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Reply: Endometrioma excision and ovarian reserve: do assessments by antral follicle count and anti-Müllerian hormone yield contradictory results?

Sir,
We read with great interest the Letter to the Editor by Ata and Urman, commenting upon our systematic review regarding the effect of endometrioma excision on ovarian reserve as assessed by antral follicle count (AFC) (Muzzi et al., 2014).
In their letter, Ata and Urman attribute to us the concept that sample stability issues limit the value of anti-Mullerian hormone (AMH) in evaluating ovarian reserve, and therefore jeopardize the conclusion of two previous systematic reviews, both of which reported a detrimental effect of endometrioma excision on ovarian reserve as assessed by AMH (Raffi et al., 2012; Somigliana et al., 2012). The limits of the two systematic reviews, however, are not only limited to sample stability issues, but also to very high study heterogeneity, high variability of study designs, reported parameters, lengths of follow-up, different techniques used to measure AMH, and different surgical techniques. A high level of expertise in the operating surgeon is also of paramount importance, and the quality of surgery can only be judged when pathological data of the excised specimens are reported (Muzzi et al., 2011; Bhat et al., 2014). In the first of the two systematic reviews (Raffi et al., 2012), sensitivity analysis limited to the studies with the lowest risk of bias did not reach statistical significance for the effect of surgery on AMH modifications. In the second review (Somigliana et al., 2012), a meta-analysis was even deemed inopportune due to the methodological problems described above. The possibility that the two previous systematic reviews may be flawed is in fact suggested by the authors of the articles themselves. Furthermore, many respected authorities affirm that caution should presently be exercised in the interpretation of AMH levels in the clinical setting (Rustamov et al., 2012; Clark et al., 2014; Ledger, 2014). As correctly pointed out by Ata and Urman, AFC, as well as AMH, may not be the perfect marker for the evaluation of ovarian reserve. We are convinced however, that reproducibility of the measurements of AFC in expert hands is very high, and that the presence of the endometrioma does not jeopardize correct evaluation of the numbers of antral follicles present in the evaluated ovary. We believe that modern ultrasound equipment allows a count that accurately corresponds to the true number of follicles present within the ovary. We would question the accuracy of the AFC only for very large cysts, where part of the ovarian parenchyma is far from the transvaginal probe. However, in the studies included in our meta-analysis, mean cyst diameter ranged from 3.7 to 6.7 cm, which would not jeopardize, in our opinion, AFC evaluations.
In their thoughtful comments, Ata and Urman conclude that both AFC and AMH suggest a decrease in ovarian reserve following endometrioma excision, and that it would still be prudent to warn patients about the detrimental effect of endometrioma excision on ovarian reserve. We absolutely agree on this second conclusion, whereas, on the other hand, we still believe that the crude evidence from meta-analyses on AMH and AFC yield conflicting results: AMH is reduced after surgery (Raffi et al., 2012), whereas AFC is not (Muzzi et al., 2014).
Subgroup analyses, such as the one proposed by Ata and Urman with the inclusion of studies with monolateral cysts only, add significant interest to the discussion of this important issue in reproductive medicine. However, when the number of patients evaluable is diminished by subgroup analyses, scientific soundness is also decreased. The reduction in the number of patients from our original meta-analysis in subgroup analyses may even bring more confusion to the clinician: the change in AFC values reported by Ata and Urman in Fig. 2 of their Letter to the Editor is in fact still far from being significant, and sound clinical conclusions cannot be drawn. Moreover, since the submission of our meta-analysis to Human Reproduction, one further study has been published (Bhat et al., 2014), reporting separate data for the monolateral endometriomas, thereby meeting the inclusion criteria for the proposed subgroup analysis. In this study, a significant increase in AFC is reported after surgery (from $3.3 \pm 1.9$ to $4.1 \pm 1.5$; $P = 0.001$). Adding this study, which has the largest sample size among the included studies, to the above subgroup meta-analysis would confirm that AFC does not decrease after surgery.
In conclusion, we are thankful to Drs Ata and Urman for the very interesting issues raised in their letter, which greatly contribute to the discussion on the effect of surgery for an endometrioma on ovarian reserve. However, the conclusions of our systematic review and meta-analysis (Muzzi et al., 2014), which we believe was correctly conducted, with rigid methodology and strictly-defined parameters, cannot be overlooked: there is no evidence that surgery for an endometrioma affects ovarian reserve when evaluated with AFC.

