Autoimmunity Reviews 11 (2012) A430–A436

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Menopause in patients with autoimmune diseases

Lisa R. Sammaritano *

Hospital for Special Surgery, Weill Cornell Medical Center, 535 East 70th Street, New York, NY 10021, United States

ARTICLE INFO

Available online 18 November 2011

Keywords:
Menopause
Systemic lupus erythematosus
Rheumatoid arthritis
Premature ovarian failure
Autoimmunity

ABSTRACT

Menopause represents a time of significant clinical and hormonal change. Given the incompletely understood interrelationship between gonadal hormones and the immune system, it is possible that menopause may affect, or be affected by, the presence of autoimmune disease. Menopause has significant effects on a number of organ systems including the cardiovascular, skeletal, central nervous and genitourinary systems. Premature ovarian failure is related to autoimmune factors in a proportion of cases, but is not generally associated with systemic autoimmune disorders unless secondary to treatment with alkylating agents such as cyclophosphamide. Gonadal hormones have been suggested to relate to both onset and activity in certain autoimmune diseases. For patients with systemic lupus erythematosus, disease activity is lower, and damage accrual higher, in the postmenopausal years, but the mechanisms responsible may relate to age, duration of disease, menopause changes, long-term effects of therapy, or some combination of these factors. Early menopause is a risk factor for rheumatoid arthritis, and post-menopausal status in RA is associated with greater damage and disability. Systemic sclerosis and giant cell arteritis may also be adversely affected by onset of menopause. Importantly, autoimmune disease and menopause may have an additive effect on risk for common comorbidities such as cardiovascular disease and osteoporosis.

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1. Introduction

As the clear endpoint of a woman's reproductive years, menopause represents a significant life event encompassing considerable hormonal and clinical changes. Given the clearly recognized but as

* Tel.: +1 212 606 1978; fax: +1 212 774 2258.
E-mail address: sammaritan@hss.edu.

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doi:10.1016/j.autrev.2011.11.006

yet incompletely understood effects of gonadal hormones on the immune system, menopause may affect, or be affected by, the presence of autoimmune disease activity. Additionally, inevitable menopause-induced organ system changes may contribute significantly to severity of later-life complications of autoimmune disease such as atherosclerosis and osteoporosis. As a result, it is critical for clinicians to have an understanding of the basic physiology of menopause and its potential interaction with autoimmune disease.

2. The menopausal years

Just as with onset of menarche and pregnancy, menopause is a distinct period of significant hormonal and other physiologic change. As life expectancy increases, an increasing proportion of the female population is postmenopausal, and an individual woman can now expect to spend one-third of her life in the postmenopausal state [1]. Menopause is specifically defined by the last menstrual period (documented by absence of menses for 12 months), but symptoms usually occur earlier, during a period termed perimenopause. The menopausal transition is therefore divided into stages: early perimenopause is defined by change in length of the menstrual cycle, late perimenopause occurs after one or more skipped menstrual cycles or greater than 60 days of amenorrhea, and early menopause is the five years after menopause, followed by life-long late menopause (Table 1) [2].

Average age of menopause is 51 years, and genetic factors predominately determine this: a genetic contribution is estimated to be responsible for up to 87% of variance in age at menopause [3]. Factors associated with earlier age of menopause include smoking, nulliparity, low body mass and high fiber diet; higher parity is associated with later age at menopause [4]. Within developed nations, socioeconomic status and ethnicity (African American and Hispanic) may also be associated with earlier age at menopause [1].

2.1. Perimenopause

A marked decrease in reproductive capacity precedes the obvious endocrine and menstrual changes of menopause. Primordial ovarian follicles number 1 million at birth and drop to 25,000 by age 37, followed by a more precipitous drop to about 1000 at the time of menopause. This accelerated follicular atresia is associated with a decrease in inhibin secretion, rising serum follicle stimulating hormone (FSH) levels, and decreased fecundity. The major and abrupt reduction in ovarian estrogen production doesn't occur until about 6 months before menopause; in contrast, there is a slow but steady age-related decline in androgen levels (androstenedione and testosterone) throughout the perimenopausal period. In addition to a decreased ability to conceive, the premenopausal period is characterized by irregular menstrual bleeding and vasomotor symptoms (hot flushes) [4].

2.2. Menopause and late menopause

2.2.1. Hormonal changes

The most significant hormonal change associated with menopause is the marked reduction in levels of estradiol (E2) and estrone (E1). The decrease in E2 levels is more pronounced, since E1 is produced from peripheral aromatization of the more-slowly declining androgens. Associated changes include increased levels of FSH and luteinizing hormone (LH) as a result of decreased E2 and inhibin levels; other pituitary hormones are not affected significantly although prolactin levels may decrease slightly. Both the ovaries and the adrenal glands continue to produce androgens throughout the menopausal and postmenopause periods, although levels decrease slowly with increasing age. The postmenopausal ovaries produce androstenedione and testosterone (but not estradiol), while the adrenal glands produce androstenedione, dehydroandrostenedione (DHEA) and dehydroandrostenedione sulfate (DHEA-S) [1].

2.2.2. Clinical changes

The effect of menopause on various organ systems is primarily a result of the lowered estrogen levels, but symptoms may combine with or exacerbate symptoms of natural aging. Importantly, various organ system changes associated with menopause may contribute to symptoms induced by autoimmune diseases. Menopause leads to significant changes in the cardiovascular system, skeletal system, central nervous system, and genitourinary tracts.

2.2.2.1. Cardiovascular effects. Risk of cardiovascular disease in women rises significantly following menopause, from one-third that of men before menopause until it equals male risk by age 70 [5]. This is due both to effects on the lipid profile (a progressive rise in LDL and total cholesterol levels) as well as more direct vascular effects resulting from loss of estrogen. Estrogen and progesterone both affect the vasculature, and receptors are present in all vascular tissues, including the coronary arteries. Estrogen deprivation results in decreased blood flow in all vascular beds with demonstrated decreased prostacyclin levels, increased endothelin levels, and decreased nitric oxide

Table 1
Clinical and hormonal changes of menopause.

	Reproductive period	Perimenopause: Early	Perimenopause: Late	Menopause	Postmenopause
Hormones:					
Pituitary:					
FSH	10 mIU/ml	Progressive increase	Progressive increase		>80 mIU/ml
LH	10 mIU/ml	Progressive increase	Progressive increase		>65 mIU/ml
Estradiol	>60 pg/m	> 60	Variable		0–15 pg/ml
Testosterone	>200 pg/ml	Slow decrease	Slow decrease		180 pg/ml
DHEA	8 pg/ml	Slow decrease	Slow decrease		3 pg/ml
Clinical:					
Gynecology	Regular cycles Ability to conceive	Variable length cycles Impaired ability to conceive Hot flushes	Skipped cycles, >60 days amenorrhea Very impaired ability to conceive Hot flushes		No cycle No ability to conceive Hot flushes
Cardiovascular					Increased cardiovascular risk
Skeletal			Increasing bone loss		Increasing bone loss Loss

FSH: follicle stimulating hormone
LH: luteinizing hormone
DHEA: dehydroepiandrostendione