Review

The menopause transition: endocrine changes and clinical symptoms

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Abstract

Several biological changes take place during the menopause transition. The number of oocytes declines progressively from before birth but reaches a critically low level by the time of the menopause. The regular pattern of the menstrual cycle becomes disrupted and the frequency of normal ovulatory cycles declines. Rising gonadotrophin levels, particularly of follicle stimulating hormones (FSH), and declining estrogen levels are thought to characterize the menopausal transition. It now appears that declining levels of inhibin may play an important role in maintaining estrogen levels until just before the menopause, while causing increased levels of gonadotrophins. Wide variations in hormonal profiles between and within individuals occur. The clinical responses to this endocrine instability include vasomotor symptoms, psychological symptoms, sexual dysfunction and irregular menstrual bleeding. Estradiol deficiency induces a rapid phase of increased bone turnover in the early postmenopausal period, which can contribute to osteoporosis later in life. Similarly, changes in lipid profiles, particularly high-density lipoprotein (HDL) and triglycerides, can also occur.

Keywords: Follicle stimulating hormone, inhibin, menopause transition, estradiol, oocyte

Introduction

The menopause is considered to be the time when menstrual periods cease. Although menopause occurs at a specific time, the actual changes leading up to it occur over a much longer period. As a woman approaches menopause, several biological changes occur. The number of oocytes declines progressively from before birth but reaches a critically low level by the time of the menopause. The regular pattern of the menstrual cycle becomes disrupted and the frequency of normal ovulatory cycles declines. Rising gonadotrophin levels, particularly of follicle stimulating hormone (FSH), and declining estrogen levels are thought to characterize the menopausal transition. It now appears that declining levels of inhibin may play an important role in maintaining estrogen levels until just before the menopause, while causing increased levels of gonadotrophins. It is apparent, however, that there are wide variations in hormonal profiles between and within individuals.

The time from when symptoms and signs of an approaching menopause begin until 12 months after the final menstrual period is normally referred to as the perimenopause. The menopausal transition is that period from the start of the perimenopause until when menses cease. The median age at onset of the perimenopause is 45.5–47.5 years, and it has an average duration of five years.[1–4]

Perimenopausal women have a higher incidence of clinical symptoms than pre- or postmenopausal women; therefore, it is important to understand the underlying pathological and endocrine changes at this time to assist with diagnosis and treatment.[1]

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Pathophysiology of the menopausal transition

Stock of ovarian oocytes

The ovary contains its greatest number of oocytes at around the fifth month of gestation, at some 7 million. The number is then continuously reduced by atresia. At birth the number is estimated to be about 1–2 million and by menarche it has fallen to 400,000. By menopause there are only a few hundred or thousand oocytes left.[5–7] There appears to be a steady and approximately linear decline of follicle numbers from menarche until around 40 years of age, but thereafter follicle numbers fall rapidly until the time of the menopause. Hormone changes at the time of the menopause reflect the decline in the number of ovarian follicles.

Menstrual cycle length

For about seven years after menarche and eight years before menopause there is greater variability in the intermenstrual cycle length. Between these two phases the variability is much smaller; it is lowest between the

ages of 36 and 40 years, just before the beginning of the perimenopausal period.[8] The median cycle length in the early years following the menarche is 29 days. This drops slowly but steadily with time and by the age of 40 it is 26 days. At the menopausal transition the menstrual cycle length becomes highly variable but with little change in the median cycle length, as long and short cycles both increase in frequency. The most striking feature in perimenopausal women is the unpredictability of cycle length and also of the volume and pattern of flow.

Endocrine changes of menopausal transition

The hormonal features of the menopausal transition have still not been fully elucidated. The information that we have is based on evidence from studies of different designs and interpretation of their results can be difficult because of the variety of definitions used for this phase of reproductive life. Many studies relate observed changes to age rather than the cycle pattern or symptoms. There are now some longitudinal studies with measurements of serum sex steroid, gonadotrophin and inhibin profiles but most observations have been from cross-sectional studies. Traditional concepts about the endocrine changes characterizing the perimenopausal period have included rising gonadotrophin levels and then gradually declining estrogen levels.

