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Title: Indirect Markers of Oocyte Quality in Patients with Ovarian Endometriosis Undergoing IVF/ICSI: A Systematic Review and Meta-Analysis

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Authors:

Sonia Gayete-Lafuente[1,2], ORCID ID: 0000-0002-7375-5848
Anna Vilà Famada[3], ORCID ID: 0000-0003-4866-3922
Nazli Albayrak[4], ORCID ID: 0000-0002-3405-028X
Juan José Espinós Gómez[1,5], ORCID ID: 0000-0003-4838-8940
Miguel Ángel Checa Vizcaíno[5,6], ORCID ID: 0000-0002-0226-3416
José Moreno-Sepulveda[7], ORCID ID: 0000-0002-4921-1162

Affiliations:

1 Obstetrics and Gynecology Department, Universitat Autònoma de Barcelona (UAB), Campus Universitari Bellaterra, Cerdanyola del Vallès, Spain

2 Department of Gynecology, Obstetrics and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut, USA

3 Department of Obstetrics and Gynecology, Catalan Health Institute. Barcelona, Spain

4 Department of Obstetrics and Gynecology, Acibadem University School of Medicine, Istanbul, Turkey

5 Fertty Clinic, Barcelona, Spain

6 Faculty of Medicine and Life Sciences, Pompeu Fabra University (UPF), Barcelona, Spain

7 Clínica de la Mujer Medicina Reproductiva, Viña del Mar, Chile

Corresponding author: Sonia Gayete-Lafuente MD, PhD
E-mail: sonia.gayete@gmail.com
Phone number: +1 (347) 777-4158
Permanent address: 330 E 15th St, Apt 3, 10003, New York, NY, USA

Indirect Markers of Oocyte Quality in Patients with Ovarian Endometriosis Undergoing IVF/ICSI: A Systematic Review and Meta-Analysis

Abstract

This systematic review and meta-analysis aimed to evaluate the impact of ovarian endometriomas (OMA) on indirect markers of oocyte quality in patients undergoing in vitro fertilization (IVF), compared to women without ovarian anatomical or functional abnormalities.

The search spanned original randomized controlled trials (RCT) and case-control or cohort studies published in MEDLINE, the Cochrane Controlled Trials Register, and the ClinicalTrials.gov database up to October 2023.

Thirty-one studies were included in the meta-analysis showing no significant differences in fertilization (OR 1.10; 95% CI 0.94, 1.30), blastulation (OR 0.86; 95% CI 0.64, 1.14) and cancellation rates (OR 1.06; 95% CI 0.78, 1.44). However, patients with OMA exhibited significantly lower numbers of total and mature (MII) retrieved oocytes (MD -1.59; 95% CI -2.25, -0.94; and MD -1.86; 95% CI -2.46,-1.26, respectively) and lower numbers of top-quality embryos (MD -0.49; 95% CI -0.92,-0.06). The Ovarian Sensitivity Index (OSI) was also similar between study groups (MD -1.55; 95% CI -3.27,0.18). The lack of data published to date prevented meta-analysis on euploidy rate.

In conclusion, although the presence of OMA could decrease the oocyte yield in patients undergoing IVF/ICSI, it does not appear to have an adverse impact on oocyte quality.

Keywords: *Endometrioma, in vitro fertilization, fertilization rate, blastulation rate, euploidy rate, oocyte quality*.

Key Message

Our systematic review and meta-analysis revealed similar fertilization and blastulation rates between patients with and without OMA, and comparable OSI. However, patients with OMA obtained a lower number of total and MII oocytes. Although it may reduce the oocyte yield, OMA does not appear to affect oocyte quality in IVF/ICSI.

INTRODUCTION

Endometriosis is a benign, chronic, hormone-dependent inflammatory disease characterized by the presence of endometrial tissue outside the uterine cavity. It affects 5-10% of fertile women (Giudice LC and Kao LC, 2004) and 25–50% of infertile women (Macer and Taylor 2012). Endometriosis is associated with infertility in 30–50% of the cases (Macer and Taylor 2012). Although the detrimental effect of endometriosis on fertility appears to be multifactorial, its etiopathogenesis remains uncertain. Plausible factors suggested in the literature include altered folliculogenesis leading to poor quality oocytes (Gupta et al., 2006), exposure to a hostile inflammatory environment (Gazvani and Templeton 2002; Iwabe, Harada, and Terakawa 2002), dysfunction of the tubo-ovarian anatomy causing mechanical interference with oocyte uptake and transport (Khamsi et al., 2001), oxidative damage (Matsuzaki and Schubert 2010; Agarwal et al., 2012) and immune reactions that may impair embryo implantation (Miller et al., 2017).

Ovarian endometriomas (OMA) are cysts containing ectopic endometrial tissue and represent a common form of endometriosis, affecting 17 to 44% of patients (Alborzi et al., 2014). The toxic inflammatory content of the cyst has been shown to cause fibrosis, structural distortion, and vascular deterioration in the surrounding ovarian cortex, leading to the loss of primordial follicles with oocyte attrition, early activation of follicular recruitment, follicular atresia, and diminished follicle density and ovarian reserve (A M Sanchez et al., 2014; Kitajima et al., 2011; 2014). Some data also suggest that free iron from OMA diffuses out of the cyst to the surrounding ovarian tissue, contributing to oocyte attrition (A M Sanchez et al., 2014; Da Broi et al., 2018; Li et al., 2020). Although some studies indicate that this damage is clinically negligible and that the presence of OMA per se does not cause infertility (Almog et al., 2011; Santulli P et al., 2016; Chung et al., 2019), some authors reported a lower number of oocytes retrieved after ovarian stimulation in patients with endometriosis compared to unaffected controls (Senapati et al., 2016; González-Comadran et al., 2017; Ana Maria Sanchez et al., 2017; Muteshi et al., 2018; Feichtinger et al., 2019). However, the impact of OMA on oocyte quality and resultant reproductive outcomes is not yet definitively determined.

Although it is plausible that the chronic inflammatory state of OMA could severely impact oocyte quality (Sanchez et al., 2017), there is still remarkable controversy regarding the detrimental effects of OMA on the competence of oocytes. Several molecular targets are being investigated in efforts to establish direct markers of oocyte quality but have not yet demonstrated clinical value. Given the current lack of direct indicators, indirect markers such as fertilization, blastulation, and euploidy rates are used to estimate oocyte quality in clinical settings (Homer et al., 2020). Due to the toxic microenvironment, the oocytes of patients with OMA have a thickened zona pellucida, protecting the nucleus of the oocyte from the increase in free radicals but acting as a barrier to sperm entry (Goud et al., 2014). This may explain why some authors have reported lower fertilization rates compared to the unaffected population (Sanchez et al., 2017) as well as higher rates of fertilization and embryonic development with intracytoplasmic sperm injection (ICSI) compared to conventional IVF using normozoospermic sperm in patients with endometriosis (Komsky-Elbaz et al., 2013). However, other authors reported higher fertilization rates (Muteshi et al., 2018) or no significant differences (Senapati et al., 2016; González-Comadran et al., 2017).

Despite considerable molecular, histological, and morphological evidence supporting that OMA detrimentally impacts IVF results, both directly by reducing ovarian reserve and indirectly as a consequence of related surgeries (Sanchez et al., 2014; Santulli et al., 2016; Bourdon et al., 2018), the available clinical data regarding fertility treatment outcomes in patients with OMA is highly heterogeneous. Recommendations concerning surgery prior to IVF are often based on expert judgment rather than robust evidence, with insufficient data to conclude whether OMA resection before oocyte retrieval definitively improves reproductive outcomes (Practice Committee of the American Society for Reproductive Medicine 2012). The most common current approach involves oocyte retrieval before OMA removal to preserve ovarian reserve (Goodman et al., 2016; Li et al., 2020), yet the precise influence of OMA on oocyte quality in IVF remains uncertain.

The main objective of our study is to compare oocyte quality in infertile women with OMA undergoing IVF/ICSI versus women without endometriosis and healthy ovaries. Secondarily, we aim to assess differences in the oocyte yield between groups.

METHODS

A systematic review of the literature and meta-analysis were conducted; therefore, institutional ethical approval and patient consent were not required. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021)

The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42022328778).

Search strategy and eligibility criteria

An advanced computerized search of MEDLINE, the Cochrane Controlled Trials Register, and the ClinicalTrials.gov electronic databases was performed using the following keyword combinations: endometriosis, in vitro fertilization, fertilization, blastulation, pre-implantation genetic testing (PGT-A) and euploidy.

The search strategy is detailed in the supplemental material (Supplemental Figure 1).

