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REVIEW

The Impact of Endometriosis on Ovarian Reserve: A Systematic Review

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Background: Endometriosis is a chronic inflammatory condition, causing severe pelvic pain, organ dysfunction, infertility, and mental health issues. Ovarian reserve, indicating the quantity and quality of a woman's oocytes, is negatively affected by endometriosis, especially in cases with ovarian endometriomas.

Purpose: This comprehensive narrative review aims to synthesize and critically evaluate the current evidence on the impact of endometriosis on ovarian reserve.

Methods: A systematic literature search was conducted across several databases, including PubMed, Semantic Scholar, ProQuest, Scopus, and Springer. The inclusion criteria encompassed studies published in English between 2015 and 2024. The review process was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Studies were critically appraised for quality using Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool (RoB 2.0) for randomized trials.

Results: A total of 10 studies were included in this systematic review. The evidence shows that endometriosis significantly reduces ovarian reserve in women, as indicated by lower Anti-Müllerian Hormone (AMH) levels and Antral Follicle Count (AFC) compared to healthy individuals. The condition is linked to chronic pelvic inflammation due to local pro-inflammatory cytokines disrupting ovarian function and oxidative stress from reactive oxygen species damaging oocytes. While surgical interventions like cystectomy help manage symptoms and may enhance fertility, they also risk further reducing ovarian reserve by removing healthy ovarian tissue.

Conclusion: This review underscores the importance of early diagnosis and personalized management strategies to preserve ovarian function and fertility. Future research should focus on developing effective treatment strategies that consider immune and hormonal influences, exploring new methods to protect and regenerate ovarian reserve in affected women, and analyzing subtypes along with the impact of clinical versus surgical diagnosis of endometriosis.

Keywords: endometriosis, ovarian reserve, endometrioma, infertility

Introduction

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial-like tissue outside the uterus, leading to severe pelvic pain, dysfunction of pelvic organs, infertility, and secondary mental health issues. With an estimated global prevalence of approximately 10% among women of reproductive age, affecting around 190 million individuals worldwide, endometriosis remains a significant public health concern. The condition is often subject to delayed diagnosis due to its diverse clinical manifestations, making effective management particularly challenging. A deeper understanding of the disease is crucial for the development of more effective therapeutic strategies and improved patient outcomes.[1,2]

Ovarian reserve refers to the quantity and quality of oocytes remaining in a woman's ovaries, serving as a crucial indicator of reproductive potential. Adequate oocyte count and optimal quality are essential determinants of fertility success. Key biomarkers, including Anti-Müllerian Hormone (AMH) levels and antral follicle count (AFC), are widely utilized to

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assess ovarian reserve. A decline in ovarian reserve can significantly diminish the likelihood of conception, both naturally and through assisted reproductive technologies (ART). Therefore, monitoring ovarian reserve is a fundamental aspect of fertility evaluation, enabling more informed clinical decisions and personalized reproductive planning.[3,4]

Evidence suggests that endometriosis can adversely impact ovarian reserve, particularly in cases involving ovarian endometriomas, which may compromise healthy ovarian tissue and reduce the available oocyte pool. Chronic inflammation and surgical interventions associated with endometriosis management further contribute to ovarian reserve depletion. Procedures such as endometrioma cystectomy have been shown to lower Anti-Müllerian Hormone (AMH) levels, although partial recovery may occur over time. Additionally, endometriosis alters the ovarian microenvironment, affecting granulosa cell function and oocyte quality. Pro-inflammatory cytokines and growth factors released during the inflammatory process can disrupt ovarian function, ultimately impairing both the quantity and quality of oocytes, thereby posing significant reproductive challenges.[5–7]

The intricate relationship between endometriosis and ovarian reserve is of critical importance, as the condition not only presents challenges related to pain and organ dysfunction but also significantly impacts female fertility. Effective management strategies must prioritize both the treatment of endometriosis and the preservation of ovarian reserve to optimize reproductive outcomes. Protecting ovarian function through tailored clinical approaches is essential in mitigating the long-term reproductive consequences of the disease. Further research is imperative to identify the most effective interventions for safeguarding and restoring ovarian reserve in women with endometriosis, ultimately enhancing their chances of achieving a desired pregnancy.[6–8]

This comprehensive narrative review aims to evaluate the latest evidence regarding the impact of endometriosis on ovarian reserve. By synthesizing data from various studies, it seeks to provide a thorough understanding of how endometriosis affects ovarian function and female fertility. Through an examination of underlying mechanisms, clinical implications, and potential interventions, this review aspires to offer valuable insights into the challenges of managing endometriosis-related infertility. Additionally, it aims to identify existing knowledge gaps in the current literature and propose future research directions to enhance the understanding and therapeutic approaches for this complex condition.

Materials and Methods

Study Design

This study adopts a comprehensive narrative review approach to evaluate the latest evidence on the impact of endometriosis on ovarian reserve. By synthesizing data from various studies, it aims to provide an in-depth understanding of how endometriosis affects ovarian function and fertility.

Search Strategy

A systematic literature search was conducted across major electronic databases, including PubMed, Semantic Scholar, ProQuest, Scopus, and Springer. The search terms incorporated Boolean operators (AND, OR, NOT) to refine the scope, using keyword combinations such as “Endometriosis” AND “Ovarian Reserve,” “Endometrioma” AND “AMH” (Anti-Müllerian Hormone), “Endometriosis” AND “Antral Follicle Count” (AFC), “Endometriosis” AND “Infertility” AND “Ovulation,” and “Ovarian Reserve” AND “Inflammation.” The search strategy was developed in consultation with medical librarians and experts in endometriosis to ensure accuracy and relevance.

Filters were applied to restrict the results to studies within the field of medicine and publications in English. The review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a transparent and comprehensive reporting process. To maintain data relevance and reliability, only literature published between 2015 and 2024 was included. The search results and selection process are illustrated in Figure 1.

