4

Premenopausal cycle anomalies

M Neves-e-Castro

Introduction • Symptoms • Clinical examination • Complementary examinations • Contraception • Treatment • References

INTRODUCTION

The important problems of premenopausal cycle anomalies can be discussed very pragmatically from a clinical perspective or they may be the basis for long speculative analysis of their etiopathogenesis. The purpose of this chapter is to emphasize the former, based, whenever possible, on information derived from the latter.

SYMPTOMS

Reported symptoms vary from longer to shorter, regular or irregular menstrual cycles, with scanty or heavy flows, or spotting or breakthrough bleeding, with or without dysmenorrhea. Between menstruation mucous vaginal discharges are also common, which may cause itching (in the absence of infections).

Many women suffer from vasomotor symptoms, e.g. hot flushes and night sweats, that are a cause of a compromised quality of life. Premenstrual tension (PMT) may also be exacerbated. Sensations of bloating and fluid retention are not uncommon. Other symptoms, e.g. emotional disturbances like changes in humor, irritability to depression, insomnia and/or decreased libido also have unpleasant repercussions on the woman's quality of life. Last, but not least, the appearance of wrinkles and gray hair are triggers of major concerns about the beginning of aging, and decreased feminity, and attractiveness to a male partner.

Most of these symptoms are not necessarily related to the lack of estrogens that characterize the early and late postmenopausal period. On the contrary, what most studies have shown is that in the premenopausal years there is either a relative hyperestrogenism (due to luteal insufficiency) or an absolute hyperestrogenism (caused by persistent follicles that later undergo atresia without ovulating).

Estrogen plasma levels are very erratic: when they are high they may cause PMT, mastodynia or fluid retention, when they suddenly drop to lower levels (without reaching a hypoestrogenic state) this is perceived by the hypothalamus, which responds with vasomotor symptoms and sweating. This endocrine disturbance was termed the *perimenopausal endogenous ovarian hyperstimulative syndrome* by Prior.[1] The trigger seems to be a decrease in inhibin during the luteal phase of the menstrual cycle, as a result of which there is a sharp increase in follicle stimulating hormone (FSH) that hyperstimulates the ovarian follicles. Although many of the follicles may not grow very much, their granulose cells contribute to an overall increase in ovarian estrogen secretion, as mentioned above.

CLINICAL EXAMINATION

In practical terms one should consider a menstrual cycle disturbance as being characteristic of the premenopausal syndrome when it occurs after 45 years of age in a woman who previously had regular cycles. There are many possible causes of menstrual cycle disturbances other than those related to the premenopause that are basically related to ovarian aging.

It is well known that undernutrition or excessive weight, which may cause profound changes in the body mass index (BMI) and in the percentage of fat content, are frequent causes of ovarian dysfunction that are determinants of menstrual cycle irregularities. Therefore, the measurement of BMI and fat is essential.

The distribution of body hair is very important too, because it may be a sign of hyperandogenism from an adrenal or ovarian origin (both tumoral or dysfunctional). This may often be associated with an oily skin, acne and male implantation of hair (front, hypogastrium, breast), i.e. from hypertrichosis to hirsutism.

A very dry skin, facial and pretibial edema may be signs of hypothyroidism, frequently present in the perimenopause. On the contrary, mild exophthalmoses, hot flushes and profuse sweating, or tachycardia, may be associated with hyperthyroidism. The pelvic examination is very informative to discard adnexal masses or uterine fibroids as causes of cycle irregularities. In their absence, inspection of the cervix will quickly negate an hypoestrogenic state when one sees an opened external os with flowing clear elastic mucous, a sign that indicates that a progestogen challenge test, if there was a delay of menstruation, will be positive. Inspection and palpation of the breasts is also mandatory.

COMPLEMENTARY EXAMINATIONS

Indispensable imaging techniques are the mammography (plus ultrasound scanning) and pelvic ultrasonography with a vaginal probe. Blood tests must include, in addition to a complete blood and platelet count, some tests of coagulation, fasting insulin and glucose, thyroid-stimulating hormone (TSH) and free thyroxin, [the sulphate ester of dehydroepiandrosterone (DHEAS) hydroxiprogesterone and testosterone, total and free, if there are signs of androgenism], urine analysis, and those carried out as routine. One can thus discard coagulation disorders, thyroid dysfunctions, insulin resistance and/or diabetes. A Pap smear test is essential, and an endometrial biopsy may be necessary.