Gonadotrophin levels

In women of reproductive age, before a break of regular cyclicity is observed as menopause approaches, the levels of both gonadotrophins – FSH and lutenizing hormone (LH) – have been shown to correlate positively with age, but with a marked difference in pattern.[9] A progressive increase in FSH from 30 years of age has been reported.[10] A similar correlation of FSH but not LH levels was found when ovulatory cycles were examined in women aged 20–50 years.[11] The observed rise in FSH preceded that of LH by almost a decade. It therefore appears that women older than 40 years have FSH levels that are significantly higher than those of younger women, and that this hormonal status can occur in the presence of regular menstrual cycles.[9,11,12] Lee *et al*. investigated 94 regularly cycling women between the ages of 24 and 50 years and showed that FSH levels during the follicular phase and early postovulatory period rose significantly with increasing age, despite the lack of a significant change in LH until close to the age of 50 years.[12] Daily determination of gonadotrophin levels in the blood of women between the ages of 46 and 51 years of age with regular cycles has also revealed an increase in FSH in the presence of normal LH levels throughout the cycle.[13–15]

After a woman enters the menopausal transition, the major endocrine finding is that of significant hormonal variability. Sherman and Korenman showed that postmenopausal levels of FSH could occur in subjects during the menopausal transition and could be associated with or followed by evidence suggestive of normal ovulation and luteal function.[13] Postmenopausal levels of FSH and LH have also been found to be accompanied by hot flushes but followed by spontaneous disappearance of the flushes and gonadotrophin levels returning to those characteristic of normal reproductive function.[16]

The FREEDOM study examined sequential daily urinary concentrations of FSH, LH, estrone 3-glucuronide (E1G), and pregnanediol 3-glucuronide (PdG) from 34 women with perimenopausal menstrual irregularity (total of 289 cycles).[17,18] It showed a subtle monotrophic rise in follicular phase levels of urinary FSH in the early part of the menopause transition (i.e. before loss of menstrual regularity), then progressive increases for later stages of the transition in some but not all cycles. For any given individual, abnormally long cycles with raised follicular FSH were infrequent at first and interspersed with normal ovulatory cycles. Later in the menopause transition, the abnormal cycles predominated but it was still possible to find some cycles with normal architecture. Later still there was a concomitant rise in LH as well as FSH in the follicular phase. Endocrine data from the Melbourne Women's Midlife Health Project showed that FSH levels began to increase from about two years before the last menstrual period, increased most rapidly 10 months before it and had reached a plateau by two years after the menopause.[19]

Endocrine measurements may therefore not be helpful in the assessment of women during the menopausal transition because apparently ovulatory cycles may occur after the observation of FSH levels in the postmenopausal range.

Overall, it has been demonstrated unequivocally that serum levels of FSH rise progressively as a function of increasing age and this starts to occur in regularly cycling women in a manner inverse to the declining numbers of follicles.

Steroid hormone levels

Early endocrine studies of women approaching the menopause suggested that this period was associated with normal urinary estrogen levels despite raised levels of gonadotrophins.[20,21] However, Sherman *et al*. found lower levels of estradiol during the early follicular phase, mid-cycle and the luteal phases in perimenopausal women than in young women.[14] In a study that found that mean FSH levels in a group of normal cycling women between the ages of 45 and 49 years were twice as high of those of a younger group, the estradiol levels were found to be lower in this group only when compared with women between 30 and 39 years of age – not when compared with younger women still, or any other age group.[22] Two other studies have reported normal estradiol levels in women older than 40 compared with younger women.[11,12] The perimenopause has in fact been associated with hyperestrogenism, because overall mean estrogen and conjugate estrogen excretion were found to be greater in perimenopausal women than in younger women, and this could occur as early as 43 years of age.[23] Estrogen levels have also been found to be high in the follicular phase of older women with ovulatory menstrual cycles.[24,25] It has been postulated that the rise in FSH that occurs in the menopausal transition is due to loss of negative feedback as a result of falling ovarian estradiol secretion. However, if the increase in FSH in regularly cycling women is not accompanied by a decline in estradiol then an alternative explanation has to be sought. It has been hypothesized that this is due to falling levels of inhibin.

