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Regulation of Disorders of the Female Cycle

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The female cycle is composed of three rhythmic processes, namely the hypothalamic-pituitary, the ovarian and the menstrual cycle (Fig. 1). They are closely related mainly in the way that the two first mentioned balance each other in a feed-back mechanism and that the menstrual cycle reflects the activity of the ovarian. The pace-maker for the female cycle is still unknown but influences from the central and the vegetative nervous system seem to be essential.

The menstrual cycle is very obvious for a woman and disorders in different ways are, therefore, readily registered. Even the ovarian cycle is observed by some women namely by those who suffer from ovulation pains or premenstrual symptoms of different kinds. The physician has good possibilities to register all three cycles even if the examination of the hypothalamic-pituitary cycle must be dependent upon the facilities of a hormone laboratory, since the only way to demonstrate that cycle is by estimation of the levels of LH and FSH in plasma or urine. A contribution from the patient in the form of basal body temperature charts and serial vaginal smears is of importance to demonstrate the ovarian cycle.

Because of the complex nature of the female cycle and its regulation, a disorder causing menstrual abnormalities may have its origin in the uterus, ovaries, pituitary and hypothalamus as well as in factors influencing indirectly the function of these organs. Such disorders may be of an organic or a functional type. Only when a careful examination fails to indicate organic lesion may disturbances of a functional type be presupposed.

Before therapy is initiated consideration must be as to whether or not hormone treatment is indicated, since there is no need to regulate all disorders of the female cycle. This seemingly nihilistic attitude is frequently used in cases of secondary amenorrhoea which in approximately 90% depend on functional disturbances at the hypothalamic-pituitary level. We treat only a minority of these patients with hormones, namely those who wish to become pregnant. In these cases human gonadotrophins or clomiphene are used. The rest of the patients, however, are only informed about the background of their menstrual abnormality, told that menstruation may recur

