Review

The impact of Sjögren's disease on ovarian reserve: a systematic review and meta-analysis

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ABSTRACT

Objective. *Because immune-mediated mechanisms in Sjögren's disease (SjD) may impair ovarian reserve, this study evaluated the association between SjD and ovarian reserve to inform fertility counselling and clinical management.*

Methods. *Following PRISMA 2020 guidelines (PROSPERO: CRD420251182803), we searched five databases (PubMed, Embase, Web of Science, Cochrane Library, and CBM) through December 1, 2025. Eligible observational studies quantitatively compared serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), antral follicle count (AFC), or ovarian volume (OV) between reproductive-age women with SjD and age-matched disease-free controls. Study quality was assessed using the Newcastle-Ottawa Scale and AHRQ tool, and continuous outcomes were synthesised using standardised mean differences (SMDs) with 95% confidence intervals (CIs).*

Results. *Across four observational studies involving 410 participants, women with SjD exhibited significantly lower AMH levels compared with controls (SMD=-0.73, 95% CI -1.09 to -0.37; p<0.0001). Additionally, a trend toward higher FSH levels was observed (SMD=0.35, 95% CI 0.14 to 0.57; p<0.001), although statistical significance remained sensitive to the inclusion of specific studies. Conversely, no significant differences were observed for AFC (SMD=-0.58, 95% CI -1.70 to 0.55; p=0.31) or OV (SMD =-0.18, 95% CI -0.57 to 0.21; p=0.36).*

Conclusion. *Although limited data prevent definitive confirmation of how SjD affects ovarian reserve, this preliminary study strongly underscores the critical need for increased clinical awareness of the condition in reproductive medicine.*

Introduction

Sjögren's disease (SjD) is a chronic systemic autoimmune disorder. Immune cells infiltrate the exocrine glands and cause progressive damage, which leads to classic sicca symptoms (xerostomia and keratoconjunctivitis sicca) (1, 2). Autoimmune epithelitis and abnormal B lymphocyte (B cell) activation drive this disease (3). Furthermore, SjD frequently extends beyond the glands, as up to 50% of patients develop severe symptoms outside the glands (4). SjD was previously called Sjögren's syndrome and was divided into "primary" and "secondary" forms. Because the disease has independent pathogenic mechanisms and a heavy systemic burden, a 2023 international consensus updated this naming system and replaced "secondary" with "associated Sjögren's disease" (5). Prevalence is about 60 cases per 100,000 people. The disease mostly affects women, with a female-to-male ratio ranging from 9:1 to 14:1 (6). Although patients are usually diagnosed between 30 and 60 years of age, SjD can affect individuals at any age (7, 8).

Given that ovarian tissue is highly sensitive to immune changes, systemic autoimmunity in SjD could negatively impact ovarian reserve (9). Infiltrating T cells release proinflammatory cytokines, such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α), which trigger oxidative stress and apoptosis in granulosa cells (10, 11). Consequently, oocytes lose essential nutritional support. Furthermore, abnormal B cell activation drives autoantibody production and immune complex deposition, factors that can disrupt local ovarian blood flow and lead to micro-thrombosis and focal ischaemia (12, 13). Together, these im-

mune mechanisms may accelerate germ cell loss and thereby compromise ovarian reserve. Similarly, other autoimmune diseases, such as systemic lupus erythematosus (SLE), show clear links to reduced ovarian reserve and an increased risk of premature ovarian insufficiency (POI) (14, 15). Because long-term inflammation can damage ovarian tissue, SjD may similarly impair ovarian reserve through immune cell infiltration and antibody-related mechanisms. Worldwide, as women are increasingly delaying childbearing, understanding how SjD affects ovarian reserve and fertility is clinically important.

The number and quality of oocytes determine reproductive potential. Defined as the pool of primordial follicles in the ovarian cortex, ovarian reserve serves as a key measure of fertility and indicates the length of the reproductive lifespan (16, 17). Although ovarian reserve naturally declines with age, several factors may accelerate this process. These include genetics, immune injury, medical treatments like chemotherapy, radiotherapy, or pelvic surgery, as well as environment and lifestyle (18, 19). Characterised by a reduction in oocyte quantity or quality, diminished ovarian reserve (DOR) is a common cause of reduced fertility (20). Consequently, women with DOR have a shorter reproductive window, respond poorly to fertility treatments, and face higher risks of negative pregnancy outcomes, such as miscarriage (21). Given that ovarian reserve strongly affects the ability to conceive and the chance of successful pregnancy, early and accurate assessment is essential to guide clinical care (22).

