SYSTEMATIC REVIEW

Evaluation of anti-Mullerian hormone as parameter of ovarian function in patients with systemic lupus erythematosus: A systematic review and meta-analysis

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ABSTRACT

Objective: The assessment of ovarian function in patients with systemic lupus erythematosus (SLE) holds paramount importance for both clinicians and patients. This systematic review and meta-analysis delves into the role of anti-Mullerian hormone (AMH) as a key marker in evaluating ovarian function among SLE patients. Our study aimed to provide valuable insights for clinicians managing ovarian function assessments and to offer practical recommendations for differences in therapy for patient care.

Materials and Methods: Studies comparing serum AMH levels between patients with systemic lupus erythematosus and healthy controls, as well as serum AMH levels between SLE patients, are necessary. PRISMA guidelines were used for this systematic review. Databases like PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central were searched using specific terms ("Anti-Mullerian Hormone" or "Ovarian Function" and "Systemic Lupus Erythematosus") for publications between 2000 and 2023. After removing duplicates, authors screened remaining articles based on abstracts, then reviewed selected abstracts in full-text. Studies meeting criteria were included based on unanimous agreement among investigators, with any disagreements resolved through author consensus.

Results: There were 12 eligible studies. In this research, we identified a link between SLE and diminished levels of AMH. Furthermore, it was observed that SLE patients undergoing cyclophosphamide (CYC) treatment also exhibited lowered AMH levels

Conclusion: The systematic review underscores the heightened risk of reduced ovarian reserve in SLE patients. Importantly, CYC treatment emerged as a factor contributing to compromised ovarian reserve. For individuals with systemic lupus erythematosus, particularly women in their reproductive years, assessing serum AMH levels can serve as a pivotal tool to inform therapeutic decisions and preserve ovarian health. Our study contributes to enhanced clinical understanding and patient care within the realm of SLE and reproductive health.

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Highlights:

1. Systemic lupus erythematosus (SLE) patients show a strong correlation between Anti-Mullerian Hormone (AMH) levels and ovarian function. Lower AMH levels indicate higher risk of impaired ovarian function and diminished reserve, as revealed by this meta-analysis.
2. The comprehensive synthesis of available data in this study has important clinical implications for the management and counseling of systemic lupus erythematosus (SLE) patients.

INTRODUCTION

The chronic autoimmune disorder called systemic lupus erythematosus (SLE) endures over time. Its future outlook and progression are uncertain, and its manifestations can range from mild to severe. SLE predominantly impacts women of reproductive age, with a much higher occurrence in females compared to males (9:1 ratio). The ability to conceive is unaffected. Nevertheless, the natural decline in fertility occurs as women age. Specifically, the ovarian reserve (OR), which refers to the number and quality of viable eggs in the ovaries, diminishes as women get older.[1–3]

Disease activity and medications used in treatment can lead to alterations in ovarian function for individuals with SLE. The use of drugs like cyclophosphamide (CYC), which have cytotoxic properties, can impact ovarian function in these patients, resulting in disruptions in menstrual cycles, inability to conceive, and primary ovarian insufficiency. The dosage of CYC and the patient's age are factors that contribute to the menstrual problems caused by CYC treatment. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) and high-dose corticosteroids might also contribute to the irregular menstrual cycles and infertility observed in individuals with SLE. Generally, those undergoing immunosuppressive therapy due to medication are potentially at a significant risk of infections.[4,5]

The identification of anti-ovarian antibodies has revealed a link to the early decline of ovarian function, leading to premature ovarian failure (POF) as indicated by findings. Nonetheless, the primary factor contributing to infertility in individuals with SLE has been the use of CYC therapy. For instance, in a study conducted in Thailand, 11 out of the total of 91 SLE patients (12%) were diagnosed with early ovarian failure. A retrospective study in Lucknow, India, showed that 17% (n=6) of SLE patients experienced early menopause.[6]

In a study, 15% (n=11) of 71 SLE patients experienced ovarian failure, while 11% (n=9) encountered premature menopause. From Helsinki, Finland, a group of SLE patients reported infertility in 16% (n=33) of cases. Among patients with amenorrhea triggered by CYC, 80% exhibited sustained amenorrhea. Appenzeller et al. also documented persistent amenorrhea in individuals with SLE. Additionally, a prospective study involving 110 SLE patients from Kolkata, India, revealed that 33% (n=22) experienced gonadal insufficiency and 2.7% (n=2) encountered early ovarian failure.[7] This study aimed to provide a systematic review of anti-Mullerian hormone's role in assessing ovarian function in SLE patients, providing valuable insights to clinicians managing ovarian function evaluation and offering practical therapy recommendations.