All randomized controlled trials (RCT), cohort, and case-control studies published in full text from January 1990 until October 2023 reporting fertilization, blastulation, and euploidy rates in IVF/ICSI cycles in patients with OMA at the time of IVF/ICSI were considered for inclusion. The search was not restricted by language or publication date.

The study eligibility criteria are described in Table 1.

Duplicate search results and unpublished articles were excluded. Publications were also removed if their titles and/or abstracts were evidently irrelevant for the study.

Study selection and data extraction

Two reviewers (AVF and SGL) independently screened and selected studies for inclusion based on the eligibility criteria described. The data was then extracted independently by both reviewers and, in cases of disagreement, a third reviewer (JMS) was consulted to reach a consensus.

Risk of bias and quality assessment

The quality of the included cohort and case-control studies was assessed following the Newcastle-Ottawa Scales (NOS). On this scale, studies are rated in three categories: subject selection, study group comparability, and outcome/exposure assessment. Studies were categorized as low-quality (NOS scores 1-3), moderate-quality (NOS scores 4-6), or high-quality (NOS scores 7-9) (Stang 2010).

The risk of bias in RCT was assessed in accordance with the Cochrane Handbook recommendations (Higgins et al., 2011).

Quantitative analysis

A Mantel-Haenszel model and a fixed-effects model were employed to determine the pooled effect of each variable. The Odds Ratio (OR) for dichotomous data accompanied by the 95% confidence intervals (95% CI) was calculated to assess the fertilization, blastulation and cancellation rates. The total numbers of retrieved oocytes, MII oocytes, OSI and number of top-quality embryos were compared by difference in means (MD). Statistical significance was established at a p-value <0.05. Heterogeneity across studies was evaluated using the I^2 statistic. In cases where I^2 exceeded 50%, a random-effects model was applied.

The Review Manager software (RevMan version 5.3) was used for statistical analysis.

RESULTS

In the initial electronic search across the three considered databases, a total of 900 original publications were identified. After removing duplicates, 890 articles were screened for eligibility, and data from 50 articles was reviewed. Finally, 31 articles were included in the quantitative analysis. The flow diagram of the identification, selection, and inclusion of studies is shown in Figure 1. The analyzed studies included a total of 12,995 participants (n= 2,809 women in the ovarian OMA group at the time of IVF/ICSI and n= 10,186 in the control group).
The details of the included studies are summarized in Table 2. Most observational studies had NOS scores ≥7, and only 3 of them had a lower score.

Primary Outcomes

The fertilization rate was analyzed in eight studies included in this review, and in four of them, no statistically significant differences were found (Opoien et al., 2012; Dong et al., 2014; Guo et al., 2020; Wu et al., 2021; Zeng et al., 2022). Our meta-analysis found no significant difference in the

fertilization rate between patients with and without OMA at the time of IVF, with an OR 1.10; CI 0.94–1.30 (Figure 2).
The blastulation rate or blastocyst formation rate was analyzed in six studies included in this review, and five of them found no statistically significant differences between study groups (Guo et al., 2020; Li et al., 2020; Yilmaz et al., 2021; Zeng et al., 2022; Dongye et al., 2023). Our results showed an OR 0.86; 95% CI 0.64–1.14 (Figure 3).
The effect of OMA on fertilization and blastulation rates is described in Supplemental Table 1. The lack of data published to date on PGT-A results in patients with OMA compared to controls prevented meta-analysis on the euploidy rate.

Secondary Outcomes

The total number of retrieved oocytes was analyzed in thirty studies included in this review, most of them reporting a lower number of oocytes retrieved in patients with OMA in comparison with the control group. Only two studies showed an increased oocyte yield in OMA (Almog et al., 2011; Chang et al., 2023). Our meta-analysis found a significantly lower total number of oocytes retrieved in patients with OMA, with a MD -1.59; 95% CI -2.25 – -0.94 (Figure 4).
The total number of MII oocytes was evaluated in seventeen studies. Fifteen of them found a significantly lower number of MII oocytes in patients with OMA compared to controls, one found no differences between groups (Demirdag et al., 2021), and one reported a higher number of MII oocytes in the OMA group (Chang et al., 2023). Our meta-analysis revealed a lower number of MII oocytes in patients with OMA, with a MD -1.86; 95% CI -2.46 – -1.26 (Figure 5).
Seven studies assessed the number of top-quality embryos. Pooled results indicated that the number of high-quality embryos obtained in patients with OMA was a significantly lower than in controls (MD − 0.49; 95% CI − 0.92 – − 0.06; Figure 6).
The OSI was analyzed in four studies included in this review. Three of them reported a lower number of oocytes retrieved relative to the magnitude of ovarian stimulation in patients with OMA versus controls (González-Foruria et al., 2020; Wu et al., 2021; Zeng et al., 2022), and one reported a comparable OSI (Bongioanni et al., 2011). Our meta-analysis did not reach statistical significance in the assessment of OSI, with a MD -1.55; 95% CI -3.27–0.18 (Figure 7).
Eight studies reported on cancellation rate. No significant differences were observed between the endometrioma and the control group (OR 1.06, 95% CI 0.78–1.44; Figure 8).
The effect of OMA on the the secondary outcomes is provided in Supplemental Table 2.

A summary of all the quantitative findings of the present meta-analysis is shown in Supplemental Table 3.

DISCUSSION

Main Findings

This review elucidated comparable fertilization and blastulation rates between patients with OMA undergoing IVF/ICSI and those with anatomically and functionally normal ovaries, along with a similar OSI and cancellation rates. However, patients with OMA exhibited a lower number of total and MII oocytes retrieved compared to controls. Our findings strongly suggest that while the

presence of OMA may reduce the overall oocyte yield, it does not seem to compromise the quality and performance of MII oocytes following IVF/ICSI procedures, which fertilization and blastulation competence were found to be comparable to those of controls.

Comparison with Other Studies

Primarily focusing on the impact of present ovarian endometriosis on oocyte quality, our meta-analysis found no differences in fertilization rates between patients with OMA and controls. A systematic review and meta-analysis including twenty-seven observational studies (n=8,984 women) showed reduced fertilization rates in patients with endometriosis stage I/II compared to controls (Relative Risk [RR] 0.93; 95% CI 0.87, 0.99, p= 0.03), but found no differences in endometriosis stage III/IV versus controls (Harb et al., 2013). However, it pooled results from seven studies with significant variation across them and without differentiation between OMA and extraovarian endometriosis. A more recent meta-analysis published in 2019 (Horton et al., 2019) found a reduced fertilization rate in the endometriosis group compared to the control group (OR 0.77, 95% CI 0.63-0.93), but the authors could not evaluate fertilization rates in their subanalysis of patients with OMA.

The blastulation rate has recently gained attention as another indirect marker of oocyte quality. In our review, blastulation rates were evaluated solely in six articles included, and no significant differences were found between patients with OMA and controls. None of the published meta-analyses evaluated this important parameter of oocyte competence, but mostly focused on quantitative reproductive outcomes.

Secondarily, we found that ovarian endometriosis negatively affects the oocyte yield and number of mature oocytes per IVF/ICSI cycle compared to controls, which is in agreement with four meta-analyses (Hamdan et al., 2015; Yang et al., 2015; Horton et al., 2019; Alshehre et al., 2021). Our meta-analysis found no differences in OSI between the OMA and the control groups. Currently, no meta-analyses evaluate this index, and hence the evidence to date is based on individual studies (Bongioanni et al., 2011; Gonzalez-Foruria et al., 2020; Wu et al., 2021; Zeng et al., 2022). While OSI is not specifically described, some meta-analyses found no differences in the total dose of gonadotropin used during ovarian stimulation between patients with OMA and controls (Yang et al., 2015; Hamdan et al., 2015; Alshehre et al., 2021). Including new data from more recently published articles, we found no differences in cancellation rates between groups, similarly to what reported a meta-analysis from 2019 based on five studies (Horton et al., 2019), but contradicting what was reported before only based on three (Hamdan et al. 2015).

Our meta-analysis identified a decreased number of top-quality embryos in patients with OMA compared to controls from eight studies included, contrarily to the previously noted in two meta-analyses, one encompassing only two studies (Yang et al., 2015) and the other, three (Alshehre et al., 2021). While the heterogeneity achieved by our analysis is debatable, it is interesting to consider extrapolating this variable to embryonic euploidy. However, we noted a significant scarcity of data on PGT-A results in patients with OMA, since only three studies evaluating their euploidy rates have been published and reported controversial results. On the one hand, a retrospective cohort study from last year (Yan et al., 2023) found that the euploidy rate in the OMA was significantly lower (52.6% vs. 61.8%, p= 0.012) but, on the other hand, two extensive studies focused in patients with endometriosis found no differences regarding aneuploidy (Juneau et al., 2017) and euploidy rates (Vaiarelli et al., 2021) compared to unaffected patients. In order to assess

the influence of OMA on oocyte quality, it is imperative for the scientific community to further study euploidy rates in this population.