Clinical evaluations assess ovarian reserve using serum biomarkers and ultrasound imaging, specifically anti-Müllerian hormone (AMH), basal follicle-stimulating hormone (bFSH), antral follicle count (AFC), and ovarian volume (OV) (16, 23). Serum AMH is the most reliable biomarker (24). Produced by granulosa cells in preantral and small antral follicles, AMH levels provide a direct estimate of the remaining primordial follicle pool (25, 26). Whereas bFSH serves as a traditional, indirect marker, elevated levels signal declining ovarian reserve due to the loss of regulatory feedback as follicles deplete (27, 28). Additionally, transvaginal ultrasound allows a direct count of the AFC, while OV acts as an anatomical index of tissue mass and atrophy (29, 30). Together, these four parameters establish a comprehensive framework to assess ovarian reserve and characterise impairment associated with specific diseases.

The effect of autoimmune diseases on ovarian reserve remains debated. Although studies found declining ovarian reserve in SLE and rheumatoid arthritis (RA), findings about multiple sclerosis (MS) remain inconsistent (14, 31, 32). Whereas most research focuses on pregnancy outcomes, including neonatal lupus and congenital heart block linked to anti-SSA/SSB antibodies, the effect of SjD on ovarian reserve has received little attention (33). This limited and inconsistent evidence on whether SjD directly compromises ovarian reserve highlights the need for a meta-analysis. Since no systematic review has quantified the impact of SjD on ovarian reserve, this is the first meta-analysis to synthesise these data. By combining biochemical (AMH, FSH) and imaging (AFC, OV) markers, our goal is to establish an evidence-based framework to guide fertility counseling and reproductive management for women with SjD.

Materials and methods

This systematic review was registered in PROSPERO (CRD420251182803) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (34). The review protocol is available in the PROSPERO registry. No amendments were made to the registered information. The PRISMA 2020 checklist and its extension for abstracts were used to ensure comprehensive reporting (Supplementary Tables S1, S2). This study was a systematic review and meta-analysis based on previously published data. No new studies involving human participants or animals were conducted by the authors. Therefore, ethical approval and informed consent were not required.

Databases and search strategy

Adhering to the Cochrane Handbook for Systematic Reviews of Interventions (35), two investigators (X.Y.K. and Y.J.Q.) independently conducted a comprehensive literature search across five electronic databases: PubMed, Embase, Web of Science, the Cochrane Library, and the Chinese Biomedical Literature Database (CBM). The search encompassed all records from database inception through December 1, 2025. Search algorithms utilised a combination of Medical Subject Headings (MeSH) and free-text keywords related to "ovarian reserve" and "Sjögren's syndrome," connected via Boolean operators. Specific terms included "Sicca Syndrome," "Ovarian Reserve*," "AMH," "anti-Müllerian hormone," "FSH," "Follicle-Stimulating Hormone," "AFC," "Antral Follicle Count," "Ovarian Volume," and "Fertility." The detailed search strategy is provided in Supplementary materials. Furthermore, to ensure comprehensive coverage, the reference lists of relevant reviews and meta-analyses on SjD and ovarian reserve were manually screened to identify additional eligible studies. Grey literature sources and the ClinicalTrials.gov registry were also searched to reduce the risk of publication bias.

Inclusion and exclusion criteria

Study eligibility was determined based on predefined criteria. We included observational studies that enrolled reproductive-aged women diagnosed with SjD according to either the 2002 American-European Consensus Group (AECG) classification criteria (36) or the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (37). Studies were eligible if they provided quantitative comparisons of ovarian reserve markers, specifically serum FSH, AMH, AFC, or OV, between reproductive-age women with SjD and age-matched healthy controls. To ensure specificity, we included only patients with SjD occurring as a standalone condition, excluding those with other concurrent systemic autoimmune diseases. Outcomes had to

be reported as means with standard deviations, medians with interquartile ranges, or confidence intervals (CIs) to allow for data pooling.

We excluded non-original research, including reviews, meta-analyses, editorials, and conference abstracts. Studies were also omitted if they lacked a control group, contained duplicate or overlapping patient cohorts, or presented insufficient data for extraction. No language restrictions were imposed.

Study selection and data extraction

Two investigators (W.J. and H.Y.F.) independently screened studies using EndNote X9 to remove duplicates and assess titles and abstracts against the predefined criteria. Full-text articles were then reviewed to confirm eligibility. Disagreements were resolved through discussion with two additional reviewers (W.W.Z. and W.Z.Q.). Data were extracted using a standardised form covering study characteristics, patient demographics, and clinical outcomes. Specifically, we recorded the author, year of publication, country, study design and period. Extracted clinical variables included diagnostic criteria, sample size, age, body mass index (BMI) and reproductive history. Furthermore, we documented treatment history alongside reported measures of ovarian reserve, utilising means and standard deviations for all subsequent analyses. When outcomes were presented as medians with ranges or interquartile ranges, means and standard deviations were estimated using established methods described by Luo *et al*. (38) and Wan *et al*. (39). In one study (40), numerical values were approximated using WebPlotDigitizer (version 4.7).