MATERIALS AND METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Figure 1). A comprehensive search was carried out across PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases, focusing on articles related to "Anti-Mullerian Hormone" or "Ovarian Function" and "Systemic Lupus Erythematosus" published between 2000 and 2023. Redundant findings were eliminated, and the remaining articles were assessed based on their abstracts by all authors independently to determine relevance. Following this, the complete content of the selected abstracts was meticulously reviewed, and those meeting the established criteria were included in the study. The definitive inclusion of studies was determined through consensus among all investigators, with any disparities resolved through mutual agreement among the authors.

RESULTS AND DISCUSSION

The titles and abstracts of retrieved articles were carefully reviewed to determine their potential relevance and suitability for inclusion in the review. Strict criteria, outlined in Table 1, were applied to select articles for inclusion. The search and inclusion criteria primarily aimed at identifying published studies that presented clinical findings or evaluated the use of anti-Mullerian hormone to monitor ovarian function in SLE patients. Pre-printed and grey literature journals were excluded from the search up to April 1, 2023.

The outcomes of the two independent searches were cross-referenced to identify common results. Any unmatched findings were re-evaluated by the physicians to ensure they met the inclusion criteria. There were no instances of further disagreement between the physicians. If disagreements had arisen, the relevant articles would have been excluded from the analysis. Among the articles meeting the selection criteria, full versions or pre-proofed journals were used for data analysis. Additionally, a secondary search of the listed citations was conducted to confirm the inclusion of all pertinent publications. Only articles written or translated into English were considered for this systematic review. The search period spanned from January 2013 to April 2023.

Table 1. The inclusion and exclusion criteria of article

	Inclusion criteria	Exclusion criteria
Types of studies	Randomized controlled trials that evaluated the sensitivity or specificity of AMH in SLE patients, regardless of their clinical condition, were included. Non-randomized controlled trials reporting effectiveness were considered eligible as long as the focus of the study matched the research scope. All levels of evidence, encompassing safety data, met the criteria for inclusion in the safety analysis.	The research conducted in the study did not make any reference to AMH. The analysis of efficacy excluded materials such as reviews, editorials, opinions, case reports, case series, comments, and letters that lacked primary data. Non-clinical investigations, including experimental, animal, or in vitro studies, were not encompassed. Clinical trials exhibiting substantial concerns regarding quality and a significant risk of bias were not included in the assessment of efficacy. Nevertheless, these trials may be taken into consideration for safety analyses.
Types of participants	Patients diagnosed with SLE, regardless of their age or racial background, who had undergone ovarian function assessments following the use of any medication.	Patients who have not received a confirmed diagnosis of SLE or whose diagnosis relies solely on a presumptive basis.
Types of intervention	Heparin with a low molecular weight or a systemic anticoagulant.	Documentation of the administration of antiplatelet agents. Reports instances of irregular usage of low molecular weight heparin or anticoagulants.
Types of comparators	Healthy individuals as controls or no comparison group.	

Data appraisal and extraction

Information obtained from the located publication comprised: details about study design and results, patient count, intervention duration, intervention specifics, and procedure sensitivity or specificity. This information was organized in a descriptive manner using a dedicated table (Table 2).

Quality assessment

Two authors independently assessed the quality of the studies using the modified Newcastle-Ottawa Scale (NOS). Each study was assigned a score ranging from 0 to 9, where studies achieving a total score above 7 were categorized as high-quality. Any disparities in the quality assessment were addressed through deliberation with a third author.

The analysis encompassed a total of 12 published works. In these studies, AMH was applied in different assessment methods and for various purposes, all of which were linked to aspects of ovarian function.

