

Hormonal reproductive status of women at menopausal transition compared to that observed in a group of midreproductive-aged women

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Summary

Objective: To compare the serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), testosterone (T) and dehydroepiandrosterone sulfate (DHEA-S) in perimenopausal women to the levels of the same reproductive hormones in younger women.

Methods: This was a case control study which compared the hormonal status (circulating levels of FSH, LH, PRL, T, E2, DHEA-S) between women at menopausal transition and younger midreproductive-aged controls. The t-test for independent samples was used.

Results: FSH, LH and E2 were higher, and T and DHEA-S were lower in perimenopausal women.

Conclusion: The reproductive hormonal patterns in perimenopausal women favor a relatively hypergonadotropic hyperestrogenic milieu.

Key words: Perimenopausal women; Hormonal status; Estrogen levels.

Introduction

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. After one year of amenorrhea, the final menstrual period is retrospectively designated as the time of menopause [1]. Perimenopause comprises the period of time (2 to 8 years in duration, mean age: 45) preceding menopause and one year following the final menses. The term menopausal transition includes only the portion of perimenopause before the final period, which encompasses the change from normal ovulatory cycles to cessation of menses. During menopausal transition menstrual cycle variability is usually increased [2].

It now seems likely that the early phase of menopausal transition begins in the mid-thirties. This may be about 10 years earlier than the first break in cyclicity that was noted in previously regularly cycling women [3]. The menopausal transition begins subtly with the onset of a gradual deterioration of ovarian function not often accompanied by disrupted cyclic menses. Initially changes entail granulosa cell compromise. Ovaries of women in perimenopause have fewer developing follicles and each follicle contains fewer granulosa cells [4]. Individual granulosa cells may also have diminished function indicated by less in vitro steroids [5], inhibin [5], glycoprotein production [5] and increased apoptosis [4] compared to granulosa cells from follicles of younger women.

The endocrinology of the postmenopausal period has been well established. Several studies of hormonal

changes occurring as a function of increasing age in regularly cycling women showed that the major endocrine change was a progressive rise in the levels of FSH. Fewer studies have examined the endocrine changes following the development of menstrual cycle irregularity.

The aim of the present study was to compare the serum levels of FSH, LH, PRL, E2, T, DHEA-S in a group of perimenopausal women to the levels of the same reproductive hormones in younger women.

Material and Methods

Participants

Given the current absence of a biochemical hormonal or symptom-cluster marker for the onset of perimenopause, it is useful to have an epidemiological definition for the onset of perimenopause. In our study, perimenopause was defined as beginning when the women reported "a self-report of increased menstrual irregularity".

A sample of 140 women was examined. None were amenorrhoeic for more than six months (natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious cause). Those women were considered as "perimenopausal" because of the presence of irregular cycles. All the perimenopausal women enrolled in the study met the following criteria: 1) their age fluctuated ± 4 yrs compared to the mean of menopause (mean age=46.5), 2) a history of regular menstrual cycles 25-35 days in length, 3) non-smoking status, 4) no excessive exercise (> 1 h/day), 5) no aggressive dieting (loss of > 1 kg/week), 6) no disease affecting gonadotropin or sex steroid hormone secretion, clearance or excretion, 7) no hormonal therapy within 2 months of the study, 8) at least 90% of normal weight for height and 9) no prior history of ablative ovarian surgery, chemotherapy or radiation.

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Table 1. — Characteristics and hormonal levels of perimenopausal women and controls (figures of weight and hormonal levels are mean \pm standard deviation/SD).

	Perimenopausal (n=140)	Controls (n=140)	p
Age (years)	41-49	20-28	
Weight	78.8 \pm 8.8	74.6 \pm 7.5	>0.05
FSH (mIU/ml)	21.6 \pm 12.3	9.3 \pm 3.4	<0.001
LH (mIU/ml)	15.0 \pm 7.2	11.8 \pm 4.3	<0.001
PRL (ng/ml)	8.1 \pm 7.0	9.3 \pm 4.6	>0.05
E2 (pg/ml)	72.4 \pm 20.5	40.6 \pm 16.7	<0.001
T (ng/dl)	32.1 \pm 12.4	63.2 \pm 21.4	<0.001
DHEA-S (ng/dl)	1816.0 \pm 1203.3	2500 \pm 800	<0.001