CONTRACEPTION

If a woman is taking an oral contraceptive and complains of cycle irregularities then the chances are very high that she has a concomitant organic disease, either uterine or hematologic. The same may be the case if she has an intrauterine contraceptive device (IUCD) inserted. Therefore, in both cases, it is mandatory to exclude by all means available such possibilities.

However, many women do not take the Pill or have an IUCD fitted. For these women the onset of perimenopausal menstrual irregularities become more of a problem.

The beginning, or continuation, of low dose oral contraception is not necessarily contraindicated (in the absence of well-known contraindications) and may have the advantage, in addition to the contraceptive efficacy, to correct the underlying pituitary–ovarian dysfunction, to relieve symptoms, and protect the endometrium and breasts from hyperestrogenism. Furthermore, oral contraception may also be beneficial in protecting the vessel walls from atherogenesis when the menopause is reached. It is likely that there is still a good endothelium that will be protected by estrogens. However, in practical terms, the problem will be to decide when to stop the Pill if one does not want to go beyond an underlying occult menopause.

The suspension of oral contraception at a later age, e.g. 50 years, followed by FSH and estradiol assays to ascertain if physiologic primary ovarian failure has already occurred is not a safe guarantee. If this option is chosen then local contraception must be started because it is not unusual for a quiescent ovary to later become spontaneously reactivated and even ovulate.

An alternative method of contraception can be a progesterone-medicated IUCD. Besides having good efficacy it protects the endometrium from hyperplasia and does not interfere with ovarian function, thus allowing one to know when the menopause is reached. In addition, when it becomes necessary to treat the postmenopausal symptoms with estrogens its protection of the endometrium permits a much better estrogen-only treatment.

TREATMENT

Assuming that no other cause has been found for the premenstrual cycle anomalies, other than the premenopause in itself, treatment must be aimed at the correction of the symptoms and the prevention of breast and uterine pathology.

If no systemic contraception is required the objective is to correct luteal insufficiency and relative (or absolute) hyperestrogenism. This can be done with a cyclic (12–13 days/month) substitution with a progestogen. If the symptoms are also alleviated with this treatment one should go on every month until there is no more uterine bleeding, which means that the woman has become hypoestrogenic and has probably entered the menopause. Then is the time to start estrogen replacement therapy (ERT), without or with systemic or intrauterine progesterone depending on each case, but this is no longer the objective of present review.

Vasomotor symptoms can also be alleviated with serotonin reuptake inhibitors (e.g. fluoxetine) that have the additional advantages of improving mood and counteracting weight gain. Night sweats may also respond to gabapentin and vagolytic agents.

Last, but not least, the onset of premenopause cycle anomalies offer a very important opportunity to inform a woman about her upcoming menopause. Proper and timely education is the best way to avoid misconceptions that may be very traumatic in a woman's life.

It must be strongly emphasized that there is no reason to be afraid of a loss of libido and a poorer sex life. One should explain that, contrary to general belief, it is not breast cancer but heart disease that is the major cause of death in older women. Whereas breast cancer can be cured this is not the case with atherosclerosis, the consequent events of which can only be attenuated, hopefully, to a more or less steady state. Woman must be informed in depth about the importance of proper nutrition, cessation of smoking moderate alcohol consumption and aerobic exercise. Much to many women's surprise these measures and strategies, sometimes more than medications, have a profound influence on health maintenance and disease prevention.

Premenstrual cycle disturbances are no doubt important clinical problems that must be duly investigated and treated, usually for a short time. But what comes next, the postmenopause, is certainly far more important for a much longer time. Therefore, premenstrual cycle disturbances provide an important opportunity for the development of the woman–doctor relationship.

REFERENCES

Further reading

1. Bastian LA, Smith CM, Nanda K. Is this woman perimenopausal? *J Am Med Ass* 2003; **289:** 895–902.
2. French L. Approach to the perimenopausal patient. *J Family Practice* 2002; **51:** 271–6.
3. Neves-e-Castro M. Los últimos años de la Premenopausia. In: (Pérez-López FR, ed) *Climaterio Y Envejecimiento*. (Seisge, Zaragoza, 1999) 1–46.
4. Seifer DB, Naftolin F. Moving toward an earlier and better understanding of perimenopause. *Fertil Steril* 1998; **69:** 387–8.
5. Soares CN, Cohen LS. The perimenopause, depressive disorders, and hormonal variability. *Sao Paulo Med J* 2001; **119:** 78–83.
6. Taffe JR, Dennerstein L. Menstrual patterns leading to the final menstrual period. *Menopause* 2002; **9:** 32–40.

Scientific paper

1. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocr Rev* 1998; **19:** 397–428.