In order to examine the influence of AMH serum levels on ovarian function in SLE, a total of 8 studies were incorporated. The data, which encompassed the utilization of anticoagulants with cyclophosphamide in SLE patients, indicated a diminished AMH in this particular group (odds ratio: 0.33 [0.24, 0.46], $p < 0.0001$; I2: 86%, $p < 0.00001$).

To the best of our knowledge, this represents the most recent systematic review and meta-analysis investigating the connection between SLE and ovarian reserve. In this research, we identified a link between SLE and diminished levels of AMH. Furthermore, it was observed that SLE patients undergoing CYC treatment also exhibited lowered AMH levels.

AMH, or anti-Müllerian hormone, has become increasingly popular as a diagnostic marker for ovarian function, especially in the quantitative evaluation of ovarian reserve, which is the central focus of this review.[9,10] AMH is expressed by developing follicles before FSH-dependent selection and is detectable in the bloodstream. Ovarian reserve, defined by the quality and quantity of primordial follicles, naturally declines with age. The number of developing follicles derived from the pool of primordial follicles is directly linked to the total count of primordial follicles. Since there isn't a direct serum marker to directly quantify primordial follicles, using a marker that reflects the count of growing follicles currently serves as the most effective surrogate for assessing the quantitative aspect of ovarian reserve.[11] Both serum AMH levels and the count of growing follicles decrease as a person ages, a trend initially observed nearly two decades ago in early research. Based on these initial studies, serum AMH was promptly proposed as an indirect indicator of ovarian reserve, despite our limited understanding of the factors regulating AMH expression in the ovaries and the lack of standardized AMH assays.[6,16,17]

