

The impact of excision of benign nonendometriotic ovarian cysts on ovarian reserve: a systematic review

Q7 Ahmed A. Mohamed, MSc; Tarek K. Al-Hussaini, MD; Mohamed M. Fathalla, MD;
Tarek T. El Shamy, MRCOG; Ibrahim I. Abdelaal, MD; Saad A. Amer, MD

Benign ovarian cysts are very commonly seen in gynecological practice with the majority requiring (excluding functional cysts) surgical excision, preferably through the laparoscope. However, there has been growing evidence suggesting a decline in ovarian reserve as a result of ovarian cystectomy with possible compromise to fertility potential.¹⁻³ It remains to be determined whether this damage to the ovarian reserve is related to the procedure itself or to the nature, size and laterality of the cyst.

Anti-Müllerian hormone is a dimeric glycoprotein, which is a member of the transforming growth factor family. In the female, it is exclusively secreted by granulosa cells of primary, preantral and small antral follicles (4–6 mm).⁴ It is now well established that circulating anti-Müllerian hormone gradually declines with advancing age, reflecting the decline in the number of the small antral follicles, rendering it an ideal marker for the early detection of reduced ovarian reserve. Furthermore, serum anti-Müllerian hormone concentration is generally stable with minimal inter- and

BACKGROUND: Benign nonendometriotic ovarian cysts are very common and often require surgical excision. However, there has been a growing concern over the possible damaging effect of this surgery on ovarian reserve.

OBJECTIVE: The aim of this metaanalysis was to investigate the impact of excision of benign nonendometriotic ovarian cysts on ovarian reserve as determined by serum anti-Müllerian hormone level.

DATA SOURCES: MEDLINE, Scopus, ScienceDirect, and Embase were searched electronically.

STUDY DESIGN: All prospective and retrospective cohort studies as well as randomized trials that analyzed changes of serum anti-Müllerian hormone concentrations after excision of benign nonendometriotic cysts were eligible. Twenty-five studies were identified, of which 10 were included in this analysis.

DATA EXTRACTION: Two reviewers performed the data extraction independently.

RESULTS: A pooled analysis of 367 patients showed a statistically significant decline in serum anti-Müllerian hormone concentration after ovarian cystectomy (weighted mean difference, -1.14 ng/mL; 95% confidence interval, -1.36 to -0.92 ; $I^2 = 43\%$). Subgroup analysis including studies with a 3-month follow-up, studies using Gen II anti-Müllerian hormone assay and studies using IOT anti-Müllerian hormone assay improved heterogeneity and still showed significant postoperative decline of circulating anti-Müllerian hormone (weighted mean difference, -1.44 [95% confidence interval, -1.71 to -1.1 ; $I^2 = 0\%$], -0.88 [95% confidence interval, -1.71 to -0.04 ; $I^2 = 0\%$], and -1.56 [95% confidence interval, -2.44 to -0.69 ; $I^2 = 22\%$], respectively). Sensitivity analysis including studies with low risk of bias and excluding studies with possible confounding factors still showed a significant decline in circulating anti-Müllerian hormone.

CONCLUSION: Excision of benign nonendometriotic ovarian cyst(s) seems to result in a marked reduction of circulating anti-Müllerian hormone. It remains to be established whether this reflects a real compromise to ovarian reserve.

Key words: anti-Müllerian hormone, benign ovarian cysts, ovarian cystectomy, ovarian reserve

Q1 From the Royal Derby Hospital, University of Nottingham, Derby, United Kingdom (Dr Amer, Mr Mohamed, and Mr El Shamy); and Department of Obstetrics and Gynaecology, Assiut University, Assiut, Egypt (Drs Al-Hussaini, Fathalla, and Abdelaal).

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Corresponding author: Saad A. K. S. Amer, MD, FRCOG. saad.amer@nottingham.ac.uk

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intracycle fluctuations.⁵ This makes it an ideal candidate for measuring changes in ovarian reserve following cyst excision.

To date, several studies have investigated the impact of ovarian cystectomy on ovarian reserve showing a postoperative decline in circulating anti-Müllerian hormone.^{2,6-19} However, given the relatively small size of these studies, further evidence is required to allow a firm conclusion. We have previously conducted a metaanalysis of studies investigating the effect of excision of endometriomas on ovarian reserve.¹

The aim of this metaanalysis was to investigate the impact of excision of benign nonendometriotic cysts on ovarian reserve as determined by serum anti-Müllerian hormone levels.