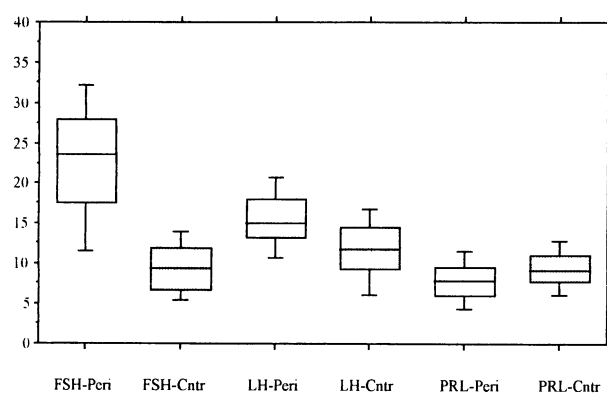


Figure 1. — Pituitary hormone levels in perimenopausal women and younger controls (Peri=perimenopausal, Cntr=controls, the boxes stand for 75th and 25th percentile).

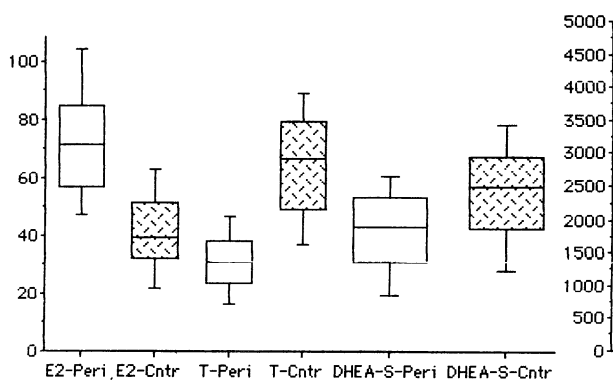


Figure 2. — Steroid reproductive hormones levels in perimenopausal women and younger controls (Peri=perimenopausal, Cntr=controls, the boxes stand for 75th and 25th percentile).

Controls

One hundred and forty normally cycling women, 20-28 yrs old, with regular cycles and without hyperprolactinemia or hypo or hyperthyroidism constituted the standard for hormonal status of midreproductive-aged women and served as a comparison group for the perimenopausal women. These women met the same criteria as the perimenopausal women, except for age and menstrual status.

All subjects (perimenopausal women and controls) were randomly recruited from the outpatient clinic of the hospital. Body mass index of perimenopausal women and controls was 25 and 24 kg/m² respectively, normally distributed in the groups.

Hormonal and related assays

Gonadotropins were measured by RIA. Estradiol and testosterone were measured using a double antibody RIA kit. For women with regular cycles the blood sample for hormone analysis was drawn between the 4th and 8th day of the menstrual cycle. Our study protocol allowed blood sampling regardless of the day of cycle for women with more than three months of amenorrhea. The 280 serum specimens were measured in about 10 assays for every hormone. In each assay 50% of the specimens belonged to each of the two groups in order to minimize the between-assay variation.

Statistical analysis

The t-test for independent samples was used to test the differences between the two groups with respect to hormonal status.

Results

Group comparisons are shown in Table 1, Figures 1 and 2.

Gonadotropin elevations were evident in the perimenopausal women. FSH levels were elevated in perimenopausal (21.6 \pm 12.3) compared to those in midreproductive-aged women (9.3 \pm 3.4) (p <0.001). Although less apparent, LH was also elevated in perimenopausal women (15.0 \pm 7.2), compared to controls (11.8 \pm 4.3) (p <0.001).

Circulating E2 levels were also elevated in perimenopausal women compared to those in younger women (72.4 \pm 20.5 vs 40.6 \pm 16.7) (p <0.001).

Serum prolactin levels did not differ significantly between the two groups (8.1 \pm 7.0, 9.3 \pm 4.6) (non-significant). Testosterone and DHEA-S levels in perimenopausal women were lower than those observed in younger controls and the differences were significant.

Discussion

The definition of the onset of the menopausal transition poses problems. The WHO definition says that it is the period before menopause when the "endocrinological, biological and clinical features of approaching menopause commence" [1]. That definition implies that there is a typical set of features that will make onset of perimenopause obvious. However, variability is the hallmark of the menopausal transition and no operational definition has been given for those features. On the other hand FSH levels increase gradually [6], are often intermittently high and normal, and are not diagnostic [7]. In our study, perimenopause was defined as beginning when the women reported "a self report of increased menstrual irregularity". An earlier study showed that this definition had a positive predictive value of 0.70 for the final menstrual period within the next three years [8]. That report and another one [9] found perimenopause duration to be an average of "about four" years. On the other hand women's reports of vasomotor symptoms or lighter flow were not very strongly predictive of the onset of perimenopause [8].