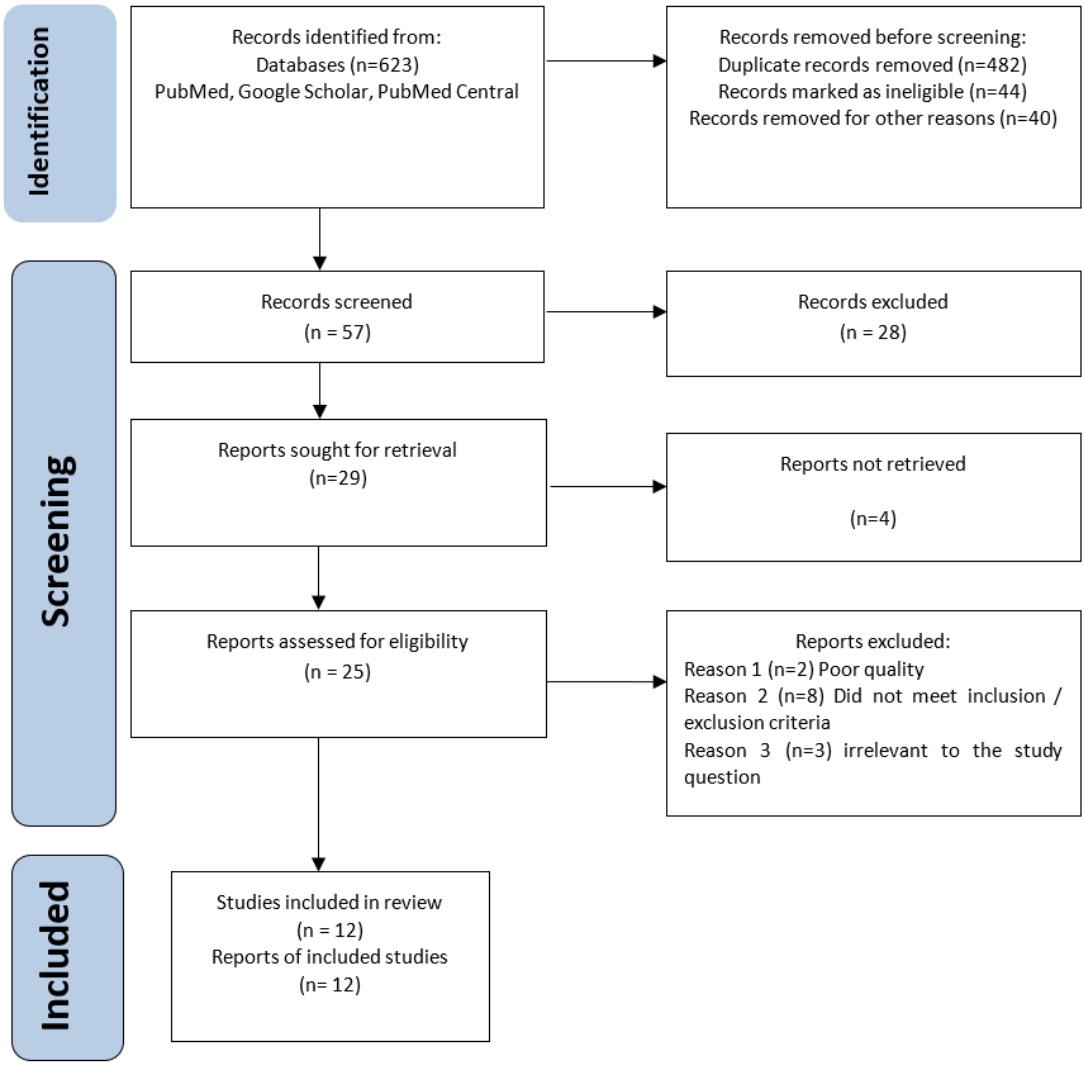

Figure 1. PRISMA flow diagram for the included studies.

Table 2. Characteristics of the included studies

Author and year	Study design	Country	Quality score	Characteristics of participants	Age (mean)	SLE	Control	Comments
Sterba et al, 2016. [8]	Prospective cohort	America	7	Adolescent females aged 14 to 19 years, diagnosed with SLE according to ACR criteria, oligoarticular and polyarticular JIA based on ILAR criteria, and healthy controls with a gynecological age (calculated as chronological age minus age at menarche) of at least 2 years.	N/A	16	26	Ovarian reserve, evaluated through AMH levels, seems to be impacted in a minor fraction of pediatric SLE patients when compared to their healthy counterparts.
Mok et al 2013.[9]	Cross-sectional	China	7	Consecutive female patients aged 18 to 52 years, who had experienced menstruation at least once in the past 12 months and met more than four criteria set by the American College of Rheumatology for the diagnosis of SLE.	N/A	216	None	AMH serves as a responsive indicator of ovarian impairment caused by prior CYC exposure in women diagnosed with SLE.
Morel et al, 2013.[10]	Randomized control trial	America	9	Hospitalized COVID-19 patients	N/A	112	N/A	AMH concentrations are diminished in individuals with SLE, and they notably decline with advancing age and exposure to cyclophosphamide. Nevertheless, the likelihood of experiencing difficulties in achieving conception was minimal and was anticipated based on age and cyclophosphamide exposure, rather than AMH levels.
Ma et al, 2013.[11]	Retrospective	China	7	Assessment of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), AMH, and antral follicle count (AFC) is performed to gauge ovarian reserve in SLE patients with consistent menstrual cycles, regardless of any prior alkylating therapy.	30 ± 4,37	42	21	Significantly increased estradiol (E2) levels (P = 0.023), as well as significantly reduced AMH values (P = 0.000) and antral follicle count (AFC) (P = 0.001), were detected in both the SLE and SLE-CTX groups in comparison to the control group. This outcome suggests that even in SLE patients who were not receiving alkylating therapy, experienced regular menstruation, and had a relatively short duration of illness, their ovarian reserve remained compromised.

