Is the era of the endometrial scratching finished?

To the Editor:

We read with great interest the recent randomized controlled trial (RCT) by Wong et al. (1). This study aimed to test whether endometrial scratching (ES) increases the live birth rate in couples with unexplained infertility scheduled for 3 cycles of free unprotected intercourse. The analysis of the results demonstrated that ES did not improve the live birth rate and other reproductive outcomes and was associated with a higher pain score compared with the sham procedure. Based on their findings, the investigators concluded against offering ES to women with unexplained infertility attempting to conceive without assistance.

We acknowledge that the published RCT (1) has several strengths, including the rigorous study design and the choice to adopt a sham procedure in the control group. Nevertheless, we believe that there are some relevant aspects of the study that warrant discussion.

First, it is unclear to us the investigators' choice to include in the study women aged $\leq$42 years and/or with a body mass index reaching 35 kg/m^2. Although we understand that such pragmatic RCTs need a large sample to achieve statistical power, we believe that their inclusion may have potentially influenced the overall results because of a low chance of conception. It is also questionable whether women with obesity aged $\leq$42 years may be actually included in the category of "unexplained infertility." Similarly, the clinical and biochemical features of polycystic ovary syndrome were not excluded, introducing another potential confounder (2).

Second, it is plausible that the study included women who had an unintentional endometrial injury due to uterine manipulation during a laparoscopy or due to the use of any intrauterine device for a hysterosalpingogram. Because we are still uncertain about the duration of ES effects, an arbitrary 3-month interval from the time of previous intrauterine manipulation may not be enough to evaluate the effects of further endometrial injury.

The third point to be discussed is the inclusion of a significantly different proportion of women with secondary infertility between the groups. Such baseline differences may have potentially influenced the rates of spontaneous pregnancies between the groups during the study period.

Last but not least, the study was initially designed to include 350 participants (3). Unfortunately, the planned sample size was subsequently revised to 216 participants, reducing the study power to 80% and not considering "adjustment for attrition." Based on these premises, we think that an interim analysis using poststudy calculation would be more useful and cheaper, especially when "the results should be interpreted with caution."

In addition, the slow recruitment process is also an important parameter to consider. More aggressive interventions for unexplained infertility proposed in previous ES trials have been strongly criticized because these were not adherent to evidence-based data or international guidelines. Furthermore, the patients, as main stakeholders, should probably be taken into consideration before being given clinical recommendations.

Finally, it is surprising that 27% of women who underwent the sham procedure reported bleeding on the day after the procedure. How can this finding be explained? Is it possible to suspect an undiagnosed uterine disease?

Stefano Palomba, M.D.[a]
Amerigo Vitagliano, M.D.[a,b]

[a] Department of Experimental and Clinical Medicine, Gynecology and Obstetrics, University "Magna Graecia" of Catanzaro, Catanzaro, Italy; and [b] Department of Women's and Children's Health, University of Padua, Padua, Italy

https://doi.org/10.1016/j.fertnstert.2022.06.019

REFERENCES

1. Wong TY, Lensen S, Wilkinson J, Glanville EJ, Acharya S, Clarke F, et al. Effect of endometrial scratching on unassisted conception for unexplained infertility: a randomized controlled trial. Fertil Steril 2022;117:612–9.
2. Palomba S, Piltonen TT, Giudice LC. Endometrial function in women with polycystic ovary syndrome: a comprehensive review. Hum Reprod Update 2021;27:584–618.
3. Lensen S, Martins W, Nastri C, Sadler L, Farquhar C. Pipelle for Pregnancy (PIP): study protocols for three randomised controlled trials. Trials 2016;17:1–14.