Our study compared reproductive hormone levels in

perimenopausal and younger aged women. The results confirmed what has been known for many years, that with increasing gynecological age, FSH levels increase first followed by LH levels [10]. On the other hand, there was a significant and clinically important finding of increased estradiol levels in perimenopausal women in contrast to the expectation that estrogen levels in perimenopause are on the decline.

Recent data suggest that there is an abrupt reduction in estradiol levels only 6 months or so before menopause [11]. This is in agreement with our findings since the perimenopausal women in our study were not amenorrheic for more than six months and the circulating levels of E2 were paradoxically increased. This observation is consistent with the clinical findings of increased endometrial hyperplasia, growth of myomata, and dysfunctional uterine bleeding that characterize this period of life. Appropriate therapy for menorrhagia or menometrorrhagia in a woman in or approaching perimenopause may be cyclic progesterone on days 14-27 of the cycle in doses sufficient to effectively counterbalance high endogenous estrogen levels. The reliance on gynecological surgeries (dilatation and curettage, hysterectomy) to treat these perimenopausal bleeding patterns may be inappropriate given a new understanding of the role that high estrogen circulating levels may play in their pathogenesis.

In perimenopausal women the adrenal continues to produce androstendione, dehydroepiandrosterone and dehydroepiandrosterone sulfate but primarily as a function of aging these values decrease somewhat (adrenopause). The ovary on the other hand continues to produce androstendione and testosterone, although testosterone levels in the ovarian vein are not reflected in the peripheral venous blood [12]. Testosterone and DHEA-S levels in perimenopausal women were significantly lower than those observed in younger controls in our study and it seems that the menopausal transition results in a pronounced decrease in the overall production of testosterone and DHEA-S.

Conclusions

In summary, we have demonstrated that the reproductive hormonal patterns in perimenopausal women favor a relatively hypergonadotropic hyperestrogenic milieu. These features render the perimenopausal woman most

likely to suffer from abnormal uterine bleeding and place her at risk for endometrial hyperplasia. The limitations of a case-control analysis, such as this, in terms of describing changes in hormone levels throughout the menopausal transition must be noted. Longitudinal observations should provide a clear picture of hormonal changes with age.

References

- [1] WHO Scientific Group 1996: "Research on the menopause in the 1990's". Vol. 866, 1.
- [2] McKinlay S. M., Brambilla D. J., Posner J. G.: "The normal menopausal transition". *Maturitas*, 1992, 14, 103.
- [3] Brambilla D. J., McKinlay S. M.: "A prospective study of factors affecting age at menopause". *J. Clin. Epidemiol.*, 1989, 42, 1031.
- [4] Seifer D. B., Gardiner A. C., Ferreira K. A., Peluso J. J.: "Apoptosis as a function of ovarian reserve in women undergoing in vitro fertilization". *Fertil. Steril.*, 1996, 66, 593.
- [5] Pellicer A., Mari M., De Los Santos M. J., Simon I., Remohi J., Tarin J. J.: "Effects of aging on the human ovary: the secretion of immunoreactive alpha-inhibin and progesterone". *Fertil. Steril.*, 1994, 61, 663.
- [6] Ahmed Ebbiary N. A., Lenton E. A., Cooke I. D.: "Hypothalamic-pituitary ageing: progressive increase in FSH and LH concentrations throughout the reproductive life in regularly menstruating women". *Clin. Endocrinol.*, 1994, 41, 199.
- [7] Burger H. G.: "Diagnostic role of follicle-stimulating hormone (FSH) measurements during the menopausal transition: an analysis of FSH, oestradiol and inhibin". *Eur. J. Endocr.*, 1994, 130, 38.
- [8] Brambilla D. J., McKinlay S. M., Johannes C. B.: "Defining the perimenopause for application in epidemiologic investigations". *Am. J. Epidemiol.*, 1994, 140, 1091.
- [9] Brambilla D. J., McKinlay S. M., Posner J. G.: "The normal menopausal transition". *Maturitas*, 1992, 14, 103.
- [10] McNaughton J., Banah M., McCloud P. I.: "Age related changes in FSH, LH, E2 and immunoreactive inhibin in women of reproductive age". *Clin. Endocrinol.*, (Oxf.) 1992, 36, 39.
- [11] Ranner K., Jeppsson S., Johnell O.: "A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density". *Maturitas*, 1995, 21, 103.
- [12] Ala Fossi S. L., Maenpaa J., Aine R., Punnonen R.: "Ovarian testosterone secretion during perimenopause". *Maturitas*, 1998, 29, 239.

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