RBMO

COMMENTARY

Does large endometrioma per se increase AMH level?

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ABSTRACT

Women with endometriosis, especially those with endometrioma, present a considerable challenge for ovarian reserve appraisal. This diagnostic difficulty arises from several fundamental questions inherently linked to patient management: the potential influence of endometrioma on ovarian reserve; the adverse effect of ovarian surgery on ovarian reserve; and the adequacy of the established ovarian reserve biomarkers, anti-Müllerian hormone and antral follicle count, to appraise ovarian reserve accurately in these women. Until recently, a key argument was that the development and growth of endometriomas is associated with a progressive damage to normal ovarian tissue, resulting in a concomitant reduction in serum AMH levels. Contrary to this widely accepted position; recent studies have reported that, in women with no previous history of ovarian surgery, AMH levels were increased in women with large endometriomas. These findings are surprising and, if replicated, would have substantial clinical implications. In this commentary, we would, however, urge caution before these reports lead to systematic changes in clinical practice, and recommend urgent replication as the finding linking large endometrioma to high serum AMH levels seems to be biologically implausible, and contradicts the existing extensive body of research.

Endometriosis is a common, chronic inflammatory disease encountered in women during the reproductive years, which typically causes debilitating pain and subfertility. Women with endometriosis, especially those with endometrioma, present a considerable challenge for ovarian reserve appraisal. This diagnostic difficulty arises from several fundamental questions inherently linked to patient management: the potential influence of endometrioma on ovarian reserve; the adverse effect of ovarian surgery on ovarian reserve; and the adequacy of the established ovarian reserve biomarkers anti-Müllerian hormone (AMH) and antral follicle count (AFC) to appraise ovarian reserve accurately in these women.

Until recently, a key argument was whether the development and growth of endometriomas is associated with a progressive destruction of normal ovarian tissue, resulting in a concomitant reduction in serum AMH levels (*Streuli et al., 2012*; *Somigliana et al., 2014*; *Kasapoglu et al., 2018*). Furthermore, surgery for endometriomas was associated with removal or damage of normal ovarian tissue, reducing ovarian reserve and AMH levels further (*Younis et al., 2019*). Contrary to this widely accepted position, two recent observational, retrospective, cross-sectional studies (n = 148 and n = 332) have reported that, in women with no previous history of ovarian surgery, AMH levels were increased in women with endometrioma measuring more than 7 cm and 6 cm, respectively (*Marcellin et al., 2019*; *Roman et al., 2020*). A weak positive dose-response relationship between volume of preoperative endometrioma and levels of AMH were observed in one study (*Marcellin et al., 2019*) but not the other (*Roman et al., 2020*). This association was maintained after adjusting for several covariates, including age, body mass index, use of oral contraceptives, infertility and the presence of bilateral cysts. Putative biological mechanisms underlying this

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KEYWORDS

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association were that an excessive amount of AMH is released into the circulation owing to endometriosis-related localized inflammation and neo-angiogenesis (*Marcellin et al., 2019*). Another explanation was that endometriomas were 'toxic' to primordial follicles and drove them to exit their dormant state and enter the later AMH producing stages of follicular development (*Marcellin et al., 2019*).

Alternatively, a methodological selection bias of included women in both studies might also be suggested. Both studies originated from gynaecological surgery departments to whom women with good ovarian reserve may have been referred and, therefore, women with infertility, low serum AMH levels, or both, may have been underestimated.

These findings are surprising and, if replicated, would have substantial clinical implications. First, it would suggest that any drop in serum AMH level encountered after endometriotic cystectomy might not be the result of ovarian reserve damage, but rather resolution and return to a normal homeostatic physiological state. Second, if the toxic theory is widely believed, it may be interpreted as endometrioma removal facilitating resolution of ongoing damage to the ovarian reserve. Lastly, it would suggest that AMH may be overestimated in the presence of a large endometrioma, questioning the reliability and utility of AMH for counselling and that the other biomarkers may have greater utility.

We would, however, urge caution, before these reports lead to systematic changes in clinical practice, and recommend urgent replication as the finding linking large endometrioma to high serum AMH levels seems to be biologically implausible, and contradicts the existing extensive body of research. In a meta-analysis of 12 prospective studies (n = 783), preoperative serum AMH levels were similar between women with unilateral and bilateral endometriomas, challenging the notion that the severity of endometriosis may be positively associated with AMH levels (*Younis et al., 2019*). Histological studies have clearly shown that endometriotic cystectomy is generally complicated by inadvertent removal of normal ovarian follicles adjacent to the pseudo-capsule, which may be unavoidable, even in the hands of experienced surgeons (*Alborzi et al., 2009*; *Roman et al., 2010*).