Progesterone secretion in perimenopausal women with irregular cycles can be normal in short cycles but can also be associated with decreased progesterone secretion in the luteal phase.[14,23] These women can also go through long spells of amenorrhoea in which progesterone secretion

is absent. The frequency of cycles with normal ovulatory progesterone levels decreases markedly as menopause approaches.[26]

Women approaching menopause may experience a mixture of normal, short and long cycles.[17,19,27] Short cycles may exhibit a normal pattern or more commonly are characterized by elevation of FSH, possibly associated with low estradiol levels or even increased estradiol secretion. Long cycles are characterized by abnormal gonadotrophin levels and often low estradiol levels for most of their length. Close to the end of such cycles, a rise in estradiol secretion is usually recorded, which may or may not be followed by indications of luteinization.

Reproductive ageing may be associated with a decrease in androgen secretion. A decline in testosterone concentration with increasing age has been reported in premenopausal women, such that levels in women in their 40s are much lower than those in younger women.[28,29] Moreover, diminished free testosterone and androstenedione levels were found at mid-cycle in older women.[30] No change was found in testosterone, dehydroepiandrosterone (DHEAS) or androstenedione levels during the 18 months after the last menstrual period, although a small decline in testosterone and androstenedione within a six-month period encompassing the last menstrual period has been described.[26,28] A large prospective longitudinal study of androgen changes through the menopause transition has been performed as part of the Melbourne Women's Midlife Health Project.[31] This study failed to show any change in total testosterone in relation to the time of final menstrual period. A fall in sex hormone binding globulin (SHBG) with the associated rise in free androgen index was observed. There was also a fall in DHEAS, which was uninfluenced by the menstrual transition and menopause. It may be, therefore, that the documented difference between testosterone levels in young and older women is associated with ageing rather that the menopause itself. However, the interactions between androgens and estrogen across the menopausal transition and into the postmenopausal period deserve further investigation, if only because of the symptoms that have been reported at this time.

Taken together, these results indicate that a fall in circulating androgens is associated with ageing but may precede menopause. Levels may remain steady during the menopausal transition and then fall again after menopause. The androgen deficiency syndrome has been described and androgens may play a part in feelings of wellbeing and sexual function. The strategy of androgen replacement in older women therefore merits further consideration.[32]

Inhibin

Inhibin is a dimeric glycoprotein consisting of two subunits (alpha and either beta A or beta B) that form dimers called inhibin A and inhibin B. It is well established that the function of the inhibins is to suppress FSH production and secretion. Inhibin, like estradiol, is a granulosa cell product.

Early data describing inhibin physiology were based on a radio-immunoassay widely referred to as the Monash assay. However, this assay cross-reacted with non-biologically active alpha subunit precursors as well as inhibin A and inhibin B. Specific assays are now available for determination of inhibin A and inhibin B levels. In the normal menstrual cycle, both are present in the circulation.[33,34] Inhibin B is elevated in the early follicular phase but then falls throughout the remainder of the follicular phase and is correlated with the fall in FSH levels in the early follicular phase. It is produced by developing antral follicles but little is produced by the dominant follicle and corpus luteum. During the late follicular phase, inhibin B rises again as FSH levels fall and they are inversely correlated, which is evidence for a feedback action of inhibin on FSH secretion.

Serum inhibin A concentrations do not change for most of the follicular phase except for a late preovulatory rise. It then falls briefly before peaking in the luteal phase. Inhibin A is produced by the developing and dominant follicles as well as corpus luteum. Inhibin A positively correlates with serum estradiol levels and is a marker of the dominant follicle.

Inhibin B is produced by the immature follicles and is under FSH stimulation; this has led to the hypothesis that inhibin B measurements during the early follicular phase may be a marker of the hormonally responsive follicle reserve in the ovary.[35,36] This is supported by studies that have shown a positive correlation between inhibin B levels and the number of oocytes retrieved in *in vitro* fertilization cycles.[37]

Ovarian reserve

The basal FSH level strongly influences the success of *in vitro* fertilization.[38] The elevation of FSH levels in the early follicular phase appears to represent a clinical marker of both decreased ovarian reserve and diminished responsiveness of the ovary to attempts to induce ovulation.[39] An age-related reduction in total inhibin but not estradiol during hyperstimulation has been demonstrated and this fall in inhibin appears to be inversely correlated with the rise in FSH.[40,41] Inhibin has also been found to be lower in older as opposed to younger women.[22,40] A falling inhibin level could therefore suggest a decline in ovarian reserve and incipient ovarian failure.[40,41]

