, Favilli A, Martins WP, Raine-Ferring N, Polanski L *et al.* Endome-

trial 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* 2019; **111**:734–746.

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.

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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 scheduled for frozen embryo transfer (FET) cycles using non-donor oocytes were assessed for eligibility. We note that FET 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 FET 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.