Gasparin et al, 2015.[7]	Case-control	USA	7	A group of 80 women who had not reached menopause, with 40 meeting the 1997 American College of Rheumatology (ACR) criteria for SLE, and the other 40 being healthy controls, matched based on their use of oral contraceptives.	32,37 ± 8,44	40	40	Females diagnosed with SLE exhibited comparable AMH levels to those of the healthy controls, indicating the maintenance of ovarian reserve.
Isgro et al, 2013.[12]	Retrospective	America	7	Assessment of AMH levels in postmenarcheal adolescent females with pediatric SLE and a background of prior CYC exposure.	N/A	23	23	The presence of CYC exposure in individuals with pediatric SLE is linked to a notable decline in AMH levels. The median AMH concentration among patients with pediatric SLE who had undergone CYC treatment was lower than that observed in patients without CYC exposure and the control group.
Kandil et al, 2022.[13]	Case control	Egypt	8	Evaluate ovarian reserve through the measurement of AMH levels in premenopausal individuals with SLE, explore various factors influencing it, and assess pregnancy outcomes among SLE patients.	N/A	30	30	There were no distinctions in AMH values between individuals with SLE and those without the condition, and the duration or intensity of the disease did not influence its level. Furthermore, the research indicated that immunosuppressive medications such as cyclophosphamide, azathioprine, and mycophenolate mofetil had no impact on fertility among SLE patients.
De Araujo et al, 2014.[6]	Cross-sectional	Brazil	7	The presence of Anti-CoL antibodies was exclusively identified in c-SLE patients (16% vs. 0%, p = 0.103), and this occurrence was not connected with demographic information, ovarian reserve measurements, disease activity or damage, or treatment. A more detailed examination of c-SLE patients subjected to cyclophosphamide treatment unveiled a higher median level of FSH compared to c-SLE patients who did not receive cyclophosphamide and the control group.	N/A	57	21	For the first time, this study revealed that a substantial cumulative dosage of methotrexate might contribute to subclinical ovarian dysfunction in adult patients with c-SLE.
Di Mario et al, 2019.[14]	Cross-sectional	Italy	7	AMH serum levels were evaluated in a consecutive group of 86 female SLE patients with consistent menstrual cycles, and this was compared with a control group of 44 healthy individuals matched for age.	31,1 ± 4,8	86	44	SLE patients exhibited AMH levels similar to those of controls. However, a decline in ovarian reserve was linked to sequential treatment involving CYC and cDMARDs, as well as the severity of the disease.
Gao et al, 20187.[4]	Case-control	China	7	The study investigates alterations in	29,4 ± 6,28	40	40	Reduced AMH levels and a notable occurrence of

				AMH, lymphocyte subsets, menstruation, and other clinical factors in individuals with SLE.				irregular menstruation revealed that the autoimmune processes associated with SLE can negatively affect the ovarian reserve in female patients. Lymphocyte functioning in individuals with SLE exhibited disarray.
Malheiro et al, 2014.[5]	Case-control	Brazil	7	The objective is to evaluate markers of ovarian reserve in females diagnosed with systemic lupus erythematosus (SLE) who experience regular menstrual cycles, and to investigate the associations between these markers, clinical features, and treatment variables.	31 ± 5	27	27	Despite women with SLE having regular menstrual cycles, there is a possibility that their ovarian reserve might be compromised. Nevertheless, it is only through extended monitoring of these individuals until the onset of ovarian insufficiency and menopause that we can ascertain whether these markers serve as dependable predictors of reproductive difficulties.
Morales-Martinez et al, 2021.[15]	Prospective	Mexico	8	The evaluation of ovarian reserve (OR) was conducted by assessing two markers, namely anti-müllerian hormone (AMH) and antral follicle count (AFC), in a group of 64 SLE patients and comparing them with individuals who have normal health.	N/A	64	70	Patients diagnosed with SLE exhibited changes in ovarian reserve (OR), irrespective of whether menstrual cycle irregularities were present. Both the antral follicle count (AFC) and anti-müllerian hormone (AMH) levels were notably lower in SLE patients, regardless of their menstrual status, when compared to the control group.

A, anticoagulant group; B,control group;COVID-19, coronavirus disease 2019; LMWH,low molecular weight heparin; N/A, not available; UFH, unfractionated heparin.

