PERGAMON

Journal of Steroid Biochemistry and Molecular Biology 69 (1999) 31–35

The Journal of Steroid Biochemistry & Molecular Biology

The endocrinology of the menopause☆

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Abstract

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Ovarian primordial follicle numbers decrease with increasing age up to about age 38 following which there is a much steeper decline in the last 12 or so years of reproductive life. At the time of the menopause itself, few follicles remain within the ovary. The recent availability of assays specific for the dimeric inhibins A and B has permitted clarification of the endocrine events leading up to and occurring around the time of final menses. Those women who show clear elevations in serum FSH above age 40, while continuing to cycle regularly have significantly lower inhibin B levels than those whose FSH levels remain in the range seen earlier in reproductive life. Early in the menopause transition, when cycle irregularity is first observed, the initial event is a decline in circulating inhibin B levels in the early follicular phase. In the late perimenopause, levels of estradiol and inhibin A also fall, inhibin B levels remain low and FSH is markedly elevated. The variability of hormone levels in women in their 40s, even in those who are continuing to cycle regularly makes FSH and estradiol unreliable markers of menopausal status. Serum androgen levels appear to fall with age rather than having any clear cut relationship to the menopause transition or menopause. The endocrine changes which occur during the menopausal transition and early postmenopausal period have clinical consequences in terms of symptoms and changes in bone mass.

Keywords: Steroid hormones; Menopause; Inhibitors; FSH

1. Introduction and definitions

The menopause is the permanent cessation of menstruation resulting from the loss of ovarian follicular activity [1]. It is recognised as having occurred after 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. The perimenopause is the period immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause. The menopausal transition is that period of time before the final menstrual period when variability in the menstrual cycle is usually increased [1]. The menopause is of global significance to health authorities as well as being of great significance for the individual woman. It is estimated that in 1990, there were approximately 467 million women in the world aged 50 years and over, a number expected to increase to 1.2 billion by the year 2030 [1]. In 1990, 60% of those women lived in developing countries, but by 2030 76% will be living in developing regions. It is estimated that by then, perhaps 50 million women worldwide will reach the menopause annually. Atherosclerotic cardiovascular disease, osteoporotic fracture and perhaps Alzheimer's dementia are major health problems which have been linked to the occurrence of menopause. For the individual woman decisions must be made at the time she reaches menopause as to whether she should consider long term hormone replacement to lower her risks of such disorders.

2. Recent advances in the physiology of the pituitary ovarian axis: the roles of the inhibins in the normal menstrual cycle

Whilst the changes in the circulating levels of the gonadotropins, follicle-stimulating hormone (FSH) and luteinising hormone (LH), together with those in

☆ Proceedings of Xth International Congress on Hormonal Steroids, Quebec, Canada, 17–21 June 1998.

* Tel.: 613 9550 4397; fax: 613 9550 4376.

0960-0760/99 $ - see front matter
PII: S0960-0760(98)00145-9

the circulating ovarian steroids, estradiol (E2) and progesterone (P) have been well described over many years, it is only recently that the changes in the circulating inhibins have been characterised [2, 3]. The inhibins are dimeric protein hormones made up of a common α-subunit, linked to 1 of 2 β-subunits, β_A or β_B, to give inhibins A and B, respectively [4]. During the normal menstrual cycle, the levels of inhibin A, believed to be derived primarily from the granulosa cells of the dominant follicle, remain low for much of the follicular phase of the cycle, with a late rise to a mid cycle peak, a subsequent fall and a further rise to reach their highest levels during the mid luteal phase, contemporaneously with the peak levels of P and E2. The levels of both steroids and inhibin A (INH-A) fall late in the luteal phase when levels of FSH begin their inter cycle increase. The levels of inhibin B (INH-B) are closely related to the levels of FSH. They rise and fall early in the follicular phase of the cycle, demonstrate a mid cycle peak and then fall progressively throughout the luteal phase to reach their lowest levels at the end of the cycle. Whereas INH-A is a dominant follicle product, INH-B is a product of the cohort of antral follicles from which the dominant follicle is derived [5]. INH-B is postulated to be an index of the size of that recruited cohort.

3. The physiology of FSH regulation

The secretion of pituitary FSH is partly under the control of gonadotropin releasing hormone (GnRH) secreted by hypothalamic neurones and is partly autonomous, regulated by local intrapituitary production of activin, a dimeric peptide made up of 2 inhibin β-subunits [6]. FSH is subject to long loop negative feedback regulation both by the ovarian steroids, E2 and P and by the inhibins. The fact that the ovary employs 2 negative feedback signals gives rise to the postulate that differential regulation of the secretion of E2 and gonadal peptides could occur. E2 is of central importance to female physiology and it is hypothesized that telelogically, it would be desirable that its levels be maintained for as long as possible during reproductive life in order to maintain overall health and cardiovascular and bony integrity.

