

Reply: Antral follicle count might be underestimated in the presence of an ovarian endometrioma

Sir,

We read with interest the Letter to the Editor by Lima *et al.*, commenting upon our systematic review of the effect of surgery for an endometrioma on ovarian reserve evaluated with antral follicle count (AFC) (Muzii *et al.*, 2014).

In their letter, the Authors underline the fact that the quality of the evidence for the systematic review is low, and invite to a more conservative conclusion regarding the effect of surgery on the ovarian tissue. In our article, we caution the reader as to the heterogeneity of the included studies, we clearly state that the conclusions are limited by the quality of the studies, and we call for randomized clinical studies with adequate sample sizes to better address the issue of ovarian reserve after surgery for an endometrioma. The same limitations, if not worse (i.e. the lower number of included studies and the lower total number of patients evaluated), are present for the systematic reviews that address the same issue with the evaluation of Anti-Müllerian hormone (AMH) instead of AFC (Raffi *et al.*, 2012; Somigliana *et al.*, 2012). In addition, AMH is burdened by methodological problems that emerged very recently, which brought many respected authorities to caution the clinician in the interpretation of AMH levels in the clinical setting (Clark *et al.*, 2014; Ledger, 2014; Rustamov *et al.*, 2014).

We agree with Lima *et al.* on the fact that AFC also has some methodological problems, but we are convinced that these may ensue only in case of very large cysts.

The Authors attribute the limitations of AFC to the reduced ability of transvaginal ultrasound to detect small follicles in the ovary with the endometrioma because of two reasons: the presence of chronic inflammation, and the increased distance between the ultrasound probe and the normal ovarian tissue.

As to the first reason, chronic inflammation and fibrosis have been demonstrated to be present with the ovarian endometrioma, even at a distance of >1.0 cm from the cyst capsule (Kitajima *et al.*, 2011). Free iron, reactive oxygen species and different markers of inflammation are present in significantly higher amounts in the ovary with the endometrioma compared with healthy ovaries (Sanchez *et al.*, 2014). These mechanisms may be the cause of an impaired folliculogenesis, which in turn results in a lower AFC. The lower AFC measured in the presence of an endometrioma may therefore be due to the endometrioma itself, and not to the inability of ultrasonography to detect follicles near the cyst capsule. Following this hypothesis, some Authors suggest surgical removal of endometriomas, even with a small diameter, in order to reduce, or even revert, the deleterious effect of the cyst on the ovarian reserve (Jadoul *et al.*, 2012; Brosens *et al.*, 2014). Moreover, we believe that the fibrosis and inflammation that accompany an endometrioma outlive the presence of the cyst, and therefore persist even after surgery. This inflammation would have a significant impact in short-term follow-up studies, such as those considered in our systematic review. Therefore, we do not believe that the presence of chronic inflammation will cause an underestimation in the AFC assessment of ovarian reserve before surgery compared with the values after surgery.

As to the second reason—the increased distance between the probe and the ovary may in fact determine a loss of resolution for ultrasonography, and therefore a lower AFC because of the inability to detect smaller follicles—we are convinced, that this may hold true only for very large cysts, and not for cysts with a mean diameter between 3.7 and 6.7 cm, as for the studies included in our systematic review. Indeed, no mention in the included studies is made on any difficulty of the measurements of AFC. Only in the Discussion section of four of the 13 included studies (Biacchiardi *et al.*, 2011; Celik *et al.*, 2012; Urman *et al.*, 2013; Alborzi *et al.*, 2014) it is hypothesized that AFC may be inaccurate in the presence of the cyst. In these four studies, AFC has a different behavior compared with AMH (in two studies AFC increases, in one it remains stable, and in one it has a decrease less than half than the one observed for AMH). The hypothesis of the inaccuracy of AFC is therefore stated *a posteriori* and may only represent a biased judgment to reject the unexpected results.

In conclusion, we are grateful to Lima *et al.* for the interesting issues raised in their letter, which contribute to the discussion on the effect of surgery for the endometrioma on the ovarian reserve. However, we are convinced that the presence of the endometrioma smaller than 6 cm does not significantly jeopardize the evaluation of AFC when this is performed by an experienced operator.

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