REVIEW OF LITERATURE

Physiology of menopause

Menopause is a universal and irreversible part of the overall aging process involving a woman's reproductive system, after which she no longer menstruates. Climacteric is the general term for the time from the period of this transition to the early postmenopausal phase of a woman's reproductive life cycle. ***(Konar and Dutta, 2013)***

Perimenopause refers to the time before menopause when vasomotor symptoms and irregular menses often commence. Perimenopause can start 5-10 years or more before menopause.

Menopause, by definition, begins 12 months after the final menses and is characterized by a continuation of vasomotor symptoms and by urogenital symptoms such as vaginal dryness and dyspareunia ***(Konar and Dutta, 2013).***

Epidemiology:

The increasing number of middle-aged and older individuals includes a concomitant and continuing rise in the number of women who live most of their lives in a hypoestrogenic state. More and more women can expect to live approximately 79 years and to experience the consequences of gonadal hormone loss ***(Konar and Dutta, 2013)***.

Although the time spent in menopause (now up to one third of the life cycle*)* has increased with the phenomenon of increasing longevity, the actual age of menopause, approximately 50-51 years, has not changed since antiquity. Women from ancient Greece experienced menopause at the same age as modern women, with the symptomatic transition to

menopause usually commencing at approximately age 45.5-47.5 years.P P(Factors that lower the age of physiologic menopause include smokingP P, hysterectomy, Fragile X carrier, autoimmune disorders, living at high altitude, or history of certain chemotherapy medications and/or radiation treatment) ***(Konar and Dutta, 2013)***.

Physiology

Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular decline and dysfunction. The oocytes in the ovaries undergo atresia throughout a woman's life cycle, and both the quantity and quality of follicles undergo a critical decline approximately 20-25 years after menarche.

Thus, the variable menstrual cycle length during perimenopause can be due to anovulation or to irregular maturation of follicles. Hormonal fluctuation may not be responsible for all irregular bleeding during this period; therefore, pelvic pathology (eg, uterine fibroids, uterine polyps, endometrial hyperplasia, endometrial cancer) becomes more prevalent during this time.

During the fifth decade of life, many women are lulled into a false sense of security, thinking that they are no longer fertile because they are so close to menopause. Although fertility declines, pregnancy can still occur, as demonstrated by a relatively high rate of unintended pregnancies in women aged 40-44 years. In fact, the number of unintended pregnancies in this age group has increased over the past decade, which underscores the need for continued contraceptive practice in heterosexual couples.

A shorter menstrual cycle length is the most common change in menstrual cyclicity that occurs during the perimenopausal period in

women who have no pelvic pathology and who continue to be ovulatory. The follicular phase of the menstrual cycle shortens because of the decreased number of functional follicles. Because these follicles, which are stimulated by follicle-stimulating hormone (FSH) during the first part of the menstrual cycle, have declined in number, less recruitment of oocytes occurs and the follicular phase shortens accordingly. However, once ovulation occurs, the luteal phase remains fairly constant, at 14 days ***(Konar and Dutta, 2013)*** .

Over time, as aging follicles become more resistant to gonadotropin stimulation, circulating FSH and luteinizing hormone (LH) levels increase. Elevated FSH and LH levels lead to stromal stimulation of the ovary, with a resultant increase in estrone levels and a decrease in estradiol levels. Inhibin levels also drop during this time because of the negative feedback of elevated FSH levels.

With the commencement of menopause and a loss of functioning follicles, the most significant change in the hormonal profile is the dramatic decrease in circulating estrogen levels. Without a follicular source, the larger proportion of postmenopausal estrogen is derived from ovarian stromal and adrenal secretion of androstenedione, which is aromatized to estrone in the peripheral circulation. Testosterone levels also decrease with menopause but this decrease is not as marked as the decline in 17-estradiol.