Although there is evidence that changes at the hypothalamo-pituitary level may contribute to the endocrine changes which occur during the menopausal transition and post menopausally [7], the major underlying pathophysiology of the menopause is the loss of ovarian follicles [8]. Ovarian primordial follicle numbers decrease steadily with increasing age up to about the age of 38 and then their number declines much more steeply during the last 12 or so years of reproductive life. At the time of the menopause itself few if any follicles remain within the ovary. The present consideration of the endocrinology of the menopause and the menopausal transition is thus based on the assumption that the changes are due to underlying changes in ovarian follicle numbers and function.

4. Changes in the pituitary ovarian axis as a function of age in regularly cycling women

Several studies have shown that the levels of serum FSH (particularly during the follicular phase of the cycle) rise progressively with increasing age in women who continue to cycle regularly [9]. The increased FSH levels become particularly marked over the age of 40 to 45. Because in most studies corresponding levels of circulating E2 do not change or even increase, it was postulated that a fall in circulating inhibin may underly the increase in FSH. Earlier studies from the author's laboratory showed that the circulating levels of immunoreactive inhibin (reflecting a combination of INH-A and INH-B and the biologically inactive inhibin α-subunit (which also circulates)) fell approximately inversely to the rising serum FSH levels in normally cycling women of different ages [10]. A recent study from the author's laboratory re-examined early follicular phase levels of serum FSH together with INH-A and INH-B during the follicular phase of the cycle [11]. Clear elevations in serum FSH were seen only in women at and above the age of 40 years. Whilst there was no clear difference in circulating inhibin levels as a function of increasing age (presumably because of a reasonably wide scatter of the normal data) there was a highly significant inverse correlation between circulating INH-B levels and serum FSH levels particularly in women over 40 years of age, suggesting that INH-B is the major regulator of follicular phase levels of FSH in normally cycling women age.

The notion that FSH and INH-B constitute a classic endocrine negative feedback system is supported by our demonstration that physiological doses of purified FSH are able to stimulate circulating levels of INH-A and INH-B during the normal menstrual cycle, the INH-B dose–response curve being steeper than that for INH-A [12]. The data indicates that both INH-A and INH-B are under FSH control.

The inverse relationship between INH-B and FSH provides further confirmation of data published by Klein *et al.* [13] in which circulating INH-B levels were found to be significantly lower in older women with elevated follicular phase FSH than they were in younger women with normal FSH levels.

On the basis of the above data and the dual feedback model of FSH control, it is postulated that a specific decrease in INH-B in women with gradually

reducing numbers of primordial follicles, leads to an increase in FSH which in turn maintains the drive necessary to stimulate continued selection of a dominant follicle with its ability to maintain E2 as well as INH-A secretion.

5. The endocrinology of the menopausal transition

Typically the normal menstrual cycle is characterised by changing levels of the gonadotropins, the ovarian steroids and the inhibins as described above. In contrast postmenopausally, there is a 10–15-fold increase in circulating FSH levels (compared to levels in the follicular phase of the cycle) a 4–5-fold increase in LH and more than 90% decrease in circulating E2. Inhibin levels postmenopausally are generally undetectable. The menopausal transition, that time when cycle irregularity begins to occur, represents the clinical manifestation of a marked decrease in ovarian follicle number [8]. It is a time of marked fluctuation in hormone levels [14].

The endocrinology of the menopausal transition has been studied in the setting of the Melbourne Women's Midlife Health Project [15]. For this project 2001 women were initially recruited for a community-based study of women's experience of the menopausal transition and menopause. From this large cross-sectional sample, 438 subjects were recruited for a longitudinal study involving annual interviews and annual blood sampling, between the 3rd and 8th days of the follicular phase of the menstrual cycle in those women who continued to cycle regularly or moderately irregularly and at any time in those with amenorrhoea. The longitudinal phase of the study began in 1991 and is ongoing. Data from this study has been analysed primarily on the basis of self report of changes in menstrual cycle regularity (with or without changes in menstrual flow). In the initial cross-sectional analysis of data obtained in the first year of this longitudinal study [15], major findings included the demonstration of a very wide range in circulating levels of serum FSH and E2, even in women who were continuing to cycle regularly but who were all over the age of 45 years. In those who had experienced a change in flow but not frequency of cycles, there was little change in hormone levels. However, in those who had begun to experience cycle irregularity FSH levels were increased but E2 levels were unchanged. It was only in those women who had experienced more than 3 months amenorrhoea, that a marked rise in FSH was accompanied by a substantial fall in circulating E2 and in immunoreactive inhibin levels. More recent analysis, again based on self reported changes in the menstrual cycle included measurement of circulating INH-A and INH-B [16]. Subjects were divided into 4 groups:

- Those who had continued to experience regular cycles, called premenopausal.
- Those who reported a change in menstrual cycle frequency but had bled within 3 months of their blood sample, called early perimenopausal.
- Those who had bled within 12 months but not within 3 months of blood sampling, called late perimenopausal.
- Those who were postmenopausal, i.e. had no menses for 12 months or more.