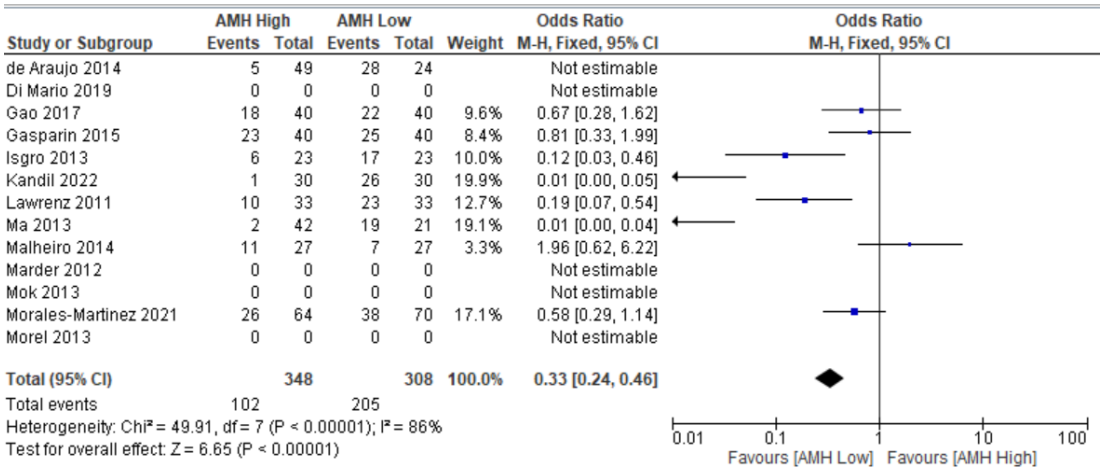

Figure 2. The meta-analysis examines the impact of serum AMH levels by comparing them between SLE patients and control groups.

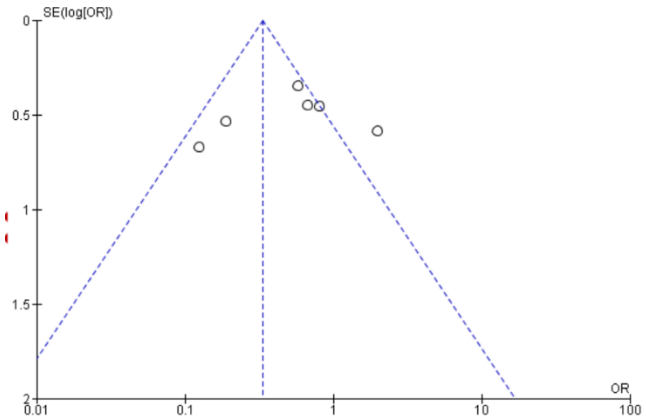

Figure 3. Funnel plot analysis

In adult females, serum AMH levels exhibit an inverse relationship with age. However, research aimed at establishing standard AMH data has also revealed that this correlation depends on the specific age group under investigation.[7,18] AMH levels rise from birth until they stabilize around the age of 25. During this period, which spans up to about 16 years of age, there is a clear positive correlation between AMH levels and age.[19–21] This positive association may be attributed to the increased recruitment rate of primordial follicles observed from birth to roughly 14 years of age. It's only after the age of 25 that a negative correlation between AMH concentrations and age becomes apparent, coinciding with the decline of AMH levels leading to menopause.[21] This pattern appears consistent across various ethnic groups over the years. Nevertheless, research suggests that at any given age, there is significant variability in serum AMH levels. This variability could be influenced by ethnicity, and it should be considered when interpreting AMH values. For instance, while Chinese women exhibit higher peak AMH levels at age 25 compared to European women, their AMH levels decline more significantly with age, resulting in a 28% reduction at age 30 and an 80% reduction at age 45, in contrast to European women.[22,23]

The remaining quantity and quality of eggs in the ovaries, referred to as ovarian reserve, serve as a predictive measure of a woman's fertility potential. To evaluate ovarian reserve, various parameters including

AFC, FSH, and AMH are frequently utilized. AMH stands out for its high sensitivity and specificity in reflecting ovarian response. AMH is produced by granulosa cells within early follicles and is not dependent on gonadotropins. As a result, serum AMH levels remain consistent throughout and between menstrual cycles.[12,24] In a study involving 12 healthy females aged 18 to 24, the highest and lowest recorded serum AMH values were 3.9 ± 1.3 ng/mL and 3.4 ± 1.1 ng/mL, respectively, indicating the stability of serum AMH concentrations throughout the menstrual cycle. Multiple other studies have also confirmed the relative stability of AMH levels throughout the menstrual cycle. Furthermore, the use of contraceptives does not appear to have a discernible impact on serum AMH levels, whether in women with or without polycystic ovary syndrome. Overall, AMH emerges as a dependable and cost-effective marker for assessing ovarian reserve.[26]

