Introduction

Premature ovarian insufficiency (POI), also known as premature ovarian aging (POA), is a clinical entity characterized by reduced ovarian function that causes reproductive failures, infertility, and early onset of menopause in women under 40 years of age [1,2]. The causes of premature ovarian aging are divided into two groups as genetic and non-genetic causes. Genetic causes include chromosomal abnormalities such as X-chromosomal defects, genetic mutations, altered protein functions due to non-coding RNAs, while non-genetic reasons consist of iatrogenic and environmental factors, autoimmune and metabolic diseases, and infections such as mumps leading to oophoritis (Fig. 1) [1,3,4].

Autoimmunity, evidenced by the presence of autoantibodies in patients with POI, appears to play an important role in altering ovarian homeostasis. In addition to ovarian-specific autoantibodies, autoantibodies associated with autoimmune disorders such as Addison’s disease and Hashimoto’s disease may also be seen [1,3,5]. In a data investigating the presence of autoantibodies in 608 normal karyotype POI patients, 16 autoantibodies were found to be positive, including antinuclear antibody, anti-dsDNA antibody, anticentromere antibody, anti-SSA and SSB antibodies, anti-SCL-70 antibody, anti-RNP antibody, anti-Jo-1 antibody. Although autoantibodies were found in 44.9% of the patients, only 15% of patients with positive autoantibodies were diagnosed with an autoimmune disorder [3].

Systemic autoimmune diseases include many diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren’s syndrome. Systemic sclerosis (SSc), one of these autoimmune diseases, is characterized with extensive fibrosis of skin and internal organs [6]. Involvement of the musculoskeletal, pulmonary, cardiovascular, gastrointestinal systems,
and, rarely, lower urinary tract in SSc has been demonstrated in many studies [7,8]. In addition, several studies have shown that SSc can cause sexual impairment by causing musculoskeletal pain, joint contractures, vaginal dryness and stenosis, decreased quality of life and physical function, and deterioration in psychological status such as depression [9-12]. However, research into premature ovarian senescence in these patients is scarce. Given the limited data in the literature, this narrative review aimed to review and summarize the studies on premature ovarian aging and ovarian reserve in patients with autoimmune diseases, especially SSc.

Methods

This narrative review was conducted by searching for peer-reviewed publications published between December 2017 and December 2022 using PubMed/Medline database [13]. Clinical studies (observational and randomized-controlled studies) and systematic reviews on ovarian aging in systemic autoimmune disease and systemic sclerosis published in English language were included. Animal or in vitro studies, review articles, case reports, editorial letters and conference papers were excluded. However, some important review articles presenting unpublished studies or data were included. The following search term was used for Pubmed search: (“systemic sclerosis” [MeSH terms] OR “systemic scleroderma” [MeSH terms] OR “scleroderma” [tiab] OR “autoimmune diseases” [MeSH terms]) AND (“ovarian aging” [tiab] OR “ovarian senescence” [tiab] OR “premature ovarian insufficiency” [tiab] OR “premature ovarian failure” [MeSH terms] OR “ovarian reserve” [MeSH terms]). Titles and abstracts were screened. The selection process of relevant publications is shown in Fig. 2. The author focused on the following key topic: premature ovarian insufficiency/aging/senescence and ovarian reserve in patients with SSc.

Results

Premature ovarian insufficiency in autoimmune diseases

A few studies contributed knowledge on the association between POI and systemic autoimmune diseases [3,14,15]. Autoantibody positivity has been reported in up to 40-50% of POI patients [3,5]. A study conducted by Dawood et al. showed that rheumatoid factor and lupus antibodies were observed in approximately 80% and 9% of POI patients, respectively [16]. However, autoimmune diseases have been diagnosed less than this rate. Almost 20-33% of patients had an autoimmune disease before POI diagnosis [3,5,16].
Grossmann et al. demonstrated that 40.4% of 52 POI patients were diagnosed at least one autoimmune disease such as Hashimoto’s disease (32.7%), systemic lupus erythematosus (3.8%), and rheumatoid arthritis (3.8%) [14]. The data from the St. Marianna University highlighted similar results, with 44.9% of patients having positive autoantibodies and only 15% of them having a specific autoimmune disease. Most patients had hypothyroidism and hyperthyroidism. Only one patient was diagnosed with SSc [3].

There are limited data on the relationship between ovarian aging and SSc. Surprisingly, however, several studies have been published evaluating ovarian reserve/POI in other systemic autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Three systematic reviews and meta-analyses were published this year that focused on the assessment of ovarian reserve in RA and SLE. Luo et al. analyzed nineteen studies involving 1272 SLE patients and 555 healthy controls. Accordingly, they found that ovarian reserve was lower in SLE than in healthy controls and patients treated with cyclophosphamide had lower hormone level. On the other hand, the authors admitted that they could not interpret the results regarding ovarian reserve between cyclophosphamide-treated and untreated patients because of the high heterogeneity [17].

Indeed, cyclophosphamide, which is used as a first-line immunosuppressive medicine in the treatment of life-threatening organ involvement of SLE, SSc and vasculitides, is an alkylating agent that causes gonodotoxicity. Consistent with this general knowledge, recent studies showed an increased risk of ovarian failure in SLE patients treated with cyclophosphamide compared to SLE patients treated with mycophenolate, azathioprine, calcineurin inhibitors, and steroids [18-20]. For RA patients, there are inconsistent studies. A meta-analysis conducted by Zhang et al. showed that RA patients tended to have ovarian failure [21]. Conversely, another study showed no difference in ovarian reserve between RA patients and healthy controls [22].

**Premature ovarian insufficiency in systemic sclerosis**

All above-mentioned articles indicated the relationship between POI and autoimmune diseases, mostly endocrine autoimmune disorders and systemic autoimmune diseases other than SSc. Interestingly, aside from the quite common systemic autoimmune diseases, low ovarian reserve or POI has been less studied and confirmed in patients with SSc.

Jutiviboonsuk et al. investigated the frequency of POI, early menopause, and low ovarian reserve in patients with SSc.
and aimed to find any association between POI and SSc [15]. In this cross-sectional study, the early menopause in SSc was associated with longer disease duration, higher cumulative dose and longer duration of cyclophosphamide used, early onset of using cyclophosphamide and steroids, and higher cumulative dose of steroids. Accordingly, the authors revealed that cyclophosphamide and steroids were the major reasons for low ovarian reserve and early menopause. However, they could not come to a certain conclusion about the effect of SSc disease on the ovaries [15]. A recent study evaluated whether ovarian reserve would change according to different underlying etiologies classified as genetic, iatrogenic, autoimmune and idiopathic. This study provided information that, unlike patients of autoimmune or iatrogenic origin, patients with genetic abnormalities had severely impaired ovaries, which resulted in decreased hormone levels [23].

Conclusion

Decreased ovarian reserve and POI are associated with autoimmune diseases. Endocrine autoimmune diseases are more common than systemic autoimmune diseases in patients with POI. Moreover, low ovarian reserve and POI are seen up to almost 67% of patients with systemic autoimmune diseases, including SLE, RA, and SSc. However, further research is required to elucidate the effect of SSc on ovarian reserve, regardless of the effect of cyclophosphamide used.

REFERENCES