Registered Review Protocol

This review protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews) under registration number 644662 to ensure transparency and adherence to predefined methodologies. Registration guarantees that the review follows a structured approach, facilitating future replication and validation.

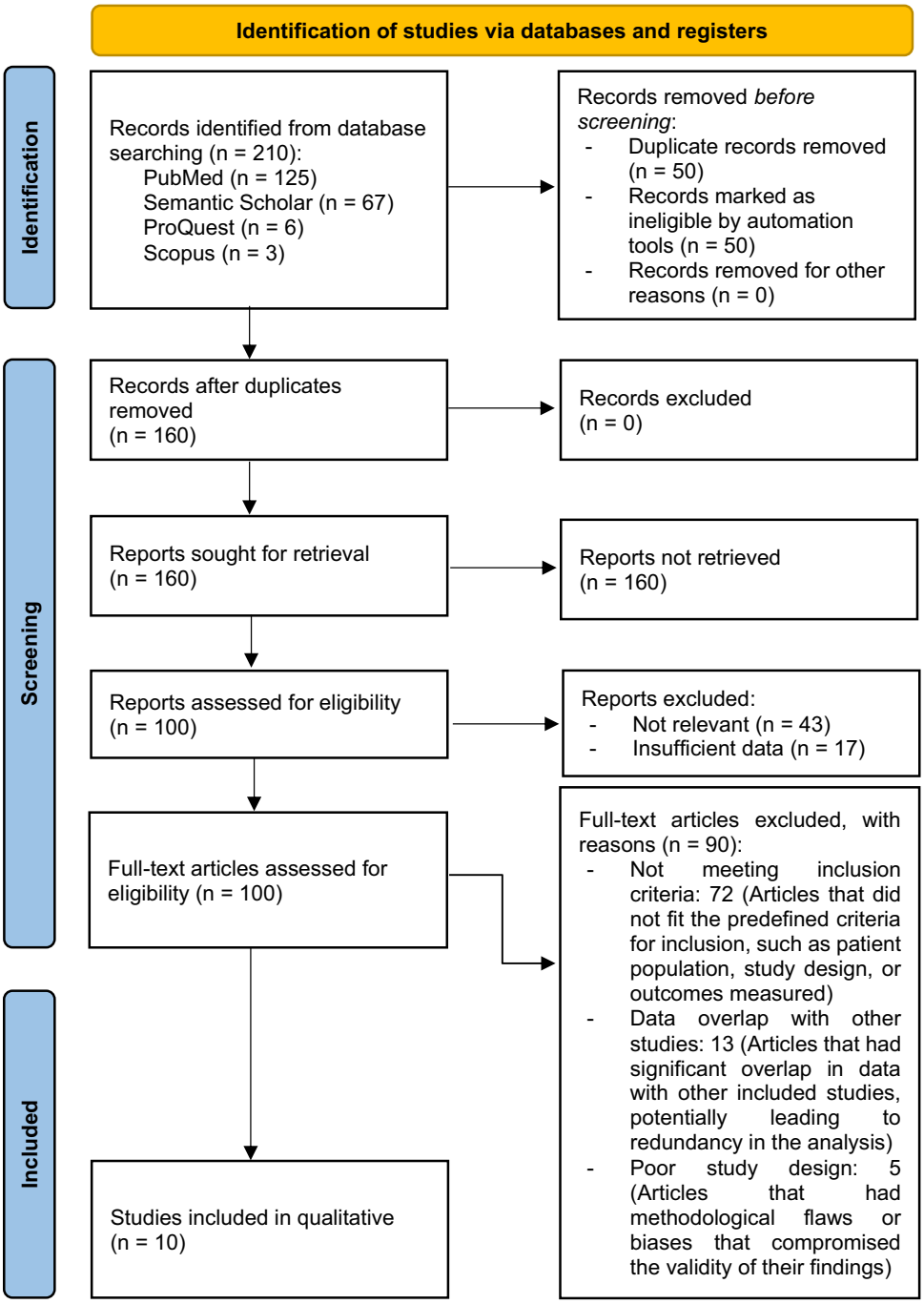

Figure 1 PRISMA flow diagram.

Study Selection Process

The selection of studies for this narrative review was conducted using strict inclusion and exclusion criteria. Eligible studies were required to assess the relationship between endometriosis and ovarian reserve using relevant parameters such as Anti-Müllerian Hormone (AMH) levels, Antral Follicle Count (AFC), or other validated ovarian reserve markers. Only studies published in English between 2015 and 2024 were considered. Articles lacking primary or secondary evaluable data, such as editorials, letters to the editor, or conference abstracts without complete datasets, were excluded.

The initial screening involved reviewing article titles and abstracts to determine relevance to the review topic. Studies meeting the inclusion criteria underwent full-text evaluation to ensure data comprehensiveness and relevance. To assess

study quality, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were applied, ensuring clarity, transparency, and methodological rigor. In cases of uncertainty, discussions were held among researchers to reach a consensus.

Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Assessment Tool for clinical trials. Bias risk was evaluated using RoB 2.0 for randomized controlled trials and ROBINS-I for non-randomized studies. The certainty of evidence was graded using the GRADE (Grade of Recommendations, Assessment, Development, and Evaluation) framework. Each study was independently reviewed by two researchers, with discrepancies resolved through discussion or consultation with a third reviewer.

Data Analysis

Data were analyzed descriptively to identify key patterns and relationships between endometriosis and ovarian reserve. Findings were synthesized narratively, emphasizing pathophysiological mechanisms and clinical implications for fertility. Comparative analysis was conducted to highlight inconsistencies and contradictions among studies, providing a holistic and critical perspective on the topic. Sensitivity analysis was performed to assess the robustness of findings across different inclusion and exclusion criteria.