Interpretation of the results

Our study strongly indicates that while the overall yield of oocytes is notably reduced in the presence of OMA, the quality of oocytes does not appear to be affected as fertilization and blastulation rates appear comparable to those of controls. While there has been considerable research and discussion on this topic, a solid explanation for the differing results among published studies remains elusive. There is controversy over whether oocyte quality and performance are affected by the presence of OMA itself or whether it is due to ovarian surgeries that many of these patients undergo prior to IVF, which would affect their ovarian reserve and, potentially, their response to ovarian stimulation. Interestingly, an observational, cross-sectional study reported that OMA per se is not associated with an increased risk of infertility incidence, while previous surgery for endometriosis is (Santulli et al., 2016). In that line, prior history of surgery for OMA has been reported to be an independent risk factor for poor ovarian response to stimulation [OR = 2.1; 95% CI: 1.1±4.0], unlike OMA without a prior history of surgery [OR: 1.5; 95% CI: 0.9±2.2] (Bourdon et al., 2018). However, ovarian response is not necessarily associated with or consequence of oocyte competence, which is the focus of our study. Furthermore, many of the studies included in our meta-analysis compared reproductive outcomes in patients with OMA who had undergone ovarian cystectomy versus who had not, identifying no significant differences regarding oocyte competence (Benaglia et al., 2013; Ashrafi et al., 2014; Nakawaga et al., 2016; Ersahin et al., 2017; Ozgür et al., 2018). These findings are also confirmed in recently published meta-analyses comparing IVF/ICSI outcomes in operated patients versus patients with intact OMA (Tompsou et al., 2009; Hamdan et al., 2015; Nickkho-Amiry et al., 2018; Alborzi et al., 2019; Wu et al., 2019), suggesting that OMA per se could be associated with detrimental impact on oocyte quality.

One potential explanation for our meta-analysis finding similar fertilization rates in patients with OMA compared to controls, unlike other authors, may be attributed to the inclusion of both conventional IVF and ICSI cycles, reflecting the real-world clinical practice. Previous reports have suggested lower fertilization rates have been reported in patients with endometriosis undergoing conventional IVF cycles versus ICSI (Komsky-Elbaz et al., 2013; Shebl et al., 2017). The superior outcomes associated with ICSI in this population support the theory of zona pellucida thickening in patients with OMA, and postulates that injecting sperm directly into the oocyte can enhance the fertilization rates. Notably, only five studies in our review analyzed conventional IVF cycles exclusively. This divergence in outcomes between ICSI and conventional IVF cycles highlights the importance of considering the IVF technique when assessing the impact of OMA on fertilization outcomes.

Regarding embryo development, our results reveal no differences in blastulation rates between patients with OMA and controls. This finding supports that the presence of OMA does not seem to impair oocyte quality, and raises questions about the necessity of surgical treatment before IVF to enhance reproductive outcomes, which remains a topic of debate. Since both OMA and ovarian surgery can notably reduce ovarian reserve, and considering that OMA does not appear to negatively impact oocyte quality and embryo development, recommendations for cyst removal is controversial and counseling should be carefully individualized. Further investigation into

euploidy rates in the presence of OMA could lead to providing more robust surgical advice. Recently, it has been suggested that both OMA and its surgical treatment can adversely affect oocyte maturation rather than embryo quality at the cleavage stage. Nevertheless, according to their findings, surgical removal of OMA seemed to have a positive influence on blastocyst development (Dongye et al., 2023), although these findings are not consistent with those of other authors. Moreover, recently published data found that the cumulative live birth rate (CLBR) was not inferior in patients with OMA compared to those with extraovarian endometriosis and controls, though they reported a reduced blastocyst formation rate in OMA (Chang et al., 2023). Undergoing OMA surgery did not yield divergent outcomes in IVF/ICSI when the ovarian reserve was similar (Chang et al., 2023). Similarly, another single-center retrospective study found a comparable CLBR between patients with and without OMA (Hernández et al., 2023).

Finally, our results indicate a distinct pattern of response to ovarian stimulation in patients with OMA, characterized by a non-significant trend toward requiring higher gonadotropin dosages for ovarian stimulation and a lower overall oocyte yield. This observed trend of a possibly lower OSI in the OMA group could be attributed to various factors associated with endometriosis, including ovarian reserve depletion, impaired follicular development, and an inflammatory microenvironment. It is plausible that the ovarian microenvironment in OMA, marked by inflammation, fibrosis, and hormonal changes, influences the response of ovarian follicles to gonadotropin stimulation, necessitating increased doses of gonadotropins to achieve a similar number of oocytes.

Limitations

The main limitation of our study lies in the assessment of oocyte quality through indirect markers, as a definition of oocyte quality using direct (molecular) markers with clinical significance has not yet been established.

Potential confounders to consider in our analysis include the possible effect of past ovarian surgeries in the study population. Although we did not exclude patients with a history of previous surgery for endometriosis/OMA or performed subanalysis based on this variable, the impact of ovarian surgery in the interpretation of our findings should be minimal, if any, given that all women in our analysis presented with normal ovarian reserve (Almog et al., 2011, Inal et al., 2019; Radzinsky et al., 2019; Yilmaz et al., 2021; Robin et al., 2021; Yan et al., 2023) after the exclusion of DOR and normal ovarian response to stimulation (Suzuki et al., 2004; Reinblatt et al., 2011, Opoien et al., 2012; Opoien et al., 2013; Gonzalez-Foruria et al., 2020). Another factor to consider is the possible influence of extraovarian endometriosis among the patients included in the study, which could not be completely excluded. Since most studies do not state neither the precise imaging testing performed to stage endometriosis neither if patients have associated abdomino-pelvic lesions, a potential uneven distribution of extraovarian implants between study groups may have affect our findings. Also, the inclusion of women with either unilateral or bilateral OMA may be a confounder playing a role in our findings. However, in the three included studies that compared unilateral and bilateral OMA, authors did not find differences between groups in the total number of oocytes retrieved, MII oocytes, fertilized oocytes or fertilization rate (Opøien HK et al., 2013; Yilmaz et al., 2021; Zeng et al. 2022), number of blastocysts (Yilmaz et al., 2021), OSI (Zeng et al. 2022) or embryos quality (Opøien HK et al., 2013; Zeng et al. 2022).

Additionally, we observed heterogeneity among the included studies. Most studies did not specify the number of IVF or ICSI cycles conducted in each group. While five studies included only conventional IVF cycles (Suzuki et al., 2005; Almong et al., 2011; Reinblatt et al., 2011; Dongye et al., 2023; Hernandez et al., 2023), and other five focused solely on ICSI (Pabuccu et al., 2004; Ashrafi et al. 2014; Ozgur et al., 2018; Robin et al., 2021; Yan et al., 2023). We also noted differences in specific patient characteristics across studies, with variability in the endometriosis extent among the studied populations and in indications for IVF in the control group. Nonetheless, most studies categorized subjects based on the severity of the disease and/or specify a subgroup with OMA, allowing accurate population selection in our review.

It is crucial to acknowledge a notable research gap highlighted in our study: the limited evaluation of euploidy rates in patients with OMA. This scarcity of data represents a noteworthy knowledge deficit.

Finally, the small sample size in some studies and the retrospective nature of the majority of them could reduce the reliability of the analysis. However, our review reflects the highest quality evidence currently available.

Strengths

This is the most up-to-date review on this subject to our knowledge. Including thirty-one observational cohort and case-control studies, our systematic review and meta-analysis constitute the largest in assessing indirect markers of oocyte quality such as fertilization rates and blastulation rates in patients with OMA.

The meta-analysis provides valuable evidence rated with reference to GRADE, showing acceptable heterogeneity values and narrow confidence levels for primary outcomes and with a large sample that allows investigation of clinically impactful secondary outcomes.

Clinical impact statement

Our study findings strongly suggest that OMA may not impair oocyte quality in the context of IVF/ICSI, despite a reduction in the overall yield of oocytes. The observed trend of a potentially lower OSI in the OMA group compared to the control group raises important considerations for clinical practice.

