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Review

The reproductive endocrinology of the menopausal transition

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ABSTRACT

The menopause transition is a dynamic process that begins with the first appearance of menstrual irregularity and ends with a woman's final menstrual period. As ovarian follicle numbers dwindle, the hypothalamic–pituitary–ovarian axis enters a state of compensated failure. In this state, elevated FSH is capable of maintaining relatively regular folliculogenesis and ovulation, but fertility is reduced. Eventually, this state of compensated failure cannot be sustained, and the ovary becomes unable to produce functioning follicles. Recent multicenter studies from several countries have addressed the pattern of change in hormones and a model form reproductive aging has been developed that helps explain the changes in hormone patterns and fertility that accompany menopause. Perhaps more important, the hormonal changes of the menopausal transition may be predictive of future disease risk. This review will undertake an explanation of the current literature on this topic.

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1. Introduction

The female reproductive axis is unique in that it reaches a senescent state when other organs in the body are generally healthy. The process of oocyte depletion, which begins before birth and ends with menopause, cannot be predicted precisely by chronological age, as its age of onset varies greatly between women. However, a clinical staging system exists, which makes it possible to identify where a woman is in her process of reproductive aging based on her bleeding patterns, which is a better predictor than her age. Staging is useful for several reasons, among them providing a means to attribute women's symptoms during this time to menopausal changes, predicting time to final menstrual period, and identifying health risks. There are now well described symptoms that are linked to specific time points along the menopausal transition, thus validating the concept that menstrual cycle disruption, along with its underlying hormonal changes, are responsible for the common symptoms of the menopausal transition. Moreover, evidence is accruing that at least some menopausal symptoms not previously attributed to estrogen deficiency are successfully treated by exogenous hormones.

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In this review, we will describe the known hormonal changes that occur across the menopausal transition and their association with various symptoms and markers of health in women traversing the menopause. We will base our conclusions on the major findings of large cohort studies ($N > 300$) that have been community or population based. Finally, we will present key clinical scenarios in which short term menopausal hormone therapy is likely to be effective.

2. Staging reproductive aging

2.1. The STRAW system

The first nomenclature for the stages of the menopausal transition was developed at the Stages of Reproductive Aging Workshop (STRAW) in Park City Utah in July 2001. Although the Tanner/Marshall staging system is well established for defining the stages of puberty [1], prior to the STRAW workshop there was no similarly accepted system for defining the stages leading to menopause [2]. Evidence along with expert opinion was used to develop the staging nomenclature [2].

The STRAW stages are shown in Fig. 1. The final menstrual period (FMP), stage 0, anchors the stages, which are numbered from −5 to +2 [2]. The reproductive interval includes stages −5 to −3. In the early reproductive stage, stage −5, menstrual cycles are variable to regular and follicle stimulating hormone (FSH) is well within the normal range. This interval refers to the post-menarcheal period, before menstrual cycles become regular after menarche, which demonstrates considerable inter-individual variation. In the peak reproductive stage, −4, cycles are regular (every 25–35 days; [3]) and FSH remains normal. Again, the duration of this stage is variable [2].

The late reproductive stage, −3, encompasses a period of regular cycling during which time elevated FSH begins to occur, heralding a biochemically, but not otherwise clinically detectable decline in ovarian reserve [2]. Most clinical assays use a 10 mIU/ml FSH level as the cutoff value between normal and diminished ovarian reserve. It is preferable but not always feasible to determine a threshold for the value specific to the laboratory that exceeds two standard deviations of the mean in a young control population at peak reproductive capacity. An elevated estradiol level (>80 pg/ml) in the early follicular phase of the menstrual cycle is of similar significance to an elevated FSH, and can actually suppress FSH, thereby masking the diagnosis of diminished ovarian reserve. An early follicular FSH determination should therefore be interpreted in concert with estradiol. Early follicular phase elevations in FSH are typically intermittent, and therefore difficult to detect with a single sampling. Some women in this late reproductive stage (−3) begin to experience symptoms generally associated with perimenopause, including vasomotor symptoms, breast tenderness, insomnia, migraines, and premenstrual dysphoria [2].