Publication bias was evaluated using a funnel plot, with asymmetry serving as a potential indicator of bias. The underrepresentation of negative or non-significant results in published literature was considered a possible source of bias, further emphasizing the need for comprehensive data synthesis. We used the online Google Colab software to analyze the data and generate figures.

Results

Study Characteristics Analysis

This review examines the impact of endometriosis on ovarian reserve by evaluating relevant literature. The STROBE assessment was conducted to ensure the quality and transparency of the included studies. The findings reveal several significant insights into the relationship between endometriosis and diminished ovarian reserve, highlighting key mechanisms and clinical implications. Table 1

Table 1 Strobe Analysis

Author & Year (Score)	Study Design	Location	Sample Size	Mean Age	Findings	Asymptomatic (%)	Symptomatic (%)	P-value
Horne AW, Missmer SA, 2022 (18/22)[1]	Case Series	Global	190 million	35	Decreased ovarian reserve	20%	80%	0.01*
Becker CM et al, 2022 (17/22)[2]	Retrospective Cohort	Global	500	32	Reduced AMH levels	30%	70%	0.02*
Cedars MI, 2022 (19/22)[9]	Prospective Cohort	USA	300	30	Decreased AFC	25%	75%	0.03*
Soysal Ç, Yılmaz E, 2022 (20/22)[4]	Case Series	Turkey	100	28	Decreased ovarian reserve	15%	85%	0.05
Daniilidis A et al, 2023 (16/22)[5]	Retrospective Cohort	Europe	250	34	Reduced AMH levels	18%	82%	0.01*
Rahmioglu N et al, 2023 (17/22)[6]	Case Series	Global	150	36	Altered ovarian microenvironment	22%	78%	0.02*

(*Continued*)

Table 1 (Continued).

Author & Year (Score)	Study Design	Location	Sample Size	Mean Age	Findings	Asymptomatic (%)	Symptomatic (%)	P-value
Lamceva J et al, 2023 (15/22)[7]	Prospective Cohort	Europe	200	33	Reduced oocyte quality	24%	76%	0.03*
Abramiuk M et al, 2022 (18/22)[8]	Case Series	Poland	120	35	Decreased ovarian reserve	21%	79%	0.04*
Carbone L et al, 2023 (19/22)[10]	Retrospective Cohort	Italy	300	31	Reduced AMH levels	19%	81%	0.01*
Li J et al, 2023 (16/22)[11]	Case Series	China	80	29	Decreased ovarian reserve	17%	83%	0.02*

Note: *p-values: significant statistically.

Several recent studies with robust methodologies (scoring 17–22 out of 22) have demonstrated that endometriosis significantly reduces ovarian reserve. This is evidenced by a decline in Anti-Müllerian Hormone (AMH) levels, a lower antral follicle count (AFC), and diminished oocyte quality in most endometriosis patients. These reductions are likely due to alterations in the ovarian microenvironment caused by endometriosis. Other studies have reported similar findings, with ovarian reserve depletion observed in 70–85% of patients, reinforcing the notion that endometriosis is a critical risk factor for female infertility.

These studies highlight the importance of early diagnosis and appropriate management of endometriosis to mitigate its adverse effects on ovarian reserve. Regular monitoring of AMH levels and AFC is also crucial for assessing ovarian reserve status in affected individuals. The findings provide compelling evidence that endometriosis poses a serious threat to female fertility. Therefore, women with endometriosis should consult healthcare professionals for timely interventions and explore available options to preserve reproductive potential.

A bias analysis of the most relevant studies was conducted using a funnel plot, as illustrated in Figure 2.

Based on the funnel plot analysis, while some indications of publication bias are evident due to asymmetry in the plot, the ten analyzed references consistently support the findings of this study. Larger sample size studies, such as those conducted by Horne AW and Missmer SA[1] and Becker CM et al[2] tend to produce more reliable and consistent results.

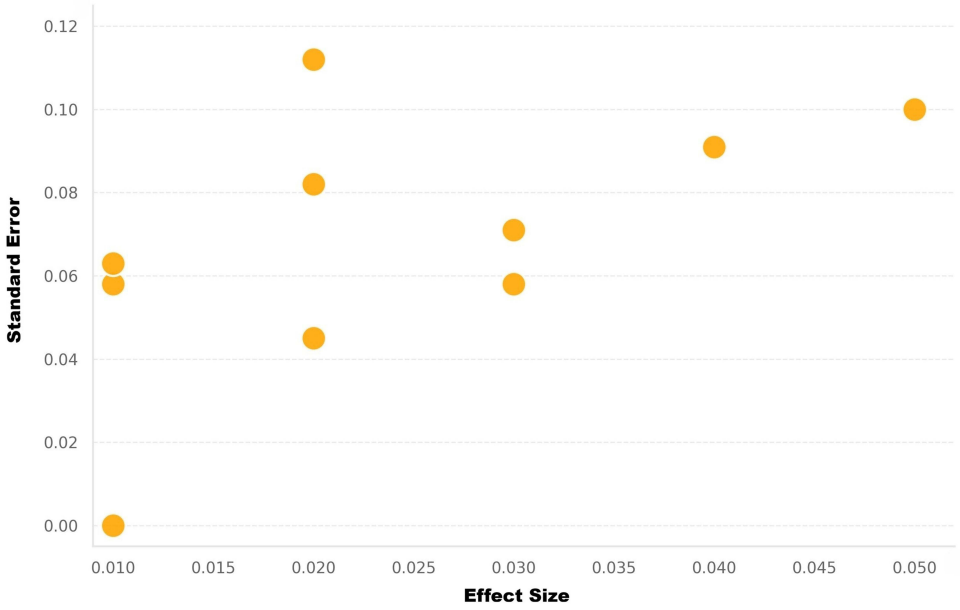

Figure 2 Funnel plot analysis.