We are not aware of any study supporting the suggestion that enhanced AMH production takes place within an endometrioma or within the immediate vicinity. On the contrary, available histological evidence shows that, in cortical ovarian samples adjacent to endometrioma, a significantly lower follicular density, fibrosis formation and concomitant loss of stroma occurs (n = 20) compared with controls (*Kitajima et al., 2011*). This suggests damage to the ovarian reserve within the immediate vicinity. With follicular AMH production, a small, matched cohort study assessing mono-follicular fluid AMH concentrations in patients undertaking natural cycle IVF did not find a difference in follicular fluid AMH concentrations in women with mild endometriosis compared with controls (*Campos et al., 2010*). Similarly, in an analysis of pooled follicular fluid samples, AMH concentrations were not altered in women with endometriosis compared with controls (*Kucera et al., 2018*). With peritoneal fluid, several investigators have found a significant correlation between serum AMH and peritoneal fluid AMH levels in women with endometriosis and control women without disease (*Hipp et al., 2015*; *Kitajima et al., 2020*; *Kostrzewa et al 2020*), with *Kitajima et al. (2020)* also showing significantly lower AMH in peritoneal fluid in women with advanced endometriosis compared with those of control women. Collectively, these data from mono-, multi-follicular samples and peritoneal fluid would all suggest no evidence that that endometriosis enhances AMH production. In cell cultures of endometrial and epithelial ovarian cancer cell lines, both of which may be Müllerian duct derivatives, AMH has growth inhibitory effects (*Kim et al., 2014*). In eutopic and ectopic endometria treated with AMH *in vitro*, AMH had reduced proliferative activity and increased intracellular markers of the apoptotic signalling cascade (*Wang et al., 2009*; *Namkung et al., 2012*; *Kitajima et al., 2014*). Although the exact role of AMH in the growth and maintenance of endometriosis is not fully elucidated, endometrium and endometriotic tissue may be a target of AMH for inhibitory actions. This suggests that reduced AMH concentrations within the ovary and peritoneal fluid may facilitate the progression of endometriosis. In mouse models of endometriosis, excessive follicular activation may take place (*Takeuchi et al., 2019*), and assessment whether this contributes to the reported increase in circulating AMH concentrations observed in humans with endometriomas is warranted. It would suggest, however, that it would only be temporary and, in time, would result in AMH concentrations being reduced as the ovarian reserve is depleted. Similarly, as surgical intervention may cause initial postoperative hyperactivation of dormant primordial follicles, investigation of whether this initial over-recruitment contributes in the longer term to accelerated depletion of the remaining ovarian reserve is required (*Matsuzaki et al., 2020*). Exploration of these hypotheses may be achieved through a combination of animal models, in-vitro cell studies and well-phenotyped human samples, accepting the overall limitations of AMH as biomarker of the true and functional ovarian reserve.

An abundance of evidence shows that ovarian surgery, particularly endometriotic cystectomy, causes significant ovarian reserve damage, with overall serum AMH levels reduced by 39% and 57% from baseline after ovarian endometriotic cystectomy, in unilateral and bilateral cases, respectively (*Younis et al., 2019*). In this meta-analysis, nine of the studies only included participants with a mean endometrioma diameter measuring over 4 cm, and that 294 women had bilateral endometrioma measuring 4 cm or over; therefore, we should have been able to detect an association between increased endometrioma size and higher preoperative AMH levels, particularly in the bilateral affected group. Consistent with this meta-analysis, a more recent study (*Yoon et al., 2020*) (n = 118), with a mean endometrioma size of 6.52 cm, did not observe any relationship between endometrioma size and AMH concentrations.

We acknowledge that certain clinical circumstances, such as polycystic ovary syndrome, have been associated with increased AMH concentrations, potentially reflecting arrested follicular development and altered granulosa cell function (*Pigny et al., 2003*; *Owens et al., 2019*). Evidence showing that the inflammation and neo-angiogenesis endometriosis-related mechanisms might

lead to high serum AMH levels, however, is lacking. Similarly, no in-vivo studies in humans have reported that the burnout theory of primordial follicles, purportedly induced by the endometrioma itself, may lead to serum AMH increase. In contrast, available evidence suggests that AMH is a paracrine regulator of primordial follicle activation that conserves the ovarian reserve, with regulation of the rate of primordial follicle activation in a context-dependent manner (*Pankhurst, 2017*).

Available studies showing that large endometrioma causes high AMH levels have been limited and should be interpreted with caution, particularly given their retrospective nature, wide inclusion criteria, cross-sectional nature and possible selection bias (*Marcellin et al., 2019*; *Roman et al., 2020*). Because of the significance of the association between level of AMH and endometrioma diameter, and its related wider implications, prospective well-conducted pre-clinical and clinical studies, with repeat measures of endometrioma volume and AMH concentrations, are urgently required. Until then, the discussion remains open.

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