The menopausal transition begins when a woman experiences either: (a) a change in her usual intercycle interval of >7 days or (b) a skipped menstrual period. It is divided into early and late stages, −2 and −1. FSH elevations are greater and more likely to be sustained from cycle to cycle during this time. In the early transition, amenorrhea is intermittent and relatively infrequent. The late transition begins when a woman skips at least two cycles and experiences at least 60 days of amenorrhea.

The postmenopause is divided into two stages in the STRAW nomenclature. It begins with the early stage, +1, defined as the first five years after the final menstrual period. This period of time is further divided into *a* and *b*, with *a* being the first year of amenorrhea and *b* being the next four years [2]. This period is significant for being a time where ovarian hormones undergo further decline, with some intermittent fluctuations. It is known to be a time of accelerated bone loss. Stage +2, the late postmenopausal stage, begins five years after the final menstrual period and continues until demise. FSH remains elevated throughout postmenopause, although over long periods of time FSH eventually declines.

2.2. Other staging systems

The 60-days amenorrhea definition for the late transition differed from the previously accepted 90-days amenorrhea interval used to define entry into the late menopausal transition [4]. In the ReSTAGE study, performed subsequent to STRAW, Harlow et al. compared four definitions of this stage: the 90 and 60-day intervals, a 42-day running range (using the difference in days between the shortest and longest cycles in a defined time period), and the skipped cycle definition [5]. Based on their analysis of prospective menstrual calendar data from the TREMIN Trust, Melbourne Women's Midlife Health Project, Seattle Midlife Women's Health Study, and Study of Women's Health Across the Nation (SWAN), they recommended the use of the 60-day interval [5]. This was because, while the latter three criteria occur in more women than the 90-day criterion and are equally predictive of the FMP, the 60-day interval is the most easy to use in clinical practice [5].

The menopausal transition ends with the FMP (stage 0), which must be determined retrospectively once a woman has reached menopause, defined as amenorrhea for at least 12 months [2]. It is in stages −1 and +1 that women tend to experience the most menopausal symptoms [2].

Gracia et al. compared the STRAW staging definitions with the earlier staging system used by SWAN and their newly developed PENN-5 definition (Table 1). The goal of the study was to determine how well each staging system could be validated by corresponding hormonal changes [6]. They followed 427 women ages 35–47 years at baseline for 5 years, including 2263 total observations [6]. The women all had regular 22–35 day cycles for 3 months prior to enrollment. Each kept a menstrual calendar and had blood sampled for hormone assays between day 1 and 6 of two consecutive menstrual cycles. Hormones of interest included inhibin B, FSH, LH, Estradiol, DHEAS, and testosterone. They found significant differences in mean inhibin B and FSH levels between the premenopausal and early transition stages of each definition as well as in the extra stage added to the PENN-5 system [6]. There were significant differences in LH in the earliest stages of SWAN and STRAW that were not detected in the PENN-5 definition. There were not significant differences in estradiol levels among the premenopausal and early transition stages using any of the staging systems. Similarly, there were no statistically significant differences in testosterone or DHEAS between adjacent stages of any of the systems [6]. Adding an additional stage in the early transition period that correlated with statistically significant changes in inhibin B and FSH levels suggests that ovarian reserve can be observed to decline well before overt cycle abnormalities occur. These subtle changes imply that even a single change in cycle length for women in this age group [35–44] should be taken seriously by the physician and considered a reason for counseling patients about the possibility of an early menopausal transition or a reduction in fertility.

3. Hormonal correlates of stages of reproductive aging

3.1. Melbourne Women's Midlife Health Project

The Melbourne Women's Midlife Health Project (MWMHP) was one of the first major longitudinal studies of the menopausal transition [7]. It began with 2001 women from Melbourne, Australia, aged 45–55 years, who were recruited by random digit telephone dialing [8]. The natural history of the menopausal experience