Quality assessment

Study quality was independently assessed by two reviewers (W.Z.Q. and W.W.Z.), with disagreements resolved through discussion. In line with recommendations from the Cochrane Collaboration, the Newcastle-Ottawa Scale (NOS) (41) was used to assess the quality of case-control and cohort studies, focusing on participant selection, comparability of study groups and assessment of exposure or outcomes. Studies scoring 5-6 points were considered of moderate quality, while scores of 7-9 indicated high quality. Cross-sectional studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ) (42) assessment tool, which consists of 11 items scored as 1 point for "yes" and 0 points for "no" or "unclear." Based on total scores, study quality was classified as low (0-3), moderate (4-7), or high (8-11).

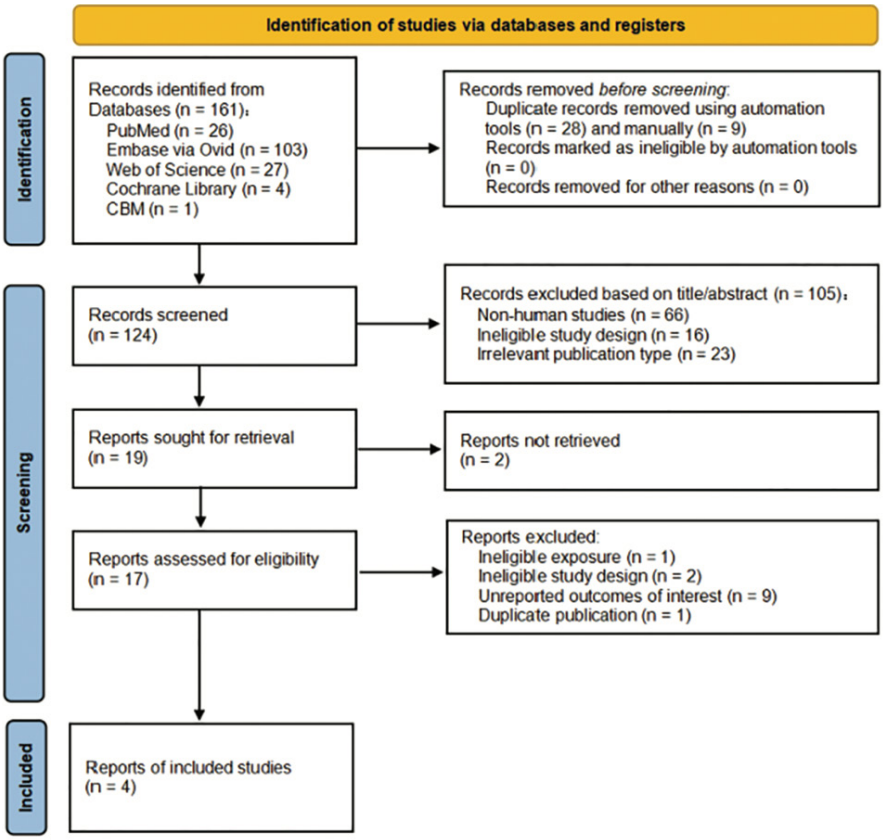

Fig. 1. PRISMA flow diagram of the study selection process.

Statistical analyses

Statistical analyses were performed using Review Manager (version 5.4), with sensitivity analyses conducted in Stata (version 17.0). Continuous outcomes were summarised using standardised mean differences (SMDs) with corresponding 95% CIs. Statistical heterogeneity was assessed using the Higgins I^2 statistic. Given the expected clinical and methodological heterogeneity across studies, random-effects models were applied to pool effect estimates. Sensitivity analyses were conducted using a leave-one-out approach to evaluate the robustness of the pooled results. Owing to the limited number of included studies, publication bias was not assessed. A two-sided p value of less than 0.05 was considered statistically significant.

Results

Study selection and characteristics

The study selection process is outlined in the PRISMA flow diagram (Fig. 1). Database searches identified 161 records. After removing duplicates, 124 records remained for screening, of which 105 were excluded based on titles and abstracts. A total of 19 studies were initially identified for full-text assessment. Two studies were excluded because the full texts were unavailable. Following detailed review of the remaining 17 studies (40, 43-58), a further 13 studies (43-48, 50-52, 54-56, 58) were excluded according to predefined eligibility criteria. Exclusions after full-text review were due to irrelevant outcomes (n=9), duplicate publication (n=1), ineligible study design (n=2), or failure to meet the di-

