

## The Menopausal Transition—Endocrinology

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### ABSTRACT

**Introduction.** The Melbourne Women's MidLife Health Project (MWMHP) and related studies have yielded valuable information regarding the endocrine changes of the menopausal transition, which are summarized in this review.

**Aim.** To describe the endocrinology of the menopause transition.

**Main Outcome Measures.** Includes changes in inhibins A and B, follicle stimulating hormone (FSH), and estradiol, cross-sectionally in regularly cycling volunteers, and longitudinally (including testosterone) in women passing through the menopause transition.

**Methods.** Early follicular phase hormone concentrations were measured by well-characterized immunoassays in normal volunteers aged 20–50 years, and in 438 subjects initially recruited between ages 45 and 55 for a longitudinal study of the menopause transition, the MWMHP, in which annual blood samples were obtained. The data summarized here includes the first 6 years of follow-up. These volunteers also recorded menstrual cycle data and responded to detailed annual questionnaires.

**Results.** In regularly cycling female volunteers aged more than 40 years, it was established that inhibin B is a significant determinant of circulating FSH levels. From the MWMHP, the central endocrine event marking the onset of menstrual irregularity was shown to be a fall in follicular phase inhibin B concentrations, with a nonsignificant rise in FSH and no change in estradiol or inhibin A. Cross-sectional analysis of data from women in the early stages of the MWMHP showed a wide variation in circulating FSH levels, irrespective of menopausal status, indicating that single FSH measurements provide little useful information regarding menopausal status. Based on the prospective determination of the date of final menses (FMP), it was shown that estradiol levels begin to fall and FSH levels to rise about 2 years before FMP. At the time of FMP, FSH levels were approximately 50% of those ultimately reached postmenopausally, while estradiol had fallen by approximately 50% from reproductive age levels. Despite a major decline in sexual function, as women transited the menopause, there was no significant decline in circulating testosterone levels, the decline in sexual function being correlated with the decline in estradiol, not testosterone. Analysis of data from related studies showed that endocrinologically normal ovulatory cycles could be observed in women who had already experienced cycle irregularity, even more than 3 months of amenorrhea, and could occur close to or at the time of FMP.

**Conclusions.** An extensive database on the endocrinology of the menopause transition, including both cross-sectional and longitudinal information, has been obtained. **Burger H. The menopausal transition—Endocrinology. J Sex Med 2008;5:2266–2273.**

**Key Words.** Menopause; Endocrinology; Follicle Stimulating Hormone; Estradiol

### Introduction

The menopausal transition was defined by the World Health Organization as that period of time before the final menstrual period (FMP) when variability in the menstrual cycle is usually increased [1]. No associated definition was given of

the meaning of increased variability. A workshop held in 2001, with the aim of developing a staging system for reproductive aging (The Staging of Reproductive Workshop—STRAW) [2], recognized two stages in the transition, with some ambiguity regarding entry into the first. The second stage was defined by the occurrence of two

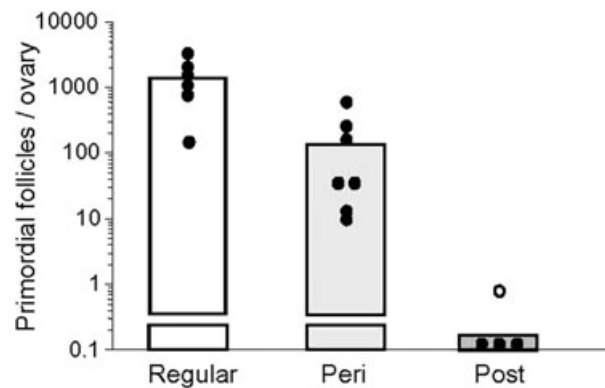
“skipped” cycles and at least one intermenstrual interval of 60 days or more. Harlow et al. [3] have endorsed the STRAW definitions of the criteria for entry into the early transition (a persistent 7-day or more difference in length of consecutive cycles) and the late transition as stated and noted that serum FSH >40 IU/L increased the ability to predict the FMP and could be incorporated into the STRAW system [3]. For the present review, two different criteria for the early transition have been used. In data for the Melbourne Women’s Midlife Health Project (MWMHP), self-report of cycle irregularity after previous regular cycles was taken as the entry point into the early transition [4]. In data from a longitudinal study of the transition [5] (done in collaboration with Swedish colleagues), the first cycle of three or more, in a series of 10 where the length was <23 or >35 days (the normal mid-reproductive cycle length range) was used to date entry into the early transition, based on the work of Taffe and colleagues [6]. For the late transition, the MWMHP used a definition of 3–11 months amenorrhea, while the Swedish study included data for both 60 and 90 days of amenorrhea.

#### Ovarian Follicle Numbers with Age: Role in the Onset of the Transition

The major factor contributing to the onset of the menopausal transition is generally regarded as a decline in the numbers of ovarian follicles to a critically low level. Thus, Richardson et al. [7] counted the number of primordial follicles per ovary in three groups of women >45 years of age, undergoing oophorectomy. Six women had had regular cycles until the time of surgery, seven had developed menstrual cycle irregularity, and four were postmenopausal. The women with regular cycles had an average of approximately 1,000 primordial follicles per ovary, those in the transition approximately 100, but with a wide range from about 10 to about 1,000; while the postmenopausal ovaries were devoid of follicles except for one follicle in one ovary (Figure 1). Thus, it appears from these data that a fall to about 100 primordial follicles per ovary, but with considerable variability, is the major factor leading to the onset of the menopausal transition.

#### Hypothalamo–Pituitary–Ovarian Relationships

The hypothalamo–pituitary–ovarian axis is a classical endocrine closed-loop negative feedback



**Figure 1** Primordial follicle numbers in three groups of women, aged 45–55, undergoing oophorectomy. The first group had been menstruating regularly, the second were cycling irregularly, and the third were post-menopausal. Mean follicle counts in each group differed from those in the other group ( $P < 0.05$ ). Reproduced with permission from Richardson et al. [7].

system. The two gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are secreted from gonadotrophs in the anterior pituitary under the stimulatory control of gonadotropin-releasing hormone from the hypothalamus. The gonadotropins regulate ovarian function, in particular follicular development and follicular hormone secretion. During the follicular phase of the menstrual cycle, the major steroid hormone produced from granulosa cells of antral ovarian follicles is estradiol, while the major peptide hormone secreted by these cells is inhibin B [8]. Both estradiol and inhibin B exert feedback effects on the hypothalamo–pituitary unit with inhibin B acting primarily on the gonadotrophs to restrict the secretion of FSH (Figure 2). The dual steroid–peptide negative feedback system provides an elegant means of differential control of pituitary FSH secretion in particular. As follicle numbers decline and reach a critical level, inhibin B secretion starts to decrease, with a consequent decrease in the negative feedback restraint of pituitary FSH secretion. FSH levels, therefore, start to rise and the increased drive to the follicles is hypothesized to maintain estradiol production. Small antral follicles produce another hormone, anti-Müllerian hormone, also termed Müllerian inhibiting substance, which does not appear to be involved in the closed-loop negative feedback system, but is nevertheless an important marker of ovarian follicle number, and hence, reproductive decline with age [9].

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