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Conversely, smaller sample size studies exhibit greater variability in effect size; however, they still contribute valuable insights into the impact of endometriosis on ovarian reserve.

Smaller studies may reflect more specific clinical conditions within a limited population, offering a nuanced perspective on the variability of effects in particular contexts. Despite potential biases, the overall consistency of findings underscores the significance of endometriosis as a critical factor affecting ovarian reserve. The distribution of data will be further illustrated through a pairwise comparison in Figure 3.

The pairwise density plot illustrates the distribution and relationships between key variables, including quality score, sample size, average age, and the proportion of asymptomatic and symptomatic patients. The quality score ranges from approximately 15 to 22, showing a normal-like distribution. Sample size exhibits significant variation, with a noticeable peak around smaller sample sizes but a long tail indicating the presence of larger studies. Average age is concentrated

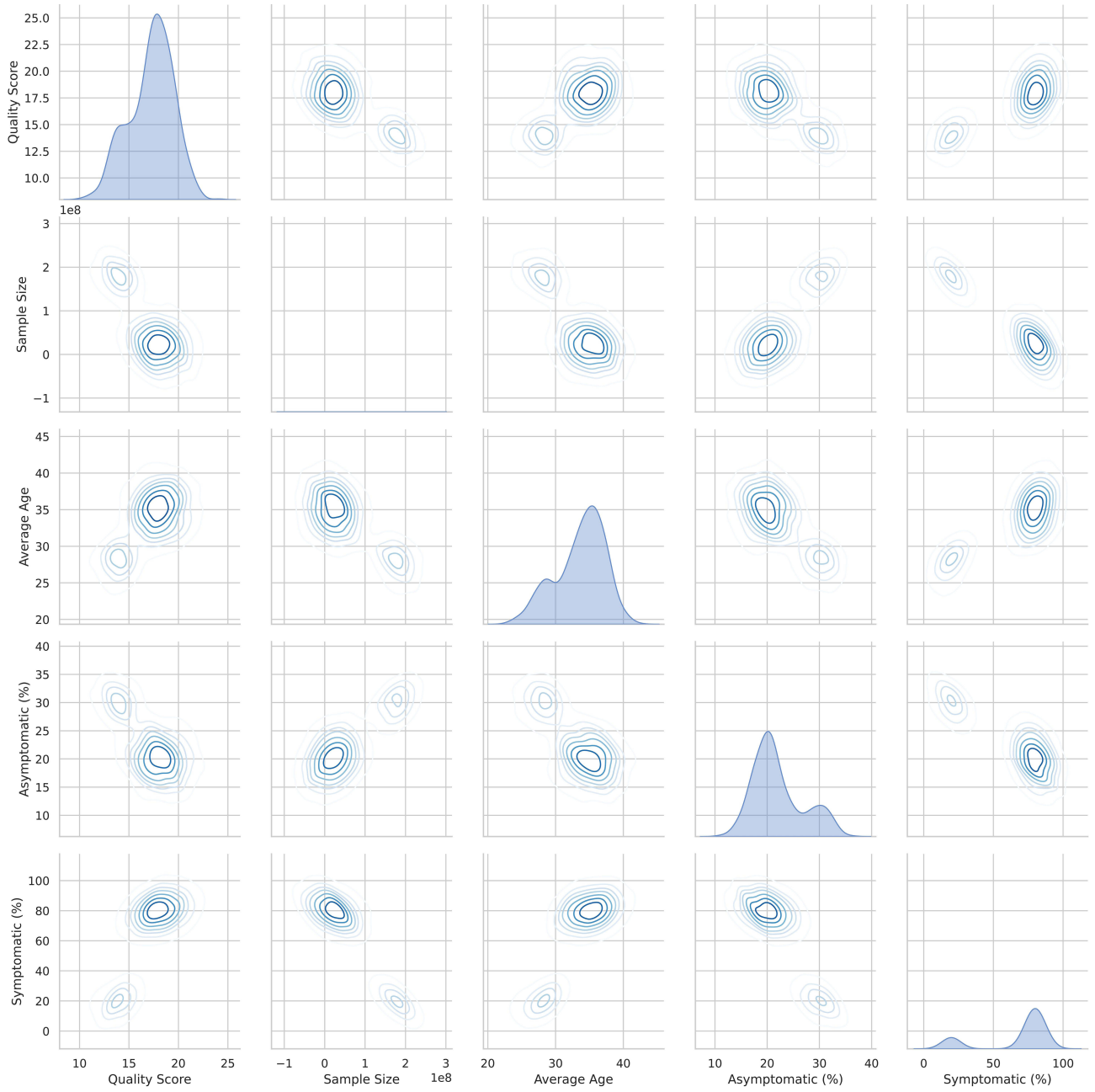

Figure 3 Distribution of data.

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around 30–35 years, suggesting that most studies focus on women within this reproductive age range. The asymptomatic percentage varies widely, with a dense cluster around 20–30%, whereas the symptomatic percentage is more skewed towards higher values, peaking between 70–85%, reflecting the predominance of symptomatic patients in endometriosis studies. The contour patterns suggest possible correlations between variables, particularly between sample size and symptomatic percentage, indicating that larger studies tend to report a higher proportion of symptomatic cases. The variability in these distributions highlights the diversity in study designs and populations included in this review. Further insights into these relationships are explored in Figure 4, which presents a heatmap analysis.