Table I Characteristics of studies included in the meta-analysis

First author	Year	Country	Study design	Diagnostic criteria	Study period	BMI (kg/m²) (mean ± SD) Case/ Control	Age (years) (mean ± SD) Case/Control	Sample size (n) Case/ Control	Gravidity Case/ Control	Miscarriage Case/ Control	Parity Case/ Control	Ovarian reserve markers	Quality score	Treatment exposure (n) Case
Karakus *et al*.(40)	2017	Turkey	Case-control study	AECG (2002)	NA	25.10±4.90/ 25.9±3.90	34.10±5.10/ 32.80±7.20	24/25	3 (0–4)/ 2 (0–4)	0 (0–5)/ 0 (0–5)	2 (0–8)/ 2 (0–4)	AMH, FSH, AFC, OV	8	NA
Pan *et al*.(49)	2021	China	Case-control study	AECG (2002)	2017–2019	23.12±1.60/ 23.35±1.48	30.59±4.48/ 31.43±4.26	61/60	NA	NA	NA	AMH, FSH	7	Alkylating agents (22)
Mao *et al*.(53)	2024	China	Cohort study	ACR/ EULAR (2016)	2014–2023	20.65±2.83/ 21.21±2.70	33.35±3.82/ 33.35±3.75	47/141	NA	NA	NA	AMH, FSH, AFC	7	HCQ (41), MTX (2)
Mandosi *et al*.(57)	2025	Italy	Cross-sectional study	ACR/ EULAR (2016)	2021–2023	21.40±3.72/ 20.72±2.09	36.84±6.48/ 34.96±5.06	26/26	1.4±1.58/ 0.68±1.07	0.52±0.87/ 0.20±0.50	0.88±0.93/ 0.48±0.71	AMH, FSH, AFC, OV	9	NA

Notes: AECG, the American–European Consensus Group (2002); ACR/EULAR, the American College of Rheumatology/European League Against Rheumatism (2016); BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone; OV, ovarian volume; NA, not available; HCQ, hydroxychloroquine; MTX, methotrexate. Gravidity, miscarriage, and parity were reported in the original studies as mean ± SD or median (range)

Table II Quality assessment NOS scores of included studies (excluding cross-sectional studies)

Study	Year	Selection (0–4)	Comparability (0–2)	Exposure/ Outcome (0–3)	Total score (0–9)	Quality level
Karakus *et al*.(40)	2017	4	2	2	**8**	High
Pan *et al*.(49)	2021	3	2	2	**7**	High
Mao *et al*.(53)	2024	3	2	2	**7**	High

Notes: NOS: Newcastle-Ottawa Scale; 7–9 points: high quality; 4–6 points: moderate quality; 0–3 points: low quality.

agnostic criteria for SjD (n=1). Four studies (40, 49, 53, 57) met the inclusion criteria and were included in the meta-analysis. Key characteristics of the included studies are summarised in Table I. In total, 410 participants were included. Two studies (49, 53) were conducted in China, one (57) in Italy, and one (40) in Turkey. Study designs included one cross-sectional study (57), two case–control studies (40, 49), and one cohort study (53). Diagnostic criteria varied, with two studies (53, 57) using the ACR/EULAR criteria and two (40, 49) using the AECG criteria. The studies were published between 2017 and 2025, and the mean participant age ranged from 30.59 to 34.96 years. All studies (40, 49, 53, 57) reported FSH as a measure of ovarian reserve. One study (53) could not be included in the quantitative analysis because its AFC data were not reported in a usable format. For two studies (40, 57) reporting bilateral ovarian outcomes separately, we averaged the left and right means and standard deviations to derive a single patient-level estimate, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (35).

Quality assessment

Overall quality assessment showed that all four (40, 49, 53, 57) included studies achieved scores of 7 or higher, indicating generally good methodological quality. The quality assessment results are summarised in Table I. Cohort and case-control studies were evaluated using the NOS (Table II). The cohort study by Mao *et al*. (53) scored 7 points and was considered of high quality, although reporting on outcome exclusion at baseline and adequacy of follow-up was limited. The two case-control studies also demonstrated good quality: Karakus *et al*. (40) scored 8 points, with points deducted due to unreported response rates in the case and control groups, while Pan *et al*. (49) scored 7 points, mainly due to limitations in control selection and response rate reporting. The cross-sectional study by Mandosi *et al*. (57) was assessed using the AHRQ tool and scored 9 points, reflecting strong performance in data sources, participant selection, and control of confounding factors; however, assessor blinding and quality control procedures were not clearly described. Overall, the main limitations across studies related to incomplete reporting of methodological details. No major sources of bias were identified that were likely to materially affect the pooled results.

Meta-analysis results

AMH. Three studies (40, 49, 57) examined the association between serum AMH levels in women with SjD and controls (Fig. 2). The pooled analysis showed that women with SjD had significantly lower serum AMH levels than controls (SMD=-0.73, 95% CI -1.09 to -0.37; $p<0.0001$).

FSH. Four studies (40, 49, 53, 57) examined the association between serum FSH levels in women with SjD and controls (Fig. 3a). The pooled analysis showed higher serum FSH levels in women with SjD than in controls (SMD=0.35, 95% CI 0.14 to 0.57; $p=0.001$).