These groundbreaking findings hold significant implications for counseling patients with OMA. The evidence presented suggests that individuals with OMA can confidently pursue IVF before surgery, obtaining oocytes with comparable potential to those from women without OMA, based on the best available evidence.

However, it is important to consider that those patients with OMA seeking fertility preservation through oocyte vitrification may obtain a lower number of total and MII oocytes compared to healthy patients. Recent studies have recommended that, in general, at least 10–15 oocytes should

be cryopreserved if the patient is willing to undergo fertility preservation to increase the chances of achieving a future pregnancy (Cobo et al., 2016; Hong et al., 2021; Henry et al., 2022)

Future Studies

Further research is warranted to expand our understanding of the cytotoxic impact of OMA on the surrounding follicles during IVF cycles and its effects on oocyte quality. Future RCT and larger observational studies are needed to establish direct markers of oocyte quality and to compare these indicators in patients with and without OMA. To minimize confounding variables, future studies should have strict and homogeneous inclusion and exclusion criteria, excluding other causes of ovarian dysfunction as well as history of pelvic surgery.

Additionally, a broader evaluation of embryonic euploidy in patients with OMA is essential. The prevalence of the noted research gap assessing PGT-A results in this population emphasizes the need for additional research aimed at elucidating the precise effects of OMA on euploidy rates and, consequently, oocyte quality. Addressing this gap by comparing PGT-A results between patients with OMA and controls would provide valuable insights, enhancing our understanding of reproductive outcomes in this patient population. Moreover, such studies could contribute to the establishment of definitive treatment strategies for patients with OMA.

CONCLUSIONS

Our systematic review and meta-analysis provide a comprehensive perspective on the relationship between OMA and IVF outcomes.

Contrary to assumptions of adverse effects on oocyte quality, we find that OMA does not significantly impact indirect markers of oocyte quality, as reflected by comparable fertilization and blastulation rates in comparison to patients without OMA. However, our study highlights a notable reduction in the number of total and MII oocytes retrieved, accompanied by a non-significant trend of reduced OSI. To confirm and build upon these findings, larger and more homogenous RCT focusing on direct markers of oocyte quality would be necessary in the future.

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Author contributions

SGL and JMS conceived the idea, designed and directed the study. SGL and AVF performed the article search and the systematic review for data inclusion. AVF collected data. All authors had full access to all data included in the study and take responsibility for its integrity. JMS conducted the quantitative analysis. All authors and the accuracy of the analysis. SGL and AVF wrote the

manuscript. All authors revised the article, made critical edits and added important intellectual content to it. All authors approved the final version of the manuscript submitted to the journal.

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Conflict of interest

The authors have no conflicts of interest to declare.

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TABLES

Table 1. Study eligibility criteria

Target population	Infertile patients with either unilateral or bilateral OMA at pelvic ultrasound at the time of ovarian stimulation for IVF, with or without prior surgery.
Intervention	IVF/ICSI with or without PGT-a
Controls	Infertile couples for other reasons without anatomical or functional ovarian anomalies
Outcome measure	**Primary Outcomes** • Fertilization rate: number of 2-pronucleus zygotes obtained divided by the number of oocytes retrieved with conventional IVF or the number of mature oocytes injected for ICSI. • Blastulation rate: number of blastocysts available divided by the number of normally fertilized MII oocytes. • Euploidy rate: number of euploid embryos divided by the number of blastocysts biopsied for PGT-A. **Secondary Outcomes** • Number of retrieved oocytes: mean number of total oocytes retrieved. • Number of MII oocytes: mean number of oocytes retrieved in metaphase of meiosis II, presenting the first polar body. • Number of top-quality embryos: mean number of total high quality embryos obtained. • Ovarian Sensitivity Index (OSI): mean number of oocytes retrieved divided by the total dose of gonadotrophins administered, which is equivalent to the number of units of exogenous gonadotropins necessary to obtain one oocyte retrieved (Revelli et al., 2020). • Cancellation rates: number of ART cycles in which ovarian stimulation or monitoring has been initiated with the intention to treat, but which did not proceed to follicular aspiration or in the case of a thawed or warmed embryo did not proceed to embryo transfer.
Design	All RCT, cohort, and case-control studies published in full text until October 2023
Exclusion criteria	• History of OMA but no lesion at the time of IVF • Suspected malignancy • Other anatomical or functional ovarian alterations (such as non-OMA cysts, masses, polycystic ovary, and ovarian insufficiency) • Diminished ovarian reserve

813 **Table 2. Description of studies included in the Meta-Analysis**

814

Study ID	Location/ Duration	Design of the Study	Number of participants		Age (years)		BMI (Kg/m2)		AMH (ng/ml)		AFC		Population	Controls	History of previous surgery	Intervention / Stimulation protocol	Fertilization method	Quality studies (NOS)
			OMA	CG	OMA	CG	OMA	CG	OMA	CG	OMA	CG						
Pabuccu et al. 2004	Turkey/ 01. 1999-08.2002	Prospective Case-control	40	46	30.1	29.5	25.2	26.1	NA	NA	4.8±2	5.4±1.9	- OMA + no previous surgery or aspiration of OMA during IVF	- Tubal factor - No endometriosis, history of ovarian surgery, tuberculosis or hydrosalpinx	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- ICSI fresh cycles - Long Protocol with a-GnRh -Trigger with HCG when 3 AF >17mm and E2 >500 pg/ml	ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Suzuki et al. 2005	Japan/ 03.1996-12.2012	Retrospective Case-control	80	283	34.6	34	22.3	22.1	NA	NA	NA	NA	- OMA at the time of oocyte retrieval	- Tubal factor - No endometriosis	Yes, approximately 50% of patients, but no poor response was observed.	- IVF cycles - Short protocol with a-GnRh. - Trigger with HCG	IVF	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3
Almog et al. 2011	Canada/ 09. 2006-11.2009	Retrospective Case-control	81	162	35.2	35.2	NA	-	NA	NA	15±1.6	14.2±1.4	- Unilateral OMA by US at the time of oocyte retrieval	- Age-matched women with no OMA	Not informed, but it was assumed that patients with previous surgery could be included No diminished ovarian reserve or poor response were observed	- First IVF cycle - Trigger with HCG when 3 AF > 18mm	IVF	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3
Bongioanni et al. 2011	Italy / 2004-2009	Retrospective Case-control	142	174	33.8	34	22.7	23.1	NA	NA	16.9±11.1	16.6±9.5	- OMA <6cm by US - No malignancy or hemorrhagic cysts	- Tubal factor - No endometriosis	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF/ICSI Cycles - Long Protocol with a-GnRh -Trigger with HCG when AF > 18mm	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3

Reinblatt et al. 2011	Canada/ 2006-2010	Retrospective Case-control	13	39	31.5	31.7	-	-	NA	NA	14.8±4.5	21.5±3.3	- Bilateral OMA by US	- Tubal factor or male factor - Age-related controls - No OMA	Yes Percentage was not informed, but no diminished ovarian reserve was observed.	- IVF Cycles	IVF	6/9 Selection: 2/4 Comparison: 2/2 Exposure: 2/3
Opøien et al. 2012	Norway/ 08.1996-03.2011	Retrospective Cohort	186	1171	32.9	33.2	22.9	23.6	NA	NA	NA	NA	- OMA by US; - Ovulatory cycles - Normal semen analysis	- Tubal factor	Yes, approximately 78% of patients, but no poor response was observed.	- IVF/ICSI Cycles - Short protocol with a-GnRh. - Trigger with HCG	IVF/ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Benaglia et al. 2013	Italy – Spain/ 01.2006-07.2010	Retrospective Cohort	39	78	36.4	36.5	21.7	22.5	2.8±1.3	3±1.8	11±1	12±8	- Bilateral OMA >10mm by US - <40 years - Exclusion: Other non-OMA ovarian cysts, atypical lesions	-Tubal factor, male factor, anovulatory or unexplained sterility. -Age-related controls -No OMA, endometriosis or other ovarian cyst	No previous surgery history	- IVF/ICSI Cycles -Trigger with HCG when AF > 18mm	IVF/ICSI	9/9 Selection 4/4 Comparison: 2/2 Exposure: 3/3
Opøien et al. 2013	Norway / 05.2009-09.2011	Prospective Cohort	OMA1. n=47 OMA2. n=17	CG1. n=28 CG2. n=25	OMA1. 34.8 OMA2. 31.9	CG1. 33.6 CG2. 33.2	OMA1. 23.1 OMA2. 22.9	CG1. 23.5 CG2. 24.1	NA	NA	NA	NA	- OMA1: Unilateral OMA unilateral by US. 27.7% previous surgery - OMA2: Bilateral OMA by US. 21.4% previous surgery	- CG1: unexplained sterility. - CG2: Male Factor - No endometriosis	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- Unexplained sterility - Protocol with antagonist or a-GnRh -Trigger with HCG when AF > 17-18mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3