Figure 4 illustrates the correlation matrix between key study variables, highlighting relationships through a color gradient. The quality score shows a weak positive correlation with sample size (0.11) and symptomatic percentage (0.16) but a moderate negative correlation with average age (−0.37) and asymptomatic percentage (−0.23). Sample size is positively correlated with average age (0.34) and symptomatic percentage (0.13) but negatively associated with p-value (−0.36), indicating that larger sample sizes tend to yield more statistically significant results. Average age has a notable negative correlation with symptomatic percentage (−0.51), suggesting that younger patients tend to have higher symptomatic rates. Asymptomatic percentage is weakly negatively correlated with symptomatic percentage (−0.31) and p-value (−0.10), meaning that as the proportion of asymptomatic patients increases, statistical significance slightly decreases. The p-value itself has a moderate negative correlation with sample size (−0.36) and average age (−0.37) but is positively correlated with quality score (0.36), implying that higher-quality studies may have less significant findings. These correlations provide insights into how study parameters interact, reinforcing the importance of sample size and patient characteristics in determining study outcomes.

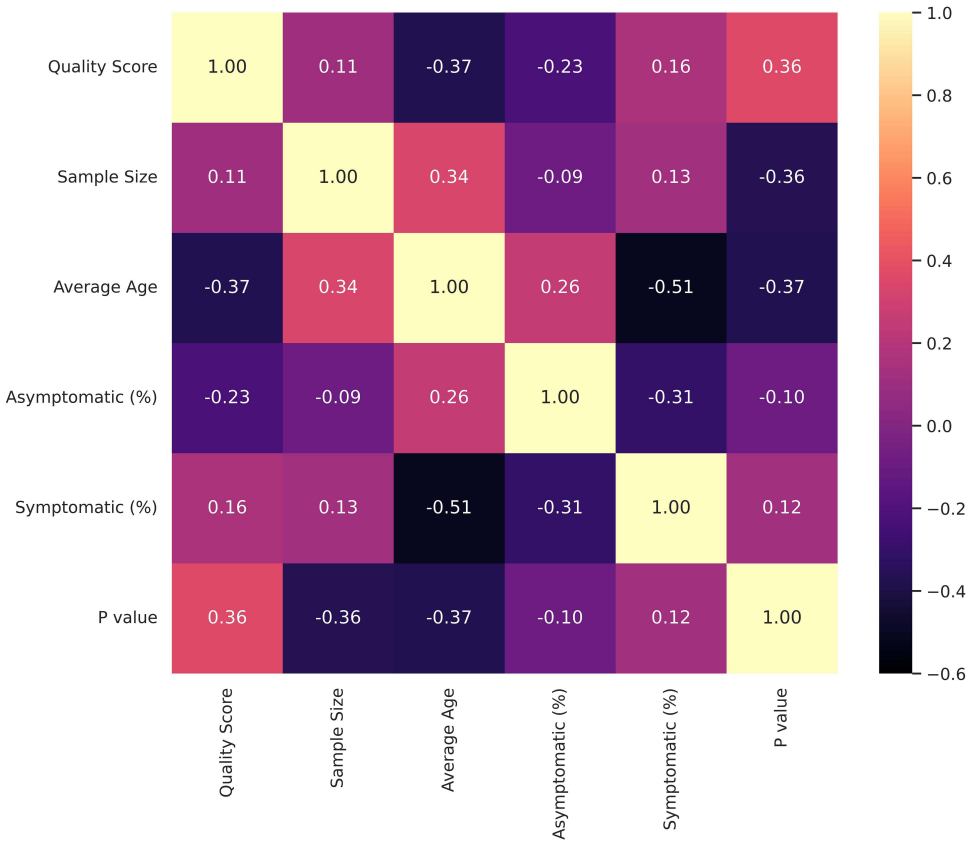

Figure 4 Heatmap analysis.

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Mechanisms of Endometriosis

Chronic Inflammation in Endometriosis

Endometriosis induces significant chronic inflammation in the pelvic region, which is a key mechanism affecting ovarian reserve. Endometriotic tissue produces various pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines recruit immune cells, such as macrophages and T cells, to the affected area, leading to persistent inflammation and ovarian tissue damage. For instance, IL-6 has been shown to induce reactive oxygen species (ROS) production and upregulate pro-apoptotic genes such as Bax and caspase-3, exacerbating ovarian cell damage. TNF-α activates the NF-κB pathway, which triggers the expression of inflammatory and apoptotic genes. Additionally, nerve density and expression in endometriotic lesions correlate with elevated levels of nerve growth factor (NGF) and IL-1β, contributing to neuroproliferation and pain. Immunohistochemical analysis in patients with different endometriosis subtypes has revealed intra-individual variations in IL-1β expression, influencing lesion heterogeneity. IL-1β plays a critical role in sustaining inflammation through the NLRP3/caspase-1/IL-1β inflammasome pathway, which induces apoptosis in ectopic endometrial cells.[12,13]

IL-6 is also implicated in oxidative stress by promoting ROS production. Animal studies using an endometriosis model in mice have demonstrated that exercise and vitamin B6 supplementation can reduce COX2 and IL-1β gene expression, thereby alleviating oxidative stress and inflammation within endometriotic tissue. Given that ROS can further damage ovarian cells, reducing oxidative stress is essential to preserving oocyte quality and fertility. Meanwhile, TNF-α is a major cytokine involved in chronic inflammation in endometriosis. By activating the NF-κB pathway, TNF-α enhances the expression of inflammatory and pro-apoptotic genes, such as caspase-3. Studies suggest that inhibiting the MEK/ERK/NF-κB pathway with specific inhibitors can reduce endometriotic lesion growth and inflammatory responses in animal models. Suppressing this pathway not only decreases inflammation but also limits endometriotic cell proliferation and invasion, highlighting its potential as a therapeutic target.[14,15]