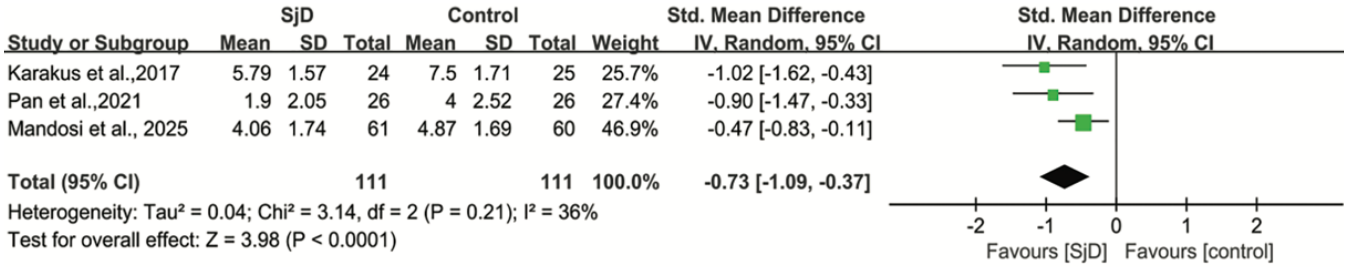

Fig. 2. Forest plot comparing serum AMH levels between women with SjD and control participants.

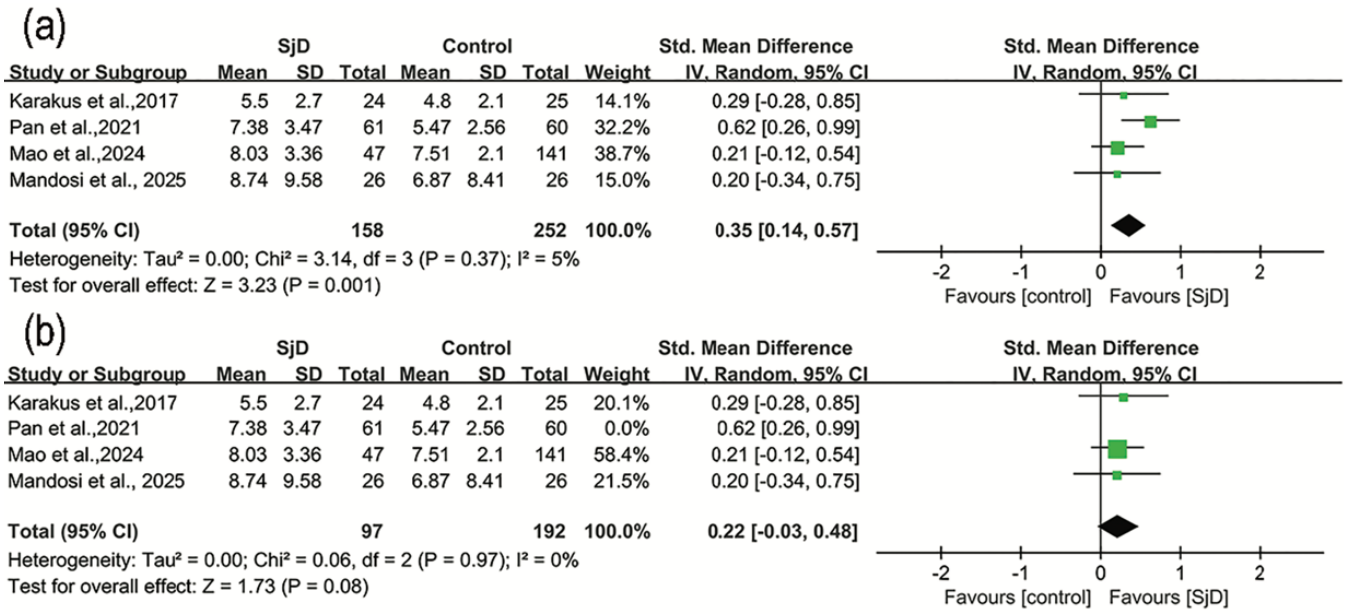

Fig. 3. Forest plots comparing serum FSH levels between women with SjD and control participants. (a) Overall analysis; (b) Sensitivity analysis after exclusion of the study by Pan *et al*.

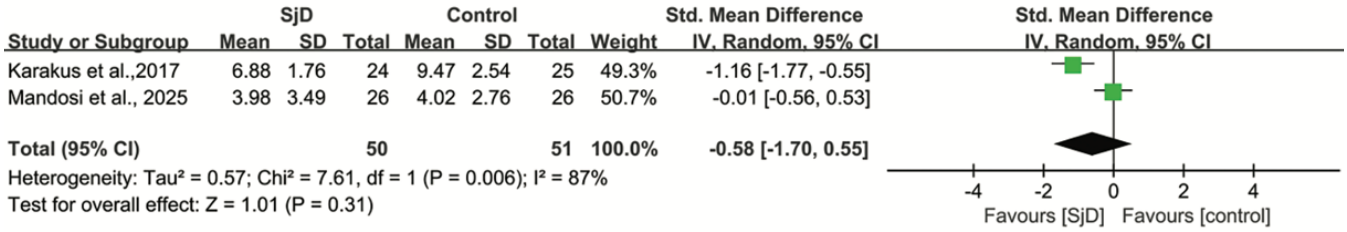

Fig. 4. Forest plot comparing AFC between women with SjD and control participants.