Ashrafi et al. 2014	Iran/ 05.05-12.2007	Prospective Cohort	47	57	31.9	30.6	NA	NA	NA	NA	NA	NA	- Unilateral or bilateral OMA by US <3cm - No neoplasic or acute hemorrhage features – Exclusion: systematic disease or malignancy, basal FSH > 15 mIU/ml, history of ≥3 unsuccessful IVF attempts, OMA > 3cm	- Male factor – Exclusion: systematic disease or malignancy, basal FSH > 15mIU/ml, history ≥3 unsuccessful IVF attempts	No previous surgery history	- ICSI Cycles - Long Protocol with a-GnRh - Trigger with HCG when 2-3 AF >17mm	ICSI	8/9 Selection:4/4 Comparison:2/2 Exposure: 2/3
Dong et al. 2014	China/ 01.2011 – 06.2013	Retrospective Cohort	68	153	31.1±4.2	30.4±4.4	19.1±5.9	20.5±5.0	NA	NA	9.3±4.9	11.0±5.3	- OMA patients operated or not. - Only the subgruop of patients with no prior surgery was included	- Infertility, no endometriosis confirmed after surgery	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- First IVF/ICSI cycles - Long protocol with a-GnRh or protocol with antagonist – Trigger with HCG when 2–3 AF ≥18mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3
Nakagawa et al. 2016	Japan/ 12.2011 – 07.2013	Prospective Case-control	26	29	37.4	37.5	-	-	2.2±1.3	2.8±1.3	NA	NA	- Unilateral OMA by US >1cm	- No endometriosis or CA125 elevated	No previous surgery history	- IVF Cycles – Trigger with a–GnRh when AF ≥16mm and E2 ≥500–600pg/ml	IVF/ICSI	5/9 Selection:1/3 Comparison:2/2 Exposure: 2/3

Ersahin et al. 2017	Turkey/ 01.2015-06.2016	Prospective Case-control	50	50	33.5	31.6	25.5	24.5	Matched AMH between 1.5-2		5.5±3.1*	12.6±6.9*	- Unilateral or bilateral OMA by US - Exclusion: suspicion of malignancy, premature ovarian failure, severe peritoneal endometriosis, a single ovary, chronic smoker or treatment with radio or chemotherapy	- Male factor - Age and AMH-related controls - No OMA or other ovarian cyst - Exclusion: suspicion of malignancy, premature ovarian failure, severe peritoneal endometriosis, a single ovary, chronic smoker or treatment with radio or chemotherapy	No previous surgery history	- IVF/ICSI Cycles - Protocol with antagonist GnRh - Trigger with HCG when AF > 17mm	IVF/ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Benaglia et al. 2018	Italia/ 03.2015-12.2015	Prospective Case-controlled	56	227	35.8	36.1	21.6	21.9	1.8±1.2	2.0±1.4	9.5±6.3*	12.5±8.1*	- OMA by US >10mm - Exclusion: adenomyosis, Fibroids >3cm, polymyomatous uterus or ovarian cyst	- Tubal factor, male factor or unexplained sterility - No previous OMA, DIE or previous surgery - Exclusion: adenomyosis, Fibroids >3cm, polymyomatous uterus or ovarian cyst	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF/ICSI Cycles - Trigger with HCG when 3 AF > 18mm	IVF/ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Ozgur et al. 2018	Turkey / 09.2014-09.2016	Retrospective Case-control	30	60	30.9	30.7	22	24	NA	NA	12.5 (6-17)	13(8-17.8)	- Unilateral or bilateral OMA by US >10mm - Age 18-42 years	- Age and AFC-related controls - No endometriosis - No uterine alteration - No previous ovarian surgery - Age 18-42 years	No previous surgery history	- Freeze all ICSI cycles - Antagonist protocol - Trigger with a-GnRh or HCG or a-GnRh + HCG when 3 AF ≥17mm	ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3

Bourdon et al., 2018	France /10.2012 - 12.2015	Observational controlled matched cohort study	201	402	33.7 ± 4.0	33.7 ± 4.0	22.9	24.1	3.4 ± 3.0	3.4 ± 3.0	13.1 ± 7.4	15.5 ± 10.1	- Unilateral or bilateral OMA by US or histological evidence, less than 42 years of age - Exclusion: vitrification oocytes procedures	- No endometriosis	Not informed, but it was assumed that patients with previous surgery were included No diminished ovarian reserve or poor response were observed	- First ICSI cycles - Long protocol with a-GnRh or protocol with antagonist – Trigger with HCG or 0.2 mg of GnRH agonist when 3 AF ≥17mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3
Coccia et al. 2019	Italy/ 01.2012 – 01.2014	Retrospective Cohort	72	144	37.9	36.6	21.8	22.6	NA	NA	NA	NA	- Unilateral or Bilateral OMA by US + no previous surgery - Exclusion: POI (FSH >30), other ovarian cysts	- Tubal factor - Exclusion: POI (FSH >30)	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- First fresh IVF/ICSI cycles - Long Protocol – Trigger with HCG when 2 AF ≥17mm	IVF/ICSI	8/9 Selection: 4/4 Comparison: 1/2 Exposure: 3/3
Orazov et al. 2019	Russia/ 2018 - 2019	Prospective Case-control	50	30	33.36	31.73	NA	NA	2.2±1.3	3.0±1.8	NA	NA	- Unilateral OMA >1cm by US - Age 24-40 years	- Tubal factor - No endometriosis - Age 24-40 years	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF/ICSI cycles	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3
Inal et al. 2019	Turkey/ 01.2016 – 06.2016	Prospective Cohort	60	60	29.52± 2.47	28.78 ±3.49	23.91± 2.11	23.62 ±2.05	1.32±0.92	1.52±0.51	6.32±2.04	9.20±1.80	- OMA by US - Operated or not - Exclusion: PCOS, low reserve, FSH >15mIU/mL, AMH <1.15 ng/mL, AI disease or a single ovary	- No endometriosis - Exclusion: PCOS, low reserve, FSH>15mIU/mL, AMH <1.15 ng/mL, AI disease, a single ovary or	Yes, but subgroup analysis of patients with previous surgery vs no surgery is not available and it is not possible to perform it with data provided	- IVF/ICSI Cycles - Long Protocol with a-GnRh. – Trigger with HCG when 2 AF ≥ 18mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3

														previous ovarian surgery	Only normoresponders included			
Radzinsky et al 2019	Russia / 2018-2019	Retrospective Cohort	70	50	33.21 ± 3.3	32.54 ± 2.8	NA	NA	2.1 ± 1.75	3.2 ± 1.4	NA	NA	- Recurrent unilateral OMA patients aged 26-40 years old	- Patients with tubal factor infertility	Yes, but subgroup analysis of patients with previous surgery vs no surgery is not available and it is not possible to perform it with data provided No diminished ovarian reserve was observed	- IVF/ICSI cycles	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3
González-Foruria et al. 2020	Spain/ 12.2014 – 12.2018	Retrospective Case-control	101	822	36.1	36.7	22.3	23.1	1.3±1.4 *	1.8±1.9 *	8.7±5.0*	11.5±6.9*	- OMA >15mm by US + no other infertility factors - Exclusion: hormonal treatment for endometriosis 3 months before IVF	- No endometriosis	Yes, approximately 32,7% of patients, but no diminished ovarian reserve or poor response were observed.	- First IVF/ICSI cycles - Protocol with antagonist – Trigger with HCG or a–GnRh when 2 AF ≥ 18mm	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3
Guo et al. 2020	China/ 11.2015-04.2016	Prospective Case-control	48	150	32.8	31.8	20.9	21.5	NA	NA	11.33± 4.84	10.14± 2.92	- OMA >3cm during ovulation monitoring or at the time of oocyte retrieval - Age 20-40 years, FSH <10 and AFC 5-20 - Exclusion: adenomyosis, PCOS,	- Tubal factor - Age and AFC related controls - No previous ovarian surgery, no OMA or ovarian cyst by US - Age 20-40 years, FSH <10, AFC 5-20 - Exclusion: adenomyosis, PCOS,	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- First IVF/ICSI cycle - Protocol with MPA + HMG - Trigger with HCG	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3

													hydrosalpinx or FSH >10	hydrosalpinx, FSH >10				
Li et al. 2020	China/ 01.2016-12.2017	Retrospective Cohort	139	360	32.5	31.8	20.7	21.2	NA	NA	8.29±5.5*	10.25±5.64*	- OMA patients aged 25-40 years, BMI 18.5-23.9 - Exclusion: male factor, gynecologycal endocrinophatolgies	- Tubal factor	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- First IVF/ICSI cycles - Trigger with HCG when 3 AF ≥18mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3
Demirdag et al. 2021	Turkey/ 09.2014 – 12.2018	Retrospective Cohort	98	1757	32.8	32.8	21.6	22.7	NA	NA	10.7±6.5	11.3±6.7	- Unilateral or bilateral OMA - Exclusion: PCOS, male factor, thaw cycles	- Tubal factor or unexplained sterility without endometriosis - Exclusion: PCOS, male factor, thaw cycles	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- Fresh IVF/ICSI cycles - Long protocol with a-GnRh or protocol with antagonist - Trigger with HCG when AF ≥18mm	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3