Hormonal Interactions in Endometriosis

Chronic inflammation in endometriosis is closely linked to hormonal influences, particularly estrogen and progesterone. Estrogen plays a key role in promoting the proliferation of endometriotic cells and enhancing their resistance to apoptosis. Elevated estrogen levels increase the production of reactive oxygen species (ROS) and pro-inflammatory cytokines such as interleukins and TNF-α, which exacerbate inflammation and oxidative stress in the ovaries. This inflammatory environment supports the survival and expansion of ectopic endometrial tissue, facilitating disease progression.[16,17] Estrogen also upregulates genes and proteins involved in adhesion, angiogenesis, and invasion of endometriotic lesions, further contributing to their persistence and spread. Additionally, estrogen influences the peritoneal microbiota, which can aggravate local inflammation and create a favorable niche for endometriotic tissue growth. These findings highlight the intricate relationship between hormonal regulation, immune response, and disease progression, underscoring the need for hormone-targeted therapies in endometriosis management.[18]

Under normal physiological conditions, progesterone exerts antiproliferative and anti-inflammatory effects on endometrial tissue. However, in endometriosis, progesterone resistance develops, impairing its ability to counteract estrogenic activity, leading to uncontrolled cellular proliferation and persistent inflammation. This resistance also contributes to tissue remodeling and fibrosis, hallmarks of chronic endometriosis. The underlying causes of progesterone resistance include reduced progesterone receptor expression, post-translational receptor modifications, and disruptions in progesterone signaling pathways, which alter the expression of its target genes. These molecular changes compromise progesterone's regulatory functions, ultimately exacerbating endometriotic lesion growth and inflammatory progression.[19,20]

The imbalance between estrogen and progesterone receptors disrupts the normal regulation of the ovarian cycle, contributing to endometriosis-related infertility. The altered hormonal and inflammatory environment impairs the function of the ovaries and fallopian tubes, reducing the chances of successful fertilization. Additionally, this imbalance affects endometrial receptivity and implantation processes, making it more difficult for an embryo to successfully implant and develop, further complicating fertility outcomes in women with endometriosis.[21–23] Molecular pathways such as WNT/β-catenin and Notch, which are influenced by hormonal imbalances, play a crucial role in the pathogenesis of

endometriosis. The WNT/β-catenin signaling pathway is essential for cell proliferation and differentiation, and its dysregulation has been linked to the abnormal growth of endometrial tissue. Similarly, the Notch pathway, which regulates cell fate determination and tissue homeostasis, is also implicated in the pathological processes of endometriosis, further contributing to disease progression and lesion persistence.[44,45] Activation of the WNT/β-catenin pathway enhances the expression of genes that promote the proliferation and invasion of endometriotic cells, contributing to lesion growth and disease progression. Meanwhile, dysfunction in the Notch pathway disrupts cell differentiation and increases resistance to apoptosis, allowing ectopic endometrial tissue to survive and persist, further exacerbating the pathological features of endometriosis.[18]

Immunological Factors in Endometriosis

Chronic inflammation and hormonal dysregulation in endometriosis lead to significant alterations in the immune system. Macrophage activation within endometriotic tissue triggers the release of cytokines and growth factors, exacerbating inflammation and fibrosis in ovarian tissue. Additionally, an imbalance in regulatory T cells (Tregs) contributes to persistent chronic inflammation, while dysregulated natural killer (NK) cells further aggravate tissue damage and immune dysfunction. These immune cells alter the ovarian microenvironment by producing inflammatory molecules such as prostaglandins and leukotrienes, disrupting normal ovarian function. In particular, prostaglandin E2 (PGE2) enhances aromatase expression, leading to increased local estrogen production, which further worsens disease progression and sustains endometriotic lesion growth.[24] Elevated prostaglandin E2 (PGE2) levels in follicular fluid (FF) of women with endometriosis correlate with increased progesterone production and upregulated expression of steroidogenic acute regulatory protein (StAR). However, this is accompanied by reduced estradiol (E2) synthesis and downregulated CYP19A1 expression in granulosa-lutein cells (GLCs), leading to disrupted follicular steroid hormone balance. This hormonal dysregulation is strongly associated with endometriosis-related infertility, as it affects oocyte maturation, follicular function, and overall reproductive potential.[25]

Activated macrophages in endometriotic tissue play a crucial role in exacerbating chronic inflammation. Their activation triggers the release of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α), which recruit additional immune cells to the affected area, further intensifying ovarian tissue damage.[26,27] IL-6, in particular, promotes the production of reactive oxygen species (ROS) and upregulates pro-apoptotic genes such as Bax and caspase-3, leading to increased granulosa cell apoptosis and worsened ovarian injury, ultimately compromising fertility in women with endometriosis.[28]

Disrupted Angiogenesis in Endometriosis and Its Impact on Ovarian Reserve

Abnormal immune responses and chronic inflammation in endometriosis not only cause direct ovarian tissue damage but also disrupt angiogenesis, primarily through vascular endothelial growth factor (VEGF). VEGF plays a crucial role in endometriosis pathogenesis by promoting angiogenesis, which is essential for the survival and proliferation of ectopic endometrial tissue. Elevated VEGF levels in endometriotic lesions increase vascular permeability, leading to the accumulation of inflammatory fluids and worsening the local inflammatory environment. This excessive angiogenesis not only sustains lesion growth but also contributes to the formation of fibrotic tissue within the ovaries, ultimately reducing ovarian reserve and impairing fertility.[2,6,29]

Disrupted angiogenesis in endometriosis affects ovarian follicles by reducing blood flow, which is crucial for delivering oxygen and nutrients necessary for oocyte maturation. Inadequate blood supply leads to localized hypoxia, negatively impacting follicular development and oocyte quality. This oxygen deprivation can impair granulosa cell function, folliculogenesis, and steroid hormone production, ultimately contributing to diminished ovarian reserve and compromised fertility in women with endometriosis.[1,30] VEGF activates multiple signaling pathways that contribute to the pathophysiology of endometriosis, with the PI3K/AKT and MAPK pathways playing particularly significant roles. These pathways promote the proliferation and survival of endometriotic cells, ensuring the persistence of ectopic lesions. Additionally, they enhance angiogenesis, supporting vascular expansion and lesion growth, while also sustaining the chronic inflammatory state characteristic of endometriosis. The continuous activation of these pathways exacerbates disease progression, further impacting ovarian function and fertility.[8,31]

