Menopause and Rheumatic Disease

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KEYWORDS

• Menopause • Systemic lupus erythematosus • Osteoarthritis • Rheumatoid arthritis

KEY POINTS

- Menopause, and its treatment, may affect rheumatic diseases; rheumatic diseases may affect menopause.
- Treatment with cyclophosphamide, especially at an older age, may induce menopause.
- Decreased ovarian reserve is a feature intrinsic to disease notwithstanding treatment.
- Osteoporosis is common in several rheumatic diseases, and menopause increases the risk of osteoporosis as well as fragility fracture.
- The effect of menopause and its treatment is difficult to define in osteoarthritis because of contradictory results.

INTRODUCTION

Menopause is defined as cessation of menses retrospectively for 12 months without a pathophysiologic cause. However, age-related changes in ovarian function begin in the middle of the fourth decade of life with decreased ovarian follicles. Resultant changes in hypothalamic and pituitary hormones to compensate for the falling reserve of ovarian follicles maintain ovulation and fertility, sometimes for decades. The transition to the menopausal state demonstrates highly variable cyclic follicle development and ovulation, along with disrupted menstrual bleeding patterns.[1] The average age at menopause is about 51 years with later age of menopause correlating with longevity.[2–15]

Rheumatic illnesses include diseases with evidence of autoimmunity as well as the common, near ubiquitous, osteoarthritis (OA). These diseases are generally more common among women compared with men. There are extensive data describing

Disclosures: The authors have nothing to disclose.
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Rheum Dis Clin N Am 43 (2017) 287–302
http://dx.doi.org/10.1016/j.rdc.2016.12.011
0889-857X/17/Published by Elsevier Inc.

the relationship of some diseases with the menopausal state, whereas the data are scant for other rheumatic diseases. In this review, the authors consider the impact of menopause on several of these diseases and the reverse, that is, the impact of the diseases on menopause.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is the prototype systemic inflammatory rheumatic disease. There is a wide range of serologic and clinical manifestations attributed to SLE with virtually every patient having a unique disease course. The disease affects women about 10 times more commonly than men with onset typically in the third or fourth decade of life.[16] Despite the usual onset well before the average age of menopause, there is a wealth of data concerning menopause and SLE, with multiple aspects of this relationship to consider. Among these are whether age of onset of menopause is a risk factor for SLE and whether onset of menopause alters the course or severity of the disease or its complications, including accelerated cardiovascular disease. Hormonal therapy for menopause may also interact with the disease. Disease with onset after menopause, although uncommon, may be a distinct entity compared with premenopausal onset. Finally, cytotoxic therapy for SLE may induce an iatrogenic and early menopause. This review considers these aspects of SLE and menopause.

A recent cross-sectional study examined menopause in 961 patients with SLE, of whom 7.9% had natural menopause.[17] Meanwhile, 4.1% had undergone a hysterectomy and 6.3% had menopause after taking cyclophosphamide. Only a small number (0.1%) had menopause associated with end-stage renal disease. The mean age at menopause was 46.4 years and the median age was 50.7 years, both similar to reported values for the general population.[17] An early age at menopause was associated with an earlier age of SLE diagnosis, however.[17] In Lupus in Minorities: Nature versus Nurture (LUMINA) study, a multiethnic SLE cohort from the United States, 37 of 316 women had premature menopause. In a multivariable regression analysis, age at receiving cyclophosphamide, cyclophosphamide induction therapy, higher disease activity, and Texas-Hispanic heritage were associated with a premature gonadal failure.[18] Older studies also show age and cumulative dose of the drug as important predictors of premature menopause.[19] Another study compared prolonged intravenous (IV) cyclophosphamide with 5 to 7 monthly doses followed by mycophenolate mofetil. In the latter group only 1 of 22 women (4%) had sustained amenorrhea, whereas in patients with prolonged cyclophosphamide treatment, 20 of 39 (51%) had sustained amenorrhea. Once again, older age at initiation of treatment was an important risk factor.[20] Neutrophil count suppression by pulse IV cyclophosphamide[21] as well as hypothyroidism[22] may also predict premature ovarian failure. In the last study, 11 of 71 patients with SLE receiving cyclophosphamide developed ovarian failure: all 11 had hypothyroidism as evidenced by an elevated thyroid-stimulating hormone.[22] Thus, treatment with cyclophosphamide can induce premature menopause in women with SLE, especially when treatment begins at an older age (>32 years), whereas hypothyroidism as a risk factor is reported but not confirmed by subsequent studies.

Nonetheless, factors unrelated to cyclophosphamide can affect ovarian reserve in patients with SLE. Using levels of anti-Müllerian hormone (AMH) as a measure of ovarian function in a study of 33 premenopausal women with SLE (without past cyclophosphamide use) and 33 age- and ethnicity-matched healthy controls, Lawrenz and colleagues[23] found lower mean AMH in SLE (2.15 $\pm$ 1.64 vs 3.17 $\pm$ 2.29); however, there was no difference in number of pregnancies or spontaneous abortions between the groups. Another study confirmed this result but found AMH levels did not predict