Wu et al. 2021	China/ 2011-2019	Retrospective Cohort	293	862	32.9	32.8	20.7	21.4	3.24±2.97*	5.74±4.53*	11.31±7.18*	17.74±10.57*	- Unilateral or bilateral OMA >15mm by US - Exclusion: adenomyosis, PCOS, rheumatic disease, contraceptives or anti-inflammatories 3 months before IVF	- Tubal factor - No endometriosis - Age, BMI and duration of fertility matched	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- 1st IVF/ICSI cycles - Protocol with antagonist or a-GnRh – Trigger with HCG when AF ≥ 18mm	IVF/ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Yilmaz et al. 2021	Turkey / 03.2015-03.2018	Retrospective Case-control	73	86	31	30.5	24	25.5	NA	NA	-1-4; 13 -5-9; 37 – ≥10; 23*	-1-4; 0 -5-9; 13 – ≥10 73*	- Unilateral or bilateral OMA by US - No endometriosis	- Male factor - AFC >5 - No endometriosis - Exclusion: endocrine dysfunctions, POI or malignancy	Not informed, but it was assumed that patients with previous surgery were included No diminished ovarian reserve or poor response were observed	- IVF/ICSI Cycles - Protocol with antagonists, long protocol with a-GnRh or microdose – Trigger when 2 AF ≥18mm	IVF/ICSI	8/9 Selection: 4/4 Comparison: 2/2 Exposure: 2/3
Robin et al. 2021	France/ 07.2007 – 12.2019	Retrospective Cohort	156	401	31.4 ± 3.6	30.4 ± 3.6	22.9 ± 3.7	24.4 ± 4.5	17.4 ± 11.3 pmol/ml	19.6 ± 12.6 pmol/ml	NA	NA	- OMA patients aged 18-42 years - Only the subgruop of patients with no prior surgery was included	- No endometriosis – Exclusion: PCOS; anovulation (premature ovarian failure, functional hypothalamic amenorrhea, hyperprolactinemia, other congenital or acquired gonadotrop	Yes Subgroup analysis of patients with previous surgery vs no surgery is available, but is not possible to compare with controls No diminished ovarian reserve or poor response were observed	- First ICSI cycles - Long protocol with a-GnRh or protocol with antagonist – Trigger with HCG or Triptorelin 0,2 mg when 3 AF ≥18mm	ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3

														ic deficits) or hyperandrogenism BMI ≥ 35 kg/m2, karyotype abnormalities				
Zeng et al. 2022	China/ 01.2018 – 12.2020	Retrospective Cohort	154	305	33.55	33.65	21.7	22	2.47±2.34*	3.32±2.82*	8.08±5.22*	12.29±7.66*	- Unilateral or bilateral OMA by US/MRI or laparoscopy before IVF. - Exclusion: donor eggs, hydrosalpinx, intrauterine adhesions or malformation fibroids >4cm, PCOS, rheumatologic disease, use of contraceptives or anti-inflammatories 3 months before IVF	- Age, BMI and duration of infertility matching cases - No previous endometriosis surgery or OMA - Exclusion: donor eggs, hydrosalpinx, intrauterine adhesions or malformation fibroids >4cm, PCOS, rheumatologic disease, use of contraceptives or anti-inflammatories 3 months before IVF	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- First IVF/ICSI cycles - Long protocol with a-GnRh or protocol with antagonist – Trigger with HCG when 2 AF ≥18mm	IVF/ICSI	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3

Chang et al. 2023	Taiwan/ 01.2014 – 12.2018	Retrospective Cohort	89	624	34.1	34.4	20.9	21.3	3.6±2.9	3.1±2.5	NA	NA	- OMA patients aged 20-40 years - Exclusion: severe male factor, uterine factor, PGT-A, donor eggs, immunological factors, FET	- Age and AMH-matched controls - No endometriosis - Age 20-40 years - Exclusion: severe male factor, uterine factor, PGT-A, donor eggs, immunological factors, FET	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF/ICSI cycles - Protocol with a-GnRh or antagonist - Trigger with HCG or a-GnRh	IVF/ICSI	7/9 Selection: 3/4 Comparison: 2/2 Exposure: 2/3
Dongye et al. 2023	China/ 01.2013 – 12.2019	Retrospective Cohort	109	532	31	31	22.1	22.2	2.35 (1.26-5.02)	2.09(1.03-3.73)	9 (6-14)	10 (7-13)	- OMA by US - Exclusion: >40 years, other ovarian cyst, male factor, ICSI, PGT-A, hydrosalpinx, pelvic adhesions, PCOS, primary ovarian failure, hyperprolactinemia, thyroid or adrenal disease, adenomyosis, donor eggs or sperm	- Tubal factor - Exclusion: >40 years, ovarian cyst, previous ovarian surgery, male factor, ICSI, PGT-A, hydrosalpinx, pelvic adhesions, PCOS, primary ovarian failure, hyperprolactinemia, thyroid or adrenal disease, adenomyosis, donor eggs or sperm	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF cycles - Protocol with a-GnRh or antagonist – Trigger with HCG when 2 AF ≥18mm	IVF	9/9 Selection: 4/4 Comparison: 2/2 Exposure: 3/3
Hernández et al. 2023	Spain/ 01.2018 - 12.2021	Retrospective Cohort	121	65	35	35	22.8	23.8	1.70±(0.87-3.32)*	3.10 (1.55-4.70)*	NA	NA	- OMA patients aged 18-40 years - Exclusion: menopausal stage, deep endometriosis, other adnexal masses, missing clinical data	- Infertility issues not related to OMA - Age, smoking habits, BMI, and other variables matched controls	Yes Subgroup analysis of patients with previous surgery vs no surgery is performed by authors or it is possible to do it with the provided dataset	- IVF cycles	IVF	5/9 Selection: 3/4 Comparison: 1/2 Exposure: 1/3