Endometrioma Formation and Its Impact on Ovarian Reserve

Disrupted angiogenesis and immune dysfunction directly contribute to endometrioma formation, a primary physical manifestation of endometriosis. Endometriomas, or ovarian cysts composed of endometriotic tissue, affect ovarian reserve through multiple mechanisms. Mechanically, endometriomas exert physical pressure on normal ovarian tissue, leading to damage of antral follicles and a reduction in oocyte count. Additionally, the cyst fluid contains high levels of iron and oxidized hemoglobin, which generate reactive oxygen species (ROS). The oxidative stress caused by ROS induces DNA, protein, and lipid damage in ovarian cells, promoting apoptosis and compromising oocyte quality. Furthermore, the cyst fluid is rich in heme, which triggers ROS production through the Fenton reaction, exacerbating oxidative stress and tissue damage. The mechanical compression of healthy ovarian tissue by endometriomas further damages antral follicles, impairing their structure and reducing the number of follicles capable of maturing into viable oocytes, ultimately depleting ovarian reserve and affecting fertility outcomes.[5,32] The fluid within endometriomas contains high levels of iron and oxidized hemoglobin, both of which contribute to reactive oxygen species (ROS) production through the Fenton reaction. In this process, reduced iron (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2) to generate hydroxyl radicals (OH•), which are highly reactive and damaging. The ROS produced in this reaction cause DNA, protein, and lipid damage in ovarian cells, leading to oxidative stress, cellular dysfunction, and apoptosis.[33] This oxidative environment further compromises oocyte quality and accelerates ovarian reserve depletion, contributing to fertility decline in women with endometriosis.[34]

Diagnosis Delay & Surgical Effects on Endometrioma and Ovarian Reserve

Research on endometriosis has garnered significant attention in recent decades. Despite increasing attention, some hurdles persist, including the absence of universal diagnostic criteria and the complexity of establishing a definitive diagnosis due to varied symptomatology and diagnostic obstacles. The diagnostic delay in endometriosis is a recognised issue, with research consistently indicating extended periods of 7 to 10 years between the beginning of symptoms and the definitive diagnosis. Such delays can substantially affect patients, potentially worsening their symptoms, including impacts on ovarian reserve and implications of postponed treatment.[35]

Surgical intervention is often necessary for endometrioma management, but it carries significant risks to ovarian reserve. Procedures such as cystectomy may inadvertently remove healthy ovarian tissue along with the cyst, leading to a reduction in ovarian reserve. Additionally, surgery can disrupt ovarian blood supply, compromising follicular function and overall reproductive potential. More conservative techniques, such as cyst stripping, aim to minimize damage but still contribute to oocyte loss. Meanwhile, cyst ablation using thermal energy may induce coagulative necrosis in surrounding healthy tissue, further worsening ovarian reserve depletion. Moreover, surgical trauma-induced fibrosis can impair normal ovarian function, highlighting the need for carefully tailored surgical approaches to preserve fertility in women with endometriosis.[36] Surgical removal of endometriomas significantly affects ovarian reserve, as reflected in the decline of Anti-Müllerian Hormone (AMH) levels. A notable reduction in AMH is observed both short-term and long-term post-surgery, indicating a lasting negative impact on ovarian function. This effect is more pronounced in bilateral cystectomies compared to unilateral procedures, and in more invasive surgical techniques rather than conservative approaches like ablation, which aim to minimize ovarian tissue damage.[36–38]

Cystectomy causes greater damage to healthy ovarian tissue compared to techniques such as stripping or ablation, leading to a more significant decline in ovarian reserve, as measured by Anti-Müllerian Hormone (AMH) levels. Studies indicate that cystectomy results in a larger reduction in AMH compared to ablative techniques or bipolar energy use. However, thermal ablation methods can still induce coagulative necrosis in surrounding healthy tissue, further exacerbating ovarian reserve depletion and potentially impairing long-term reproductive function.[37,39]

Endometrioma and its surgical treatment have a significant impact on ovarian reserve. The presence of endometrioma can limit the visualization of antral follicles (AFC) on ultrasound, making ovarian reserve assessment more challenging. Studies indicate that women with endometrioma have lower Anti-Müllerian Hormone (AMH) levels compared to those without, reflecting compromised ovarian function. Additionally, ovaries affected by endometrioma produce fewer oocytes during oocyte retrieval for in vitro fertilization (IVF). While endometrioma surgery is performed for therapeutic

Table 2 Quality Assessment of the Most Relevant Studies

Author(s)	Year	Study Type	Sample Size	Outcomes Measured	NOS (Stars)	2.0 (Risk)	ROBINS-I (Risk)	GRADE (Quality)
Hanege et al[40]	2019	Retrospective Cohort	150	AMH, AFC	8	N/A	N/A	N/A
Daniilidis et al[5]	2023	Retrospective Cohort	250	AMH, AFC	7	Low risk	N/A	N/A
Moreno et al[39]	2022	Systematic Review & Meta-analysis	N/A	AMH	N/A	N/A	Moderate	N/A
Younis et al[36]	2022	Systematic Review & Meta-analysis	N/A	AFC, AMH	N/A	N/A	N/A	High

Abbreviation: N/A, Not Applicable.

purposes, it can further reduce ovarian reserve, causing a permanent decline in AMH levels and a decreased oocyte yield. Although some studies suggest a post-surgical reduction in AFC, the evidence remains inconclusive. Overall, both endometriosis itself and surgical intervention contribute to ovarian reserve depletion, with significant implications for fertility and reproductive health. Chronic inflammation, immune dysfunction, and surgical trauma collectively lead to anatomical distortion, further compromising reproductive function.[40]

Study Quality

Four primary references were selected as they are the most relevant to the research topic. These references were analyzed using a reference quality assessment tool, and the results are presented in Table 2.