Serum FSH levels were somewhat higher in the early perimenopausal group as compared with the premenopausal but rose markedly in the late perimenopausal and postmenopausal groups. INH-A and E2 were not different in early perimenopausal women compared to the premenopausal controls but fell markedly in the late perimenopause. E2 was even lower in postmenopausal women. In contrast, INH-B levels had fallen markedly in the early perimenopausal group, compared with those who were still premenopausal, with the majority of samples being undetectable. No further significant fall was seen in the late perimenopause or postmenopausally. Thus the major significant event of the menopausal transition, based on self-reported changes in menstrual cycle regularity, was a decline in INH-B levels in the first half of the cycle. We would postulate that the decline in INH-B would allow a rise in FSH sufficient to stimulate follicular development and maintain dominant follicle function.

Examination of the changes in circulating FSH and E2 in women during the menopausal transition shows a marked variability within a given cycle in these levels [14]. Thus findings from both cross-sectional and longitudinal studies indicate the marked variability of circulating FSH and E2 and shows that menopausal status cannot reliably be determined from such hormone measurements.

6. Endocrine events related to final menses

A few studies have examined the hormonal changes surrounding the final menstrual period. These have indicated that when final menses is used as the reference point, circulating levels of FSH begin to rise a year or two prior to final menses but E2 levels are well maintained until just a few months before that event [17]. No endocrine event clearly differentiates the time just prior to and just after final menses. E2 levels have fallen by approximately 50% compared with earlier follicular phase levels at the time of final menses and FSH levels have risen about 50% of the ultimate peak they will reach postmenopausally.

7. Changes in progesterone and androgens

The menopausal transition is a time of increased frequency of anovulatory cycles. Hence measurements of P show progressively fewer concentrations indicative of the normal post ovulatory state [18]. Changes in circulating androgens are the subject of some controversy. Recent data suggests that serum testosterone levels fall by approximately 50% between ages 20 and 40 [19]. There are only minor changes in circulating testosterone levels in relation to the menopausal transition and final menses [15, 17]. Androgen levels fall little after the menopause. Thus previous concepts of a fall in androgens across the time of the menopause probably reflect the experimental design on which those data are based. The major changes in androgens appear to occur before the menopausal transition.

8. Clinical consequences of changes in endocrinology at and around the menopause

Data from the Melbourne Women's Midlife Health Project has provided evidence for an inverse relationship between circulating E2 and the frequency of hot flushes [20]. In general the classical symptoms of the menopause such as hot flushes, vaginal dryness, urinary frequency are considered to result from falling or low E2 levels. In the Melbourne Women's Midlife Health Project, it was also possible to demonstrate that changes in bone mineral density occur only during the late perimenopause and the early postmenopause, corresponding to the time of maximal fall in circulating E2 levels [21].

9. Conclusions

Circulating FSH levels increase during the follicular phase in women who continue to cycle regularly as they become older. FSH levels rise markedly during the menopausal transition, particularly in women who have had more than 3 months amenorrhoea. The rise in FSH with increasing age appears to be due to a selective fall in circulating levels of INH-B. A fall in INH-B also marks the entry into the menopausal transition when cycle irregularity is first reported, i.e. in early perimenopausal women. It is postulated that the fall in INH-B is a result of the fall in the size of the recruited cohort of follicles or to a decrease in the ability of granulosa cells in older women to secrete INH-B or both. The presence of a dual feedback system controlling FSH secretion may allow maintenance of circulating E2 by the selective fall in inhibin, allowing FSH levels to rise. The endocrine changes occurring during the menopausal transition and the early postmenopausal period have clinical consequences, both from the point of view of symptoms and the point of view of changes in bone mass. Study of the menopausal transition and menopause certainly presents substantial methodological and analytical challenges but studies such as the Melbourne Women's Midlife Health Project are providing useful data and generating hypotheses for further research.

Acknowledgements

The collaboration of my colleagues in the Melbourne Women's Midlife Health Project (Lorraine Dennerstein, Emma Dudley, John Hopper, Adele Green, John Wark, Peter Ebeling, Janet Guthrie) is acknowledged. David Robertson and his staff at Prince Henry's Institute of Medical Research provided the INH-A and INH-B assays for which Nigel Groome, Oxford Brookes University, Oxford, U.K. provided the reagents. Mr N. Balazs and his staff in the Department of Chemical Pathology, Monash Medical Centre, provided the FSH and estradiol measurements. The Melbourne Women's Mid-Life Health Project is supported by Grants from the Victorian Health Promotion Foundation and the Public Health Research and Development Committee of the Australian National Health and Medical Research Council. Support for the Hormone Assays has also been provided by Organon Australia Pty.

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