References
Endometrial scratching for women with repeated implantation failure

Sir,

We were perplexed with a recently published opinion regarding ‘endometrial scratching’ and the utility of systematic reviews (Simon and Bellver, 2014). There are several problems with the opinion, many of them being addressed in an editorial published simultaneously; but there are many more. For example, the authors only identified four randomized controlled trials (RCTs) while there are at least 10 published RCTs with two more having recently been completed and currently being prepared for publication. Additionally, it does not seem that the authors have read in detail the few RCTs they cite as they state that implantation rates were not mentioned in one study (Nastri et al., 2013) when they are clearly reported: ‘48/134 (35.82%) versus 29/136 (21.32%) for endometrial scratching versus control groups (P = 0.01)’.

Additionally, we observed several fallacies in this opinion. One of them is to suggest that we should reject all the evidence that was not published in journals with high impact factors. We do agree that articles published in journals with high impact factors are generally better; however, there are many publications expressing biased views in these journals (this opinion paper in question is a good example), whilst good unbiased research is published in non-English journals without impact factors. Perhaps we should all take a step back and look at the whole picture. Low cost interventions for assisted reproduction, such as clomiphene citrate for controlled ovarian stimulation (Figueiredo et al., 2013) or endometrial scratching (Nastri et al., 2012), are frequently studied by researchers from countries with limited resources where there is a lot of concern about treatment access and consequences of its costs (Dyer et al., 2013). Unfortunately, these authors frequently face major difficulties when trying to publish their results in journals with high impact factors, partly because of language and financial problems, but also because of prejudice. Whether the competition and peer-review process are important or not could be a topic of another paper; but a bright speech from the astrophysicist Neil de Grasse Tyson can be easily used here in the context of inequality in research opportunities: ‘You gotta come up with a system where there’s equal opportunity; then we can have that conversation’. Simon and Bellver not only criticized evidence published in journals with low impact factors, but they also demonstrated several other examples of intentional fallacy; including insult of reviewers’ character (or argumentum ad hominem) when they state ‘...some authors became meta-analyzers increasing their scientific CV by performing numerous meta-analyses about different topics’ and identification of a false cause and effect (or post hoc ergo propter hoc) when they state ‘The weakness of published meta-analyses is so evident that some societies such as the Royal College of Obstetricians and Gynaecologists have created guidelines subdividing the level of evidence’.

Why have such esteemed authors felt so compelled to convince readers against endometrial scratching? Is this because a poorly performed systematic review or RCT was recently published in Human Reproduction? No, we couldn’t find any. Did the authors complete a study showing that endometrial scratching reduces pregnancy rates? On the contrary, they themselves have observed high pregnancy rates after endometrial biopsy using a Pipelle endometrial sampler in women with previous repeated implantation failure (Ruiz-Alonso et al., 2013). Is endometrial scratching expensive and/or risky? Not at all, endometrial biopsy using a Pipelle is an affordable procedure, and millions have been performed per year for diagnostic indications for decades; it is deemed a safe and well-tolerated procedure (Check et al., 1989).

We do agree that more studies are still needed. In the previous Cochrane review the available evidence regarding the beneficial effect of endometrial scratching was properly judged and it was considered to be of moderate quality; additionally it should only be generalized to women with repeated implantation failure undergoing a new fresh embryo transfer (Nastri et al., 2012). However, one should consider that this evidence is probably better than that existing for all other interventions aiming to improve the reproductive outcomes of women with repeated implantation failure (Farquhar et al., 2013), and fortunately, there are several new studies on the horizon.

References


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