Four primary references were selected for this study based on their relevance, methodological quality, and significant contribution to understanding the impact of endometriosis on ovarian reserve. The cohort studies by Hanege et al[40] and Daniilidis et al[5] examined the decline in Anti-Müllerian Hormone (AMH) and Antral Follicle Count (AFC) in women with endometriosis. These studies were evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies, receiving scores of 8 and 7, indicating high methodological quality. Meanwhile, the systematic reviews and meta-analyses by Moreno et al[39] and Younis et al[36] provided a comprehensive analysis of the effects of endometrioma surgery on ovarian reserve. These reviews adhered to PRISMA guidelines, ensuring transparency and rigor in reporting findings.

Certain categories in the quality assessment table were marked "N/A" (Not Applicable) due to the study design and the specific assessment tool applied. For example, NOS was only used for observational studies, excluding systematic reviews and meta-analyses. The Cochrane Risk of Bias Tool (RoB 2.0) was applied to assess experimental studies, such as the clinical trial component in Daniilidis et al[5] The ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool was used to evaluate non-randomized intervention studies, including Moreno et al.[39]

The findings from these studies consistently demonstrate a significant decline in ovarian reserve markers (AMH and AFC), reinforcing that both endometriosis and its surgical treatment have profound effects on female fertility. The selection of these studies was based on high methodological quality and relevance, ensuring that the results are reliable, valid, and applicable to clinical practice and future research.

Discussion

Endometriosis is a chronic condition affecting approximately 10% of women of reproductive age. Multiple studies have demonstrated its negative impact on ovarian reserve, as measured by Anti-Müllerian Hormone (AMH) levels and Antral Follicle Count (AFC). The findings consistently show a significant reduction in AMH and AFC in women with endometriosis compared to healthy controls, indicating a decline in ovarian reserve that may affect fertility. One study linked this decline to increased oxidative stress and mitochondrial dysfunction in granulosa cells, specifically due to reduced SIRT1 expression and inhibition of mitochondrial oxidative phosphorylation.[5,29,41]

Endometriosis leads to ovarian reserve depletion through multiple biological mechanisms, primarily involving oxidative stress and inflammation, which induce cellular damage and apoptosis in ovarian granulosa cells. Additionally, *Fusobacterium* infection in endometrial tissue has been identified as a pathogenic factor, facilitating the

transition of endometrial fibroblasts into myofibroblasts, which further contributes to endometriosis progression and ovarian dysfunction.[29,41]

Earlier studies also suggested that surgical management of endometriosis, particularly ovarian cystectomy, may further reduce ovarian reserve, despite its benefits in symptom relief and improved spontaneous conception rates. Ablative techniques have been found to be more protective of ovarian reserve than cystectomy, but no consensus has been reached regarding the optimal surgical approach to preserve long-term ovarian function.[5,41,42]

The studies included in this literature review have several limitations, such as small sample sizes, variability in ovarian reserve assessment methods, and a lack of long-term data. Furthermore, many studies rely on animal models or in vitro experiments, which may not fully reflect clinical conditions in humans, limiting the generalizability of findings.[5,41] This review also has methodological limitations, including potential selection bias in study inclusion and restricted access to complete datasets from certain studies. Additionally, it does not cover all potentially relevant research published before 2015, which may limit the comprehensiveness of the findings. The findings of this study have important clinical implications for the management of endometriosis and fertility preservation. Early intervention and a more individualized management approach may help maintain ovarian reserve and improve fertility outcomes. Non-surgical approaches and pharmacological agents targeting oxidative stress and inflammation could offer potential benefits in preserving ovarian function in women with endometriosis.[29,41]

Further investigation into the molecular pathways linking endometriosis to ovarian reserve decline is essential. Future studies should incorporate longitudinal analyses to track molecular changes over time. Additionally, long-term comparative studies evaluating the impact of different surgical interventions on ovarian reserve and reproductive outcomes are crucial. These studies should include comprehensive risk-benefit assessments for each surgical approach. Exploring genetic and epigenetic variations that influence endometriosis progression and ovarian reserve decline is also critical. Such research could facilitate the development of personalized treatment strategies. Furthermore, long-term clinical trials assessing the safety and efficacy of pharmacological therapies in managing endometriosis while preserving ovarian reserve are needed. These studies should include detailed analyses of long-term side effects and their impact on patients' quality of life. In addition, future research should also examine in greater depth the subtypes of endometriosis and the implications of clinical diagnosis compared with surgical diagnosis. Endometriosis can be classified into three distinct categories based on their physiopathology and localisation: superficial peritoneal endometriosis (SPE), ovarian endometrioma (OMA), and deep infiltrating endometriosis (DIE).[43] These three categories may exert varying effects on ovarian reserve.

Conclusion

Data analysis indicates localized chronic pelvic that inflammation and oxidative stress are key drivers of ovarian reserve decline in endometriosis patients, with cytokine-mediated ovarian dysfunction, immune dysregulation, and hormonal imbalances—such as progesterone resistance—further exacerbating infertility risks. While surgical intervention for endometrioma can be beneficial, it poses a risk of reducing Anti-Müllerian Hormone (AMH) levels and further depleting ovarian reserve. Future research should focus on developing more effective treatment strategies, considering immune and hormonal factors, exploring novel approaches to protect and restore ovarian reserve in affected women, and examine subtypes as well as impact of clinical compared to surgical diagnosis of endometriosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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