AFC. Two studies (40, 57) examined the association between AFC in women with SjD and controls (Fig. 4). The pooled analysis showed no statistically significant difference in AFC between women with SjD and control participants (SMD=-0.58, 95% CI -1.70 to 0.55; p=0.31).

OV. Two studies (40, 57) examined the association between OV in women with SjD and controls (Fig. 5). The pooled analysis showed no statistically significant difference in OV between women with SjD and control participants (SMD =-0.18, 95% CI -0.57 to 0.21; p=0.36).

Heterogeneity and sensitivity analyses

Sensitivity analyses showed differences in the stability of results across outcomes. Findings for AMH were consistent, with effect size and direction remaining unchanged after removing individual studies. This consistency supports the reliability of the pooled results for these measures (Supplementary Fig. S1).

Sensitivity analysis for FSH indicated that the findings were generally stable. When the study by Pan *et al*. (49) was excluded, the result approached but did not reach statistical significance (p=0.08); however, the direction of the effect remained unchanged (Fig. 3b). Statistical significance was preserved in all other exclusion scenarios (Supplementary Fig. S2). Overall, these results suggest a consistent trend toward elevated FSH levels in women with SjD, which is unlikely to be driven by a

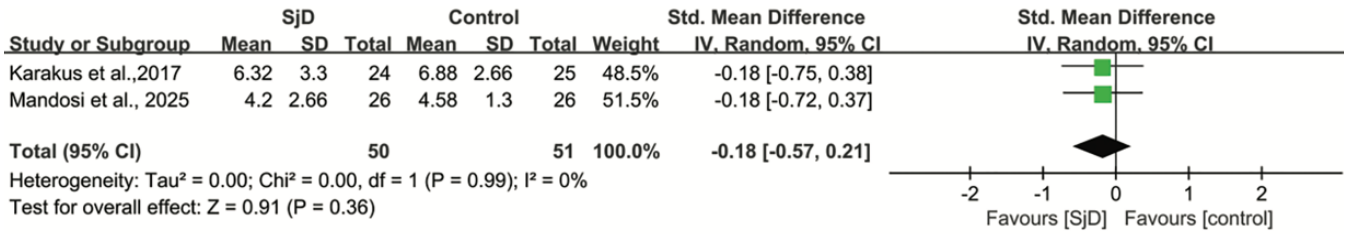

Fig. 5. Forest plot comparing OV between women with SjD and control participants.

single study. Larger studies are needed to confirm this association.

Sensitivity analysis was not performed for the pooled analysis of AFC and OV because of the limited number of included studies (n=2). Furthermore, high heterogeneity was observed in the analysis of AFC (I^2=87%).

Discussion

Summary of main findings

This meta-analysis synthesised observational evidence focused on ovarian reserve in women with SjD. Specifically, lower AMH levels suggest that women with SjD may have lower ovarian reserve compared to controls. Although a trend toward elevated FSH levels was also observed, statistical significance depended on specific studies. In contrast, structural measures like AFC and OV showed no consistent differences between groups. The high heterogeneity observed in AFC results is likely due to differences in imaging methods, interpretation, and disease stage (59). Overall, our meta-analysis suggests that SjD may affect ovarian reserve. However, given our limited statistical power, these findings remain preliminary and hypothetical.

Agreement and disagreement with previous findings

In 2023, the International Rome Consensus introduced the term "Sjögren's disease," defining the condition as a systemic autoimmune disorder with defined pathogenic mechanisms (5). Consequently, immune effects on the ovaries are biologically plausible. Aligning with current knowledge of SjD, our findings suggest that the disease may affect ovarian reserve. Although we observed lower AMH levels and a tendency toward higher FSH levels, structural markers like AFC and OV showed no clear change. This difference between hormone measures and ovarian structure may reflect key features of SjD, such as widespread immune activation and slow disease progression (1, 2). However, our sample size was small, and we lacked long-term follow-up data. Therefore, larger studies with long-term follow-up are needed.

Our findings are similar to those of Karakus *et al*. (40). Specifically, the lower ovarian reserve observed in SjD may reflect an early stage of premature ovarian insufficiency (POI). By combining data from numerous observational studies, this meta-analysis reduces the random errors typically seen in small, single-centre investigations. Furthermore, our careful interpretation of the summarised results strengthens our overall conclusions.