With cessation of ovulation, estrogen production by the aromatization of androgens in the ovarian stroma and production in extragonadal sites continue, unopposed by progesterone production by a corpus luteum. Perimenopausal and menopausal women are thus often

exposed to unopposed estrogen for long periods, which can lead to endometrial hyperplasia, a precursor of endometrial cancer.

Estradiol levels decrease significantly because of loss of follicular production with menopause and postmenopause, but estrone, which is aromatized from androstenedione from nonfollicular sources, is still produced and is the major source of circulating estrogen in the postmenopausal female ***(Konar and Dutta, 2013)***.

Androgen-to-estrogen aromatization can occur in adipose tissue, muscle, liver, bone, bone marrow, fibroblasts, and hair roots. Because most conversion of androgens to estrogens occurs in adipose tissue, it is frequently assumed that obese women, who have more circulating estrogen, should have fewer complaints of vasomotor symptoms.

However, this is not always the case, and vasomotor symptoms of menopause can be as frequent and severe in heavier women as they are in thinner women.

The clinical indication that menopause has occurred is the measure of an elevated FSH level. The FSH level rises more than the LH level because of the reduced renal clearance of FSH compared with LH. A slightly elevated or borderline menopausal FSH level in a perimenopausal women may not be a reliable indicator of menopause because of the wide variation of FSH and LH levels in response to increased release of gonadotropin-releasing hormone (GnRH) by the hypothalamus and increased pituitary sensitivity to GnRH.

Measuring FSH and LH levels again in the perimenopausal patient after 2-3 months is helpful in establishing whether the woman is progressing through menopause. Women with elevated, but not postmenopausal, FSH levels are still at risk for pregnancy and

contraception should still be used until FSH levels remain in the postmenopausal range.

Normal sonographic appearance of postmenopausal endometrium:

The normal postmenopausal endometrium should appear thin, homogeneous, and echogenic. There is controversy regarding endometrial thickness with menopause. Although some authors have found that endometrial thickness decreases with age, others believe there is no statistically significant change during menopause ***(Nalaboff et al., 2001).***

In general, a double-layer thickness of less than 5 mm without focal thickening excludes significant disease and is consistent with atrophy. Homogeneous, smooth endometria measuring 5 mm or less are considered within the normal range with or without hormonal replacement therapy.
(Fig. 1) ***(Nalaboff et al., 2001).)***

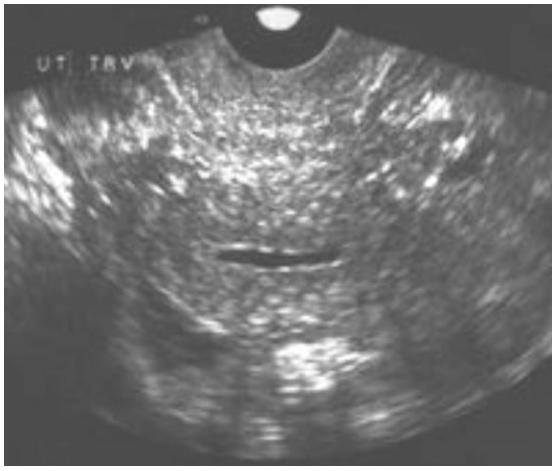

Fig.1: Postmenopausal endometrium.

Transvaginal US image demonstrates postmenopausal endometrium with thin walls and outlined with fluid ***(Nalaboff et al., 2001).***

The endometrium in a patient undergoing hormonal replacement therapy may vary up to 3 mm if cyclic estrogen and progestin therapy is being used. The endometrium will appear thickest prior to progestin exposure and thinnest after the progestin phase. Imaging should be performed at the beginning or end of a cycle of treatment, when the endometrium will be at its thinnest and any pathologic thickening will be most prominent ***(Nalaboff et al., 2001).***

References

Konar, H. and Dutta, D.C. (2013). DC DUTTA's Textbook of Gynecology 6th edition.

Nalaboff, K.M., Pellerito, J.S. and Ben-Levi, E. (**2001).** Imaging the Endometrium: Disease and Normal Variants. Radiographics, 21:1409.