Summary of endocrine changes during the menopausal transition

A monotrophic increase in FSH is well established as a marker of ovarian ageing as a result of depletion in follicle numbers. Factors responsible for the increase in FSH without a concomitant increase in LH and while estradiol levels do not change or even increase need to be elucidated. The increase in FSH can be associated with responsive ovarian follicles and although there are fewer granulosa cells in older women they may produce more estradiol. Inhibin has been postulated for some time to be responsible for the monotrophic rise in FSH associated with the menopausal transition and ovarian ageing. Both inhibin A and inhibin B have been found to be reduced in older women,[36] and inhibin B alone has also been reported to be reduced.[40–45]

The inhibins, estradiol and FSH were examined in perimenopausal women in the Melbourne Women's Midlife Project.[46] This study found that the first endocrine event in the early perimenopausal phase of the menopausal transition was a fall in inhibin B, with no change in inhibin A or estradiol. Progression to late perimenopausal status was accompanied by a decrease in inhibin A and estradiol, and a rise in FSH without further change in inhibin B.

Few studies have examined the change in hormones through the menstrual transition. This was, however, investigated further in the Melbourne Women's Midlife Project.[47] Hormone levels were examined in relation to final menstrual period. The study confirmed previous findings: levels of FSH rose progressively at the time when final menses occurred whereas estradiol and inhibin levels fell. There was, however, marked individual variation. This suggests that interpretation of isolated hormonal measurements in women during the menopausal transition cannot be reliably used to define reproductive status.

Hormone changes of the menopausal transition are dynamic. The early perimenopausal phase reflects a state of compensated ovarian failure. The underlying cause of this is loss of ovarian follicles. As a result of a smaller follicular cohort, less inhibin B is produced, which results in an increase in FSH. The raised FSH, however, is able to sustain inhibin A and estradiol until later in the menopausal transition. At this stage both eventually fall and FSH rises further as follicular numbers continue to decline.

Clinical symptoms related to the menopausal transition

The menopausal transition can last for years and is marked by variability and unpredictability of hormone secretion. The clinical responses to this endocrine instability include vasomotor symptoms, psychological symptoms, sexual dysfunction and irregular menstrual bleeding. Women in the perimenopausal years are more likely to seek medical help than are pre- or postmenopausal women.

A large proportion of women complain of hot flushes; these begin well before the last menstrual period and probably reflect fluctuating hormone profiles.[48] Psychological symptoms and a poor sense of well-being also occur during the perimenopausal period.[49] Fluctuating estradiol levels give rise to symptoms of estrogen excess and deficiency, including breast tenderness, menorrhagia, nausea, migraine, variable menstrual cycle length and unpredictable vaginal bleeding.

Estradiol deficiency induces a rapid phase of increased bone turnover in the early postmenopausal period, which can contribute to osteoporosis later on in life. The Melbourne Midlife Project showed significant increased rate of bone loss late but not early in the perimenopausal period, which has also been suggested by other authors.[50–52] It would therefore appear that women who are already at risk of osteoporosis may benefit from intervention in the perimenopausal period. Similarly, changes in lipid profiles, particularly of high-density lipoprotein (HDL) and triglycerides, can also occur during the perimenopause.[53]

Conclusions

Further understanding of the endocrine changes in pituitary and ovarian hormonal patterns at various stages of the menopausal transition is required. However, this time is typified by a decline in oocyte numbers with a consequent decrease in inhibin B, fluctuating estradiol levels and an increasing FSH level. This menopausal transition is associated with significant vasomotor and psychological symptoms, menstrual irregularity and abnormal vaginal bleeding, adverse patterns of bone loss and lipid changes. Improved understanding of the endocrine changes should improve the management of the menopausal transition. Present studies in perimenopausal women have found marked fluctuations in hormone levels, which make these measurements unreliable for the diagnosis of approaching menopause and for predicting the stage of the menopausal transition.

Competing interests: None declared.

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