Other systemic autoimmune diseases provide critical context for our findings. For instance, women with SLE may exhibit lower AMH and AFC levels even without cyclophosphamide (CTX) treatment, suggesting a direct effect on ovarian reserve (60). Given that many autoimmune diseases show links to lower AMH levels, reduced ovarian reserve may represent a common feature of widespread immune problems (31, 61, 62). However, this link is not observed in all inflammatory conditions, as studies on Crohn's disease (CD) demonstrate no major changes in AMH levels (63). Therefore, ovarian involvement likely depends on specific immune mechanisms, inflammatory burden, and past treatments.

Potential mechanisms underlying the association

Although our study did not explore underlying mechanisms, past studies suggest reasons for the possible decline in ovarian reserve in SjD. Specifically, this decline may involve a mix of factors, including chronic inflammation, immune injury to the ovaries, and altered endocrine stress responses.

Driven by T helper 1 (Th1) and T helper 17 (Th17) immune responses, SjD involves long-term, body-wide inflammation. These responses keep pro-inflammatory cytokines at high levels, including TNF-α, interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (64-66). Because TNF-α can harm the growth of granulosa cells by reducing FSH receptors and aromatase, these cells become less responsive to gonadotropins. Furthermore, pro-inflammatory cytokines may cause granulosa cell apoptosis through oxidative stress and mitochondrial damage (67). Given that the number and function of granulosa cells control AMH levels in the blood, this damage may explain the lower AMH levels observed in our meta-analysis (68). Additionally, IL-6 and IL-1β fibrotic signalling may initiate early stromal remodelling in the ovary, which could disrupt normal follicle development before overt structural damage appears (69, 70).

Abnormal B cell activation and autoantibody-mediated immune injury may contribute to ovarian impairment. Specifically, a study finding indicates that approximately one in four women with SjD have anti-ovarian antibodies (AOA), which attack granulosa cells, theca cells, and luteal structures (71, 72). Consequently, this immune attack may lead to hidden autoimmune oophoritis, where immune cells enter the tissue and slowly destroy follicles (73).

Clinical implications and future directions

Although current data cannot confirm a clear causal link, this meta-analysis

adds evidence regarding the reproductive risks of SjD. Consequently, in women of reproductive age, evaluation should extend beyond glandular and joint symptoms to include potential risks to reproductive health. Ideally, this assessment should begin from the early stages of the disease.

Given our finding of reduced AMH levels, adding this sensitive and stable marker to routine care may detect declining ovarian reserve earlier (16). Because ovarian involvement in SjD may progress over time, repeated checks of ovarian reserve could help with reproductive planning and guide decisions about fertility preservation.

As stressed by EULAR guidelines, treatments should control the disease while minimising risks to reproductive health. To allow for a personalised long-term approach, we must consider how therapies affect ovarian reserve and future pregnancies (4, 74).

When women with SjD develop infertility and require assisted reproductive technology, disease-related factors may affect ovarian response and pregnancy outcomes (53). This highlights the importance of controlling the disease before fertility treatments and shows the need for coordinated care across medical fields. Additionally, common symptoms such as vaginal dryness and pain during intercourse may interfere with natural conception and quality of life (75). Therefore, treating these symptoms alongside systemic therapy may improve reproductive outcomes.

Because SjD mostly affects women and happens more often around the perimenopausal period, sex hormones likely play a role in disease development (76,77). Clinically, more lifetime oestrogen exposure is linked to a lower risk of SjD, suggesting that oestrogen may have a protective effect (78). Providing support for this link, Mendelian randomisation studies show a causal relationship between higher disease risk and lower blood oestradiol levels, indicating that immune disturbances may disrupt hormonal balance through feedback mechanisms (79). In this context, the changes in ovarian reserve markers found in our analysis may indicate disrupted bidirectional regulation between oestrogen signalling and immune function. Consequently, future studies should examine how the reproductive axis affects SjD and explore whether this axis can be a therapeutic target.

Strengths and limitations

Synthesising observational evidence to assess the impact of SjD on ovarian reserve, this study followed the PRISMA 2020 guidelines and prospectively registered the protocol. By pooling data, we reduced the statistical limits of small sample sizes and obtained a clearer picture of the mixed results from individual studies. Furthermore, the high methodological quality of the included studies strengthens confidence in our findings. Although this analysis offers initial evidence for this risk, it does not provide definitive conclusions. Ultimately, these findings build a foundation for future large-scale prospective studies and guide mechanistic research.

However, our findings have several notable limitations. First, most studies did not report cumulative damage or standard disease activity scores, such as the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (80). Consequently, we cannot determine whether active inflammation or long-term immune damage directly lowers ovarian reserve. Because disease activity varies between patients, with some experiencing only glandular symptoms and others having systemic disease, these distinct forms may affect ovarian reserve differently (81). Although we collected basic demographic data like age, body mass index (BMI), and reproductive history, the pooled data did not allow for subgroup analysis. Specifically, most original studies missed key details, such as SjD duration, severity, or autoantibody levels. This missing data, combined with the small number of studies, prevented us from conducting meta-regression. Therefore, we could neither explore differences between studies nor assess how these clinical factors impact ovarian reserve.