One of chronic autoimmune disorder such as SLE, is associated with a range of clinical manifestations. This condition exhibits a distinct predilection for females, and women of childbearing age are disproportionately affected. Among SLE patients, menstrual cycle irregularities have been observed in 54%, and these are linked to the activity of the SLE disease, suggesting that ovarian dysfunction is prevalent in SLE-afflicted women.[9,25] However, our systematic review, which compared serum AMH levels between SLE patients and healthy controls, yielded a pooled SMD of 0.79 (95% CI, 1.41 to 0.18), and as a result, we could not definitively confirm the aforementioned conclusion. SLE has the potential to induce systemic inflammation, potentially implicating the ovaries, as seen in autoimmune oophoritis, which can lead to a decline in ovarian function. Persistent inflammation can also disrupt the hypothalamic-pituitary-ovarian (HPO) axis. Furthermore, SLE may impact the HPO axis, leading to elevated serum prolactin and FSH levels, as well as reduced progesterone and LH levels. This hormonal imbalance may contribute to ovarian dysfunction, resulting in issues like infertility, menstrual irregularities, and ovarian failure.[15] Nevertheless, current research on the relationship between SLE and serum AMH levels presents conflicting findings, potentially due to uneven sample sizes. Our results, derived from the combined analysis of individual studies, are considered more reliable than previous studies.

Immunosuppressive agents are commonly employed in the treatment of moderate and severe lupus nephritis, central nervous system involvement, and various other conditions.[26] Among these medications, CYC is notably associated with the most detrimental impact on ovarian health. Several investigations have highlighted that ovarian failure frequently accompanies CYC therapy, with factors such as cumulative dosage, prolonged treatment duration, and older age at the commencement of treatment influencing its occurrence. Our research consistently revealed that CYC treatment led to a reduction in AMH levels among SLE patients. In the body, CYC yields two active metabolites: phosphoramide mustard and acrolein. Of these, phosphoramide mustard predominantly instigates follicular damage within the ovaries, inducing ovarian dysfunction by instigating apoptosis in oocytes and somatic granulosa cells.[15,26] In a cohort study, it was observed that 17.5% of SLE patients treated with a dose of 0.75 mg/m^2 of CYC experienced sustained amenorrhea, whereas no such amenorrhea was noted among SLE patients administered 0.5 mg/m^2 of CYC. This study underscores the significance of cumulative CYC dosage as a substantial risk factor for ovarian failure. Furthermore, other studies have indicated a correlation between AMH levels and CYC dosage, although conflicting findings exist. Notably, Mok et al. reported no discernible link between CYC dose and AMH levels. Resolving the existing controversy regarding the impact of CYC dosage on ovarian reserve in SLE patients remains an important task for future research.[22] The decrease in AMH levels may not be a direct outcome of the therapy but instead could be attributed to the severity of the SLE condition that necessitates the treatment by autoimmune oophoritis itself. In other words, it is suggesting that the decrease in AMH levels might not be due to the therapy, but rather, the underlying severity of the SLE condition being treated which potentially causing premature ovarian failure (POF).[27]

There are some limitations in writing this systematic review, including the use of a single parameter to approximate ovarian function. Nevertheless, AMH still has an advantage in measuring ovarian reserve and does not require invasive tests like the others, such as FSH, E2, LH, and AFH. Lastly, the studies in the research generally have a small sample sized which leads to conflicting or inconsistent result from each individual study. Furthermore, these small sample sizes make it difficult to draw definitive conclusions from the collective research finding.

CONCLUSION

This comprehensive systematic review indicates that SLE is linked with a raised risk of reduced ovarian function. Moreover, the treatment of CYC can be harmful to ovarian function. Individuals diagnosed with SLE, especially women in their reproductive age should consider having their serum AMH levels assessed to

assist in making treatment decisions and preserving their ovarian health.

DISCLOSURES

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Author contribution

Each author has participated in all stages of this research, encompassing preparation, data collection and analysis, manuscript drafting, and granting approval for its publication.

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