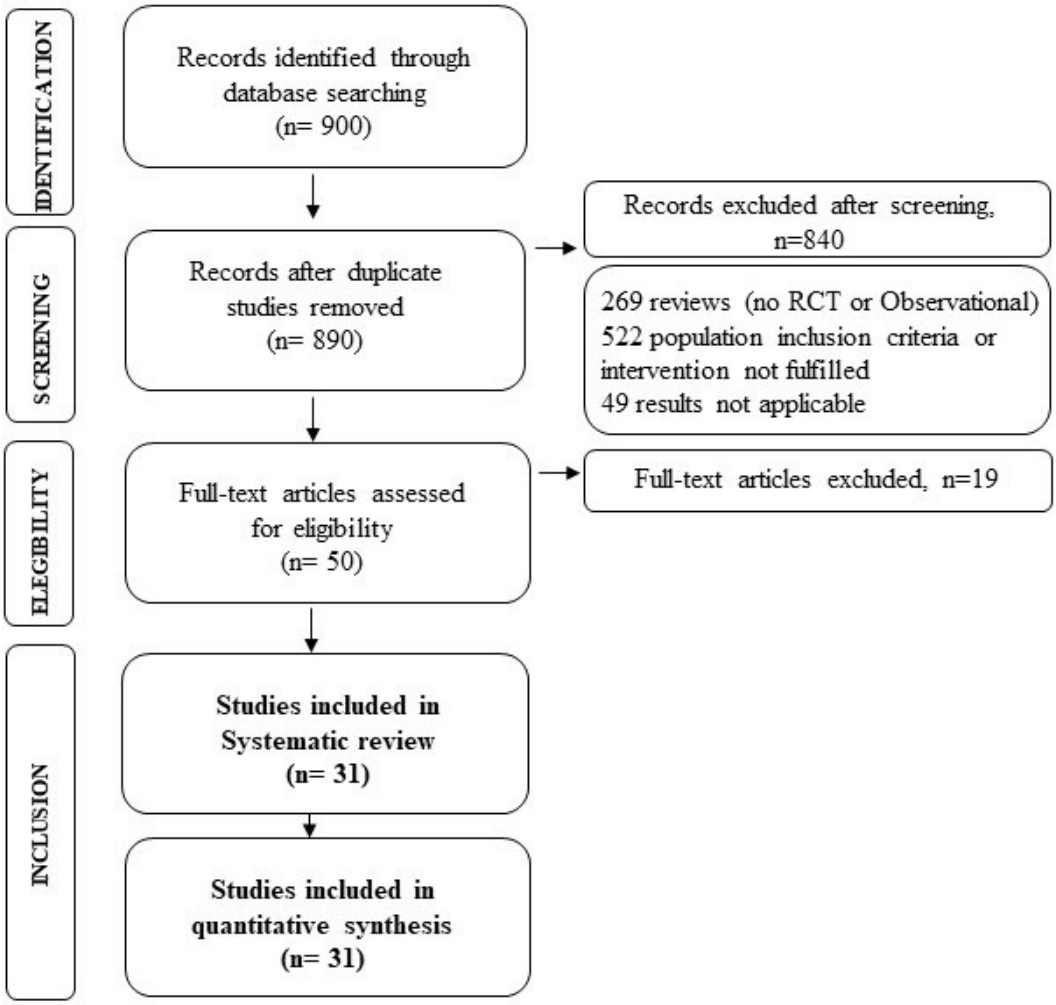
Yan et al., 2023	China/ 01.2012 – 12.2020	Retrospective Cohort	53	954	31.46 ± 4.14	31.69 ± 4.34	21.11 ± 3.18	21.37 ± 2.67	3.65 ± 2.74	4.28 ± 3.49	NA	NA	- Unilateral or bilateral OMA by US and histological evidence +PGT-M treatment with aneuploid screening -Exclusion: infertility and spontaneous abortion history	- No endometriosis -Exclusion: infertility and spontaneous abortion history	Yes, but subgroup analysis of patients with previous surgery vs no surgery is not available and it is not possible to perform it with data provided No diminished ovarian reserve was observed	-1st ICSI cycles - Long protocol with a-GnRh or protocol with antagonist -Trigger with HCG when 3 FA > 18mm	ICSI	7/9 Selection:3/4 Comparison:2/ 2 Exposure 2/3

*P<0.05 was accepted significant, data are presented mean ±SD

AF: Antral follicles / AFC: antral follicle count; AI: Autoimmune; AMH, anti-Müllerian hormone; BMI: Body mass index; ; CG: Control Group; DOR: Diminished ovarian reserve; FET: Frozen embryo transfer; IVF: In vitro fertilization; ICSI: Intracytoplasmic microinjection; NOS: Newcastle-Ottawa Scale; OMA: Ovarian endometrioma, present at the time of IVF; PCOS: Polycystic ovary syndrome; PGT-A: Preimplantation Genetic Testing for Aneuploidies; PGT-M: Preimplantation Genetic Testic for Monosomies; POI: Premature ovarian insufficiency; US: ultrasound

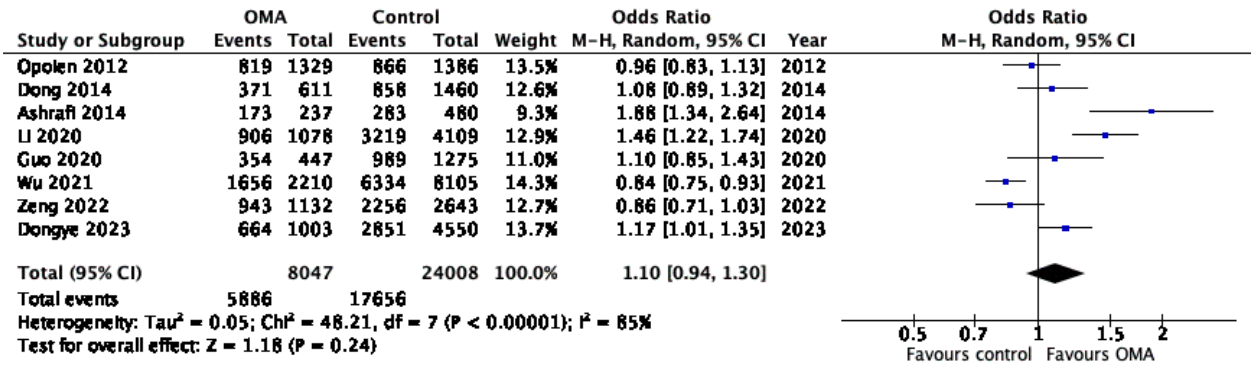
FIGURES

Figure 1. PRISMA Flowchart. Search and selection process for studies included in the meta-analysis



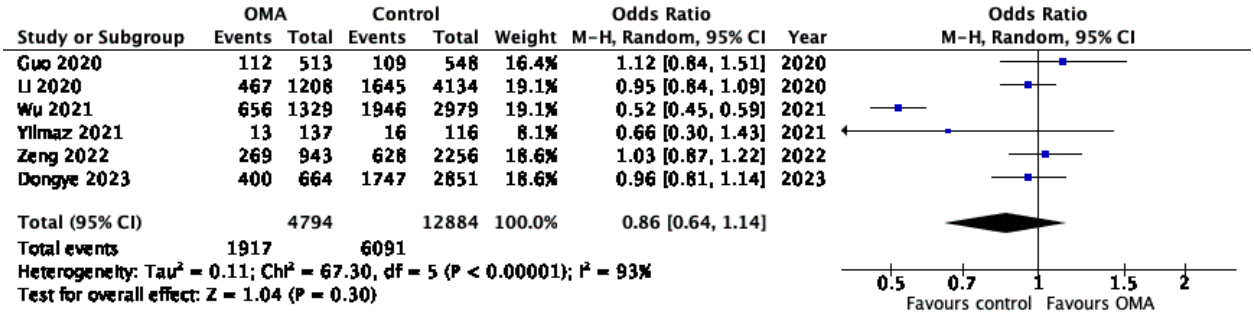
RCT: randomized controlled trial

Figure 2. Fertilization rates



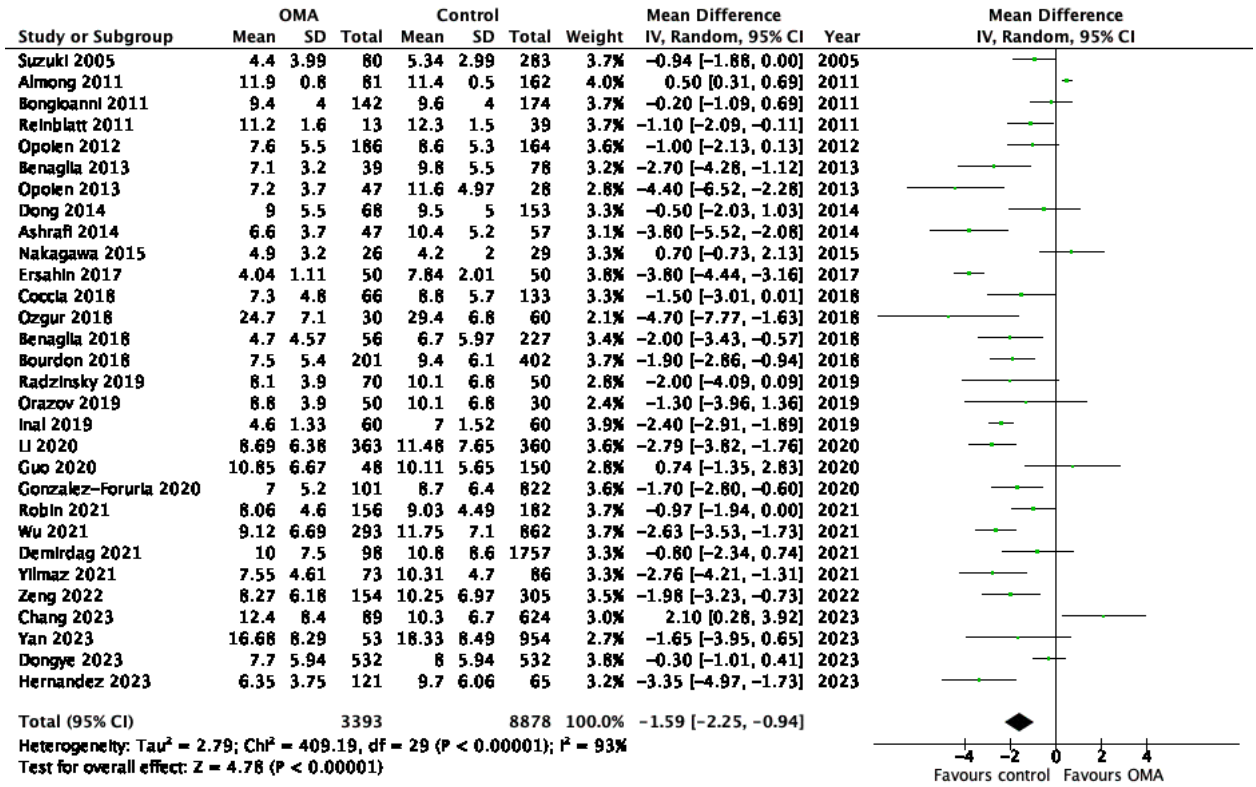
95%CI: confidence Interval 95%; Chi^2: chi-squared test; df: degrees of freedom; I^2: statistic test for quantifying inconsistency; M-H: Mantel-Haenszel method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau^2:estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 3. Blastulation rates



