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Is ovarian reserve reduction following endometriotic cystectomy predicted? The implication for fertility preservation counseling

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Introduction

Ovarian reserve depletion secondary to an intact endometrioma continues to be actively debated (1, 2) and has been recently challenged (3). Conversely, endometriotic cyst surgery, specifically endometriotic ovarian cystectomy, seems to have an irreversible damaging impact and is of concern for women and practitioners alike. Past histological studies have demonstrated inadvertent primordial follicle removal adjacent to the endometrioma, which seems inevitable even in experienced hands (4, 5). Furthermore, well-performed systematic reviews and meta-analyses have resulted in a significant irreversible reduction in serum AMH levels (3, 6), suggesting potentially lasting damage to the reproductive life span.

Recently, our group has shown a significant drop in serum AMH levels by 1.65 ng/ml (95% CI: 1.15 to 2.15) and by 2.03 ng/mL (95% CI: 1.47 to 2.58) at 9-12 months postoperatively as compared to baseline in the unilateral and bilateral ovarian endometriotic cystectomy groups, respectively, corresponding to 39% and 57% decline of the functional ovarian reserve following surgery (3). Furthermore, we have shown that AMH is a much more sensitive biomarker than AFC in this setting (7). Since our publication considered studies that employed the stripping technique (3), more conservative and less invasive modalities of endometrioma treatment impact on ovarian reserves, such as ultrasound-guided sclerotherapy or laser vaporization, ought to be further explored (8, 9).

The impact of endometrioma cystectomy on ovarian reserve argues that these women need fertility preservation counseling. However, the main question remains whether fertility preservation should be recommended to every woman with ovarian endometriosis considering surgery and planning for a future pregnancy and whether preoperative serum AMH levels are essential for adopting this strategy.

Fertility preservation in ovarian endometriosis

At present, many papers suggest fertility preservation, particularly oocyte vitrification, in women with intact endometrioma considering surgery and postponement of pregnancy. Interestingly, most of these publications are opinion papers and experts' viewpoints. At the same time, only a few cohort studies of actual oocyte vitrification in women with endometriosis have been published (10–16). Although ovarian tissue cryopreservation is suggested in this setting, only a few case reports have been published so far (17). The utility of such an approach in this setting needs further assessment.

Overall, although the true benefit of fertility preservation in women with endometriosis remains unknown, the recent guidelines of the ESHRE endometriosis core group recommend discussing the pros and cons of such practice, especially in women with extensive ovarian endometriosis (18).

Among published papers on oocyte vitrification in women with endometriosis, all retrospectively conducted (Table 1), the most comprehensive so far is from Spain (12). It contains 1044 women with intact endometrioma that underwent oocyte preservation, of which 43% came back to thaw their gametes to attain pregnancy. The main findings of this study suggest oocyte preservation before 35 years of age and before endometriotic surgery to obtain significantly better oocyte yield and cumulative live birth rate (CLBR) (12). A recent report by a different group from France (n = 146) corroborates these findings and advocates integrating fertility preservation into endometriosis management (16).

The magnitude of surgery's impact on ovarian reserve is unpredictable

The relevance of preoperative serum AMH levels in predicting the likelihood of pregnancy attainment or the need for fertility preservation is unclear since studies reporting on this topic have made inconsistent conclusions (18).

Counseling for oocyte preservation in women with ovarian endometriosis may depend on several composite and interrelated factors: age, preoperative serum AMH level, endometrioma diameter and laterality, uni- or multicystic display, pelvic anatomy and adhesions, surgical skills, techniques, and complexity, hemostasis methods, and previous surgery. While some of these factors may be readily assessed before surgery, others would not.

While the decrease in functional ovarian reserve following endometriotic cystectomy is exemplified by statistically significant serum AMH levels reduction, the range in AMH reduction among individual-operated women seems vast. Some women may exhibit a substantial serum AMH reduction, while others may show a minor decrease in serum AMH levels. In many cases, the magnitude of serum AMH decrease is unpredictable. Nowadays, there is no means to predict individual AMH reduction since many interrelated measurable and non-measurable confounders are involved.

Extreme damage to ovarian reserve, causing premature ovarian insufficiency, has been shown at an advanced reproductive age following bilateral endometriotic cystectomy and repeat surgery (19–21). However, it occurs only in 2.4% of cases (19), while the impact on the ovarian reserve is unanticipated in other women.

To quantify the wide variation of AMH reduction following endometriotic cystectomy, we have looked again into eligible studies in our recent systematic review examining the impact of endometriotic cystectomy on serum AMH levels (3). Twelve studies were eligible for meta-analysis, including 783 women: 489 and 294 in the unilateral and bilateral groups, respectively. This time, we calculated the coefficient of variation (CV) in serum AMH reduction following endometriotic cystectomy at

TABLE 1 Fertility preservation (Oocyte Vitrification) in Cases with Endometriosis: Summary of the Literature.

Study	Publication site	Country	Design	Number of women	Women returned
Garcia-Velasco et al., 2013 (10)	Fertil Steril	Spain	Retrospective multicenter observational	38	5
Raad et al., 2018 (11)	J Obstet Gynecol Reprod Biol	France	Retrospective observational cohort	70	ND
Cobo et al., 2020 [#] (12)	Fertil Steril	Spain	Retrospective observational cohort	1044	485
Kim et al., 2020 (13)	RBMOnline	S. Korea	Retrospective cohort	35	ND
Cobo et al., 2021 [#] (14)	RBMOnline	Spain	Retrospective observational cohort	1044	485
Hong et al., 2021* (15)	Fron Endocrinol	S. Korea	Retrospective cohort	62	ND
Santulli et al., 2021* (16)	RBMOnline	France	Retrospective observational cohort	146	ND

*Including embryo freezing.