Furthermore, reproductive history is poorly controlled in this analysis. Because SjD patients often experience adverse pregnancy outcomes, treatments like curettage can cause physical trauma (82, 83). Alongside immune system changes during and after pregnancy, these factors can significantly disrupt ovarian function (84). Given that the included studies lacked detailed reproductive data, we could not separate the effects of pregnancy trauma from the direct impact of SjD. Without adjusting for these factors, our meta-analysis results might exaggerate the harm caused by the disease. Future studies must record complete reproductive histories, including miscarriage and curettage records as key variables.

Additionally, we must consider the toxic effects of medications, which we could not separate from direct SjD injury. Medical treatments influence ovarian reserve in distinct ways. For instance, glucocorticoids suppress the hypothalamic-pituitary-adrenal (HPA) axis, potentially causing a lack of androgens (85). While traditional immunosuppressants are toxic to the ovaries, alkylating agents are especially harmful because they cause permanent follicle loss (86). Conversely, biologics seem safe for reproduction and might even improve AMH levels by lowering systemic inflammation (87). Because our study lacked data on medication doses and treatment lengths, we could not use meta-regression to adjust for these interventions. Consequently, our findings likely reflect the combined damage from the autoimmune disease and its medical treatments. Future long-term studies should use methods like propensity score matching to adjust for medication effects and isolate the true impact of SjD on the ovaries.

Furthermore, outside hormones, especially hormonal contraceptives (HCs), can also confound the results. By suppressing the hypothalamic-pituitary-ovarian (HPO) axis through negative feedback, long-term HC use causes a temporary drop in AMH and AFC levels (88). Because it takes several months for these markers to return to normal, the exclusion rules in most original studies (usually less than 3 months) were likely too short and highly variable (89). Consequently, some patients might still have suppressed hormone levels, making this temporary

drop look like ovarian damage from SjD. To address this, future studies require stricter and longer waiting periods after stopping hormonal therapies.
Including *in vitro* fertilisation (IVF) patients might also introduce selection bias. Because patients seeking fertility treatments have a higher baseline risk of low ovarian reserve compared to average SjD patients, our combined results might overestimate the true impact on reproduction. Moreover, because SjD often develops later in life, the included studies featured very few women of reproductive age. This demographic constraint limited statistical power (especially for age-sensitive markers like AMH), hindered robust subgroup analyses, and increased the risk of publication bias (23).
To handle high methodological heterogeneity, we pooled all outcomes using the SMD. For example, AMH measurement techniques varied significantly, ranging from traditional enzyme-linked immunosorbent assays (ELISA) to automated chemiluminescence enzyme immunoassay (CLEIA) platforms (*e.g.*, Fujirebio, YHLO). Because different assay principles, antibodies, and calibration standards create systematic biases, direct comparisons of absolute values become unreliable. Although the SMD controls for these differences and provides reliable estimates, our small sample of studies prevented further subgroup analyses. Therefore, we could not precisely measure the confounding effects of specific assay methods.
The pooled analysis of AFC showed high heterogeneity, driven by several methodological factors. Because AFC measurement lacks standard protocols and is highly operator-dependent, it remains prone to variation between observers (59, 90, 91). Furthermore, differences in ultrasound equipment and examiner experience reduce comparability across centres. Crucially, we excluded some studies due to incompatible reporting formats, an exclusion that may have hidden true clinical associations. For instance, Mao et al. (53) reported a significant reduction in AFC in a large cohort; however, their data showed skewed distributions unsuitable for transformation using the methods of Luo *et al*. (38) and Wan *et al*. (39). Additionally, some studies reported AFC and OV at the level of individual ovaries rather than per patient (40, 57). Although we pooled the bilateral ovarian data, the primary studies did not report information on paired variances, a gap that may introduce further statistical bias. Ultimately, the limited number of eligible studies may have constrained overall statistical power, highlighting the urgent need for validation in larger, high-quality prospective studies.
Because current data do not provide a clear understanding of how SjD affects ovarian reserve, this evidence gap presents an opportunity for rigorous future research to enhance our clinical knowledge.

Conclusion

Overall, this analysis suggests a link between SjD and lower ovarian reserve. Specifically, this association is evidenced by lower AMH levels and a trend toward higher FSH levels, although statistical significance remained sensitive to the inclusion of specific studies. Given our data limitations and limited statistical power, these findings should be considered a preliminary assessment. Nevertheless, we aim to increase clinical awareness and assist with reproductive counselling. Ultimately, future large-scale prospective studies are necessary to draw definitive conclusions regarding how SjD affects ovarian reserve.

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