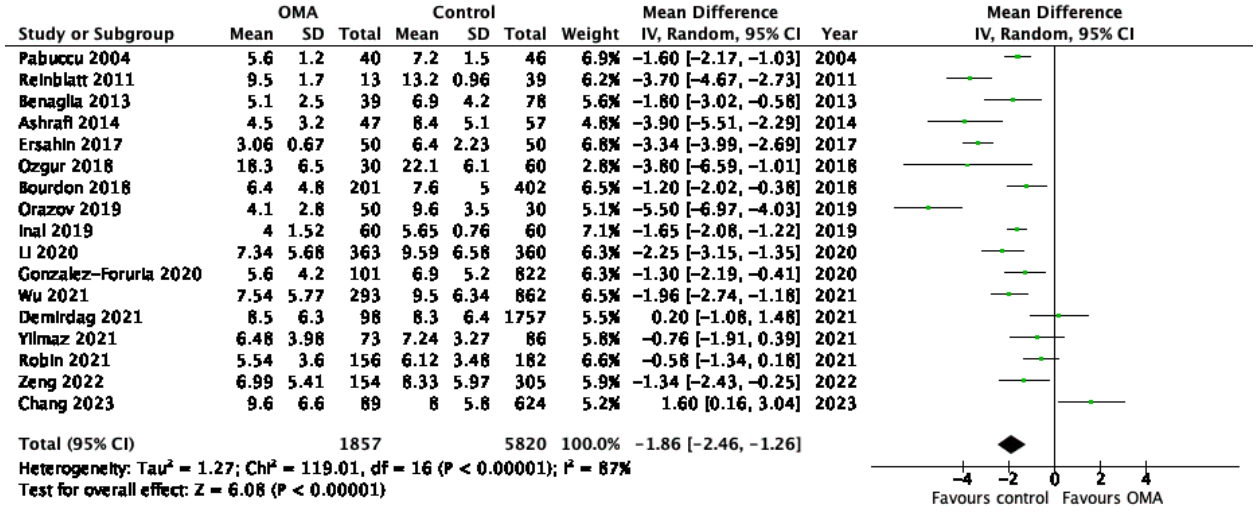
95%CI: confidence Interval 95%; Chi^2: chi-squared test; df: degrees of freedom; I^2: statistic test for quantifying inconsistency; M-H: Mantel-Haenszel method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau^2: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 4. Number of oocytes retrieved



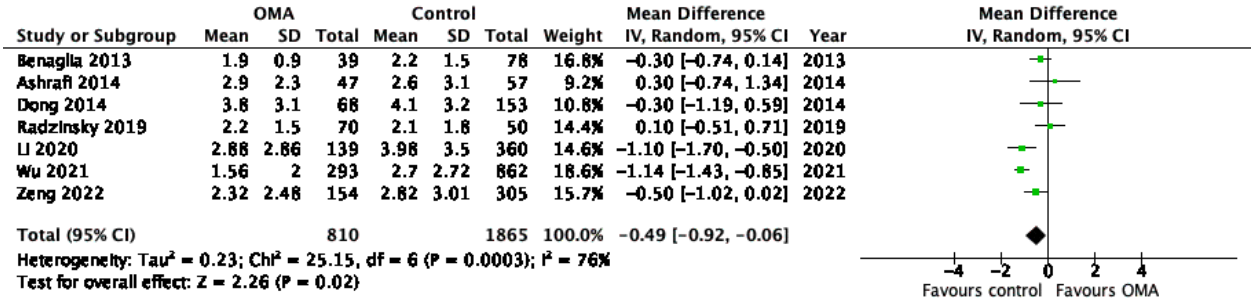
95%CI: confidence Interval 95%; Chi²: chi-squared test; df: degrees of freedom; I²: statistic test for quantifying inconsistency; IV: instrumental variables method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau²: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 5. Number of MII oocytes



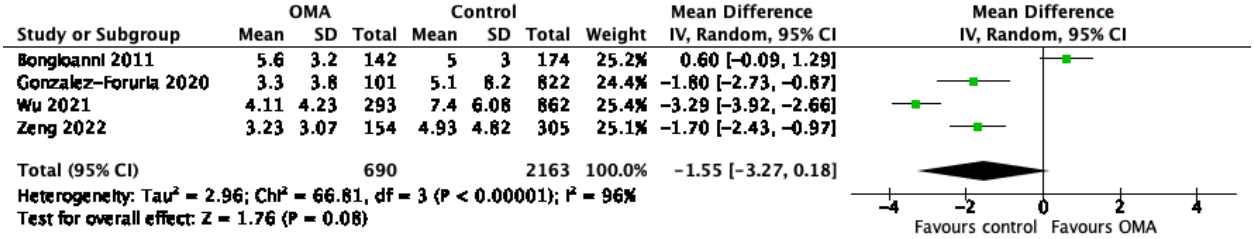
95%CI: confidence Interval 95%; Chi²: chi-squared test; df: degrees of freedom; I²: statistic test for quantifying inconsistency; IV: instrumental variables method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau²: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 6. Number of top-quality embryos



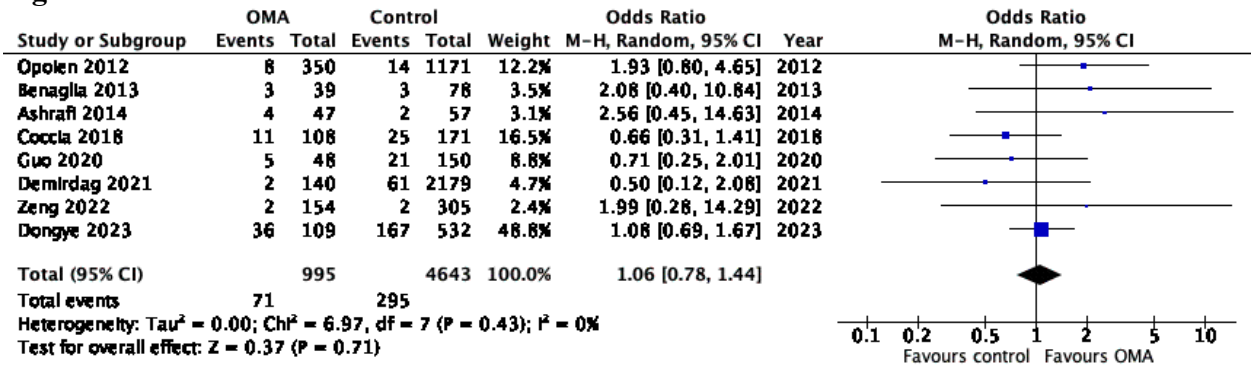
95%CI: confidence Interval 95%; Chi²: chi-squared test; df: degrees of freedom; I²: statistic test for quantifying inconsistency; IV: instrumental variables method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau²: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 7. Ovarian Sensitivity Index



95%CI: confidence Interval 95%; Chi²: chi-squared test; df: degrees of freedom; I²: statistic test for quantifying inconsistency; IV: instrumental variables method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau²: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.

Figure 8. Cancellation rates



95%CI: confidence Interval 95%; Chi²: chi-squared test; df: degrees of freedom; I²: statistic test for quantifying inconsistency; M-H: Mantel-Haenszel method; OMA: Ovarian endometrioma; P<0.05 was accepted significant, data are presented mean ±SD; Tau²: estimated standard deviation of underlying true effects across studies; Z: Z-Test, statistical test to compare group means on data that approximately follows a normal distribution.