[#]Same cohort.

ND, not disclosed.

the early (1 – 4 weeks), intermediate (6 weeks – 6 months), and late (9 – 12 months) postoperative periods. The CV is the ratio of the standard deviation to the mean difference of serum AMH values. The higher the coefficient of variation, the greater the level of dispersion around the mean, suggesting a wide variation of postoperative serum AMH reduction. The CV among unilateral and bilateral groups in all three time periods, except in the late bilateral group, was substantial, ranging from 35% to 73% (Table 2), implying a vast and unpredictable span of serum AMH reduction following surgery. The modest CV in the bilateral cases during the late postoperative period is not surprising. There is an agreement that bilateral endometriotic cystectomy is constantly associated with significant harm to the ovarian reserve (22–24). Collectively, these results imply that whatever the pre-surgical serum AMH levels, the variation in post-surgical AMH levels reduction is vast, rendering them from being an obligatory requisite for fertility preservation counseling.

Serum AMH levels and live-birth prediction

Although serum AMH level is a robust biomarker of ovarian reserve, its reliability in live-birth prediction in the ART setting is poor (25). Furthermore, age was considered a better predictor than AMH for live-birth achievement (26). Recently, in a nationwide high-order study with a validated database, serum AMH levels were highly correlated with the CLBR in women with low ovarian reserve (AMH < 1 ng/mL) (27). This was mainly related to its association with the quantitative ART cycle outcomes, primarily the number of oocytes retrieved. Furthermore, AMH and female age each

independently provided prognostic information regarding the probability of CLBR. Higher AMH levels were associated with greater CLBR for each age category. In women < 35 years of age, the CLBR ranged between 22.1% and 41.2%, stratified with AMH levels in-between < 0.1 and 0.91–1.0 ng/mL, respectively. In contrast, in women 41–42 years of age, the CLBR ranged between 6.1% and 11.1%, stratified with the same AMH levels (27). Accordingly, for women with intact endometrioma with serum AMH levels < 1.0 ng/mL, considering ovarian surgery and planning for future pregnancy, fertility preservation counseling should not be precluded, especially if they are < 35 years of age.

Conclusion

There are no guidelines for fertility preservation in women with endometriosis, especially in women with intact endometrioma, planning for a future pregnancy. Furthermore, the true benefit of fertility preservation in young women with endometriosis remains unknown. Nonetheless, the recent guidelines of the ESHRE endometriosis group recommend discussing the pros and cons of such practice. The topic of fertility preservation in women with endometriosis is evolving, and only a few cohort studies have been published. Although there is a consensus on the harmful impact of endometriotic cystectomy on ovarian reserve, the effect of endometrioma per se on the quantitative and qualitative aspects of the ovarian reserve is still debated (1, 2, 28) and has been recently challenged (3, 29). The present opinion focuses on preoperative AMH levels and whether to be included in counseling women undergoing endometriotic cystectomy, specifically in those with low serum AMH levels.

There is a general agreement that age, endometrioma bilaterality, and previous ovarian surgery are key risk factors for significant serum AMH reduction and the threat of premature ovarian insufficiency in women undergoing endometriotic cystectomy. In most other cases, the degree of AMH reduction following surgery is unpredictable.

Serum AMH levels are reliable measures of functional ovarian reserve, essential for the patient's counseling, and a good reference for future management, particularly in women postponing pregnancy. However, for women undergoing endometriotic cystectomy, preoperative AMH values do not predict surgical damage to the ovarian reserve. They should not be considered a critical measure to counsel fertility preservation before surgery. After surgery, serum AMH drop has a wide variation through a composite occurrence with numerous case-by-case interrelated factors that are largely unmeasurable and unpredictable. Until developing a reliable measure or score capable of predicting individual postoperative serum AMH reduction, discussing the pros and cons of fertility

TABLE 2 Weighted mean difference, standard deviation (SD), and coefficient of variation (CV)* between preoperative and postoperative serum AMH levels in the unilateral and bilateral endometriotic cystectomy groups at the early, intermediate, and late postoperative periods.

	Weighted Mean Difference Pre- minus Postoperative ng/mL	SD	CV
Unilateral cystectomy			
1 – 4 weeks	1.38	0.88	64%
6 weeks – 6 months	0.92	0.67	73%
9 – 12 months	1.52	0.53	35%
Bilateral cystectomy			
1 – 4 weeks	2.11	1.34	64%
6 weeks – 6 months	1.50	1.07	71%
9 – 12 months	2.73	0.29	11%

*The coefficient of variation (CV) is the ratio of the standard deviation to the mean. The higher the CV, the greater the level of dispersion around the mean. It is expressed as a percentage.

preservation with every woman planning a pregnancy regardless of her preoperative AMH levels seems plausible. Even in cases with low preoperative serum AMH levels (< 1 ng/mL), practitioners should not avert fertility preservation counseling, since reasonable CLBR may be achieved, notably in women below 35. Such a policy's economic and psychological implications need further evaluation.

Author contributions

JSY contributed to the conception and design of the manuscript and drafted the article. All authors contributed to data acquisition, analyses, and interpretation and approved the paper.

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