Materials and Methods

Criteria for study selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.²⁰ All published cohort studies and randomized trials (including at least 5 patients) that investigated the

TABLE 1
Modified Newcastle-Ottawa Scale for risk of bias and quality assessment of the included studies

Author	Year	Selection	Comparability	Outcome	Total score
Chang et al ¹⁰	2010	*	*	**	4
Iwase et al ¹¹	2010	**	***	*	6
Mohamed et al ⁷	2011	**	****	**	8
Kim et al ¹³	2013	*	*	**	4
Chen et al ¹⁵	2014	**	***	*	6
Huang et al ¹²	2014	**	****	*	7
Kwon et al ⁸	2014	**	****	**	8
Yoon et al ⁹	2014	**	***	**	7
Amooee et al ¹⁴	2015	**	***	**	7
Ergun et al ⁶	2015	*	****	**	7

Mohamed. Impact of ovarian cystectomy on ovarian reserve. *Am J Obstet Gynecol* 2016.

impact of excision of benign non-endometriotic ovarian cysts on ovarian reserve as determined by changes in postoperative serum anti-Müllerian hormone concentration were included in this metaanalysis.

Outcome measures

Primary measure. This included postoperative changes in serum anti-Müllerian hormone concentration.

Secondary measures. These included postoperative changes in serum follicle-stimulating hormone concentration and antral follicle count.

Search strategy

An extensive electronic database search was performed using MEDLINE, Scopus, Embase, and ScienceDirect to identify published research articles between January 2000 and Jan. 31, 2016, on the impact of excision of benign ovarian cysts (excluding endometriomas) on ovarian reserve as determined by serum anti-Müllerian hormone concentration. No restrictions were placed on language. A combination of the following search terms was used: laparoscopy, laparotomy, ovarian cystectomy, excision, anti-Müllerian hormone, benign ovarian cysts, and ovarian reserve. All searches were carried out by the first author and then independently repeated using the

same criteria by an accredited clinical librarian. All relevant reports were retrieved, and their reference lists were reviewed manually to identify further studies. A manual search of related articles on PubMed was also performed. We also considered published abstracts from conferences.

Data extraction

All the identified papers were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two investigators scored the studies and collected the information independently. In the case of discrepancies in scoring between the 2 investigators, a consensus was reached after discussion or after involvement of the senior investigator. In 5 studies the mean $\pm$ SD was not presented.^{2,11,14,16,17} The authors of these studies were contacted, but only 2 replied, providing the missing data, which were used in our analysis.^{11,14}

In another study, which was a conference abstract, the authors did not describe the methods of recruitment (inclusion and exclusion criteria), nor they specified the type of anti-Müllerian hormone assay kit.¹³ This study was included in the initial analysis but was excluded from the sensitivity analysis. The authors were contacted to provide

the missing information, but no response was received.

Quality of included studies and risk of bias assessment

The quality and risk of bias of the included studies were assessed using the modified Newcastle-Ottawa Scale, as previously described.¹ The original Newcastle-Ottawa Scale assesses 3 main categories including selection, comparability, and outcomes, giving a maximum of 4, 2, and 3 stars for each category, respectively.^{21,22} This scale was modified to suit the nature of this study, giving a maximum of 3 stars for selection, 4 for comparability, and 2 for outcome criteria.

Selection was rated according to recruitment bias, selection of consecutive patients, and power calculation. Comparability was assessed based on studies adjusting their analysis for 4 confounders including patients' age (<40 years), cyst diameter (>5 cm), baseline serum anti-Müllerian hormone (≥ 3.1 ng/mL), and cyst laterality.

Outcome was scored according to completeness of at least 3 months of follow-up after surgery. It is generally agreed that a limit of 5 stars could identify studies at low risk of bias.^{23,24} However, in this study, we have given more weight to comparability factors and used the cutoff level of 6 stars, with a minimum of 3 stars in the comparability category.¹ Table 1 shows the results of quality scores of the studies included in this analysis.

Data analysis

Pre- and postoperative data including mean $\pm$ SD serum concentrations of anti-Müllerian hormone (nanograms per milliliter) and follicle-stimulating hormone (milliinternational units per milliliter) and antral follicle count were extracted from the individual studies and pooled using RevMan software (Review Manager, version 5.1, The Cochrane Collaboration, 2011; The Nordic Cochrane Centre, Copenhagen, Denmark).

The weighted mean difference between the pre- and postoperative values was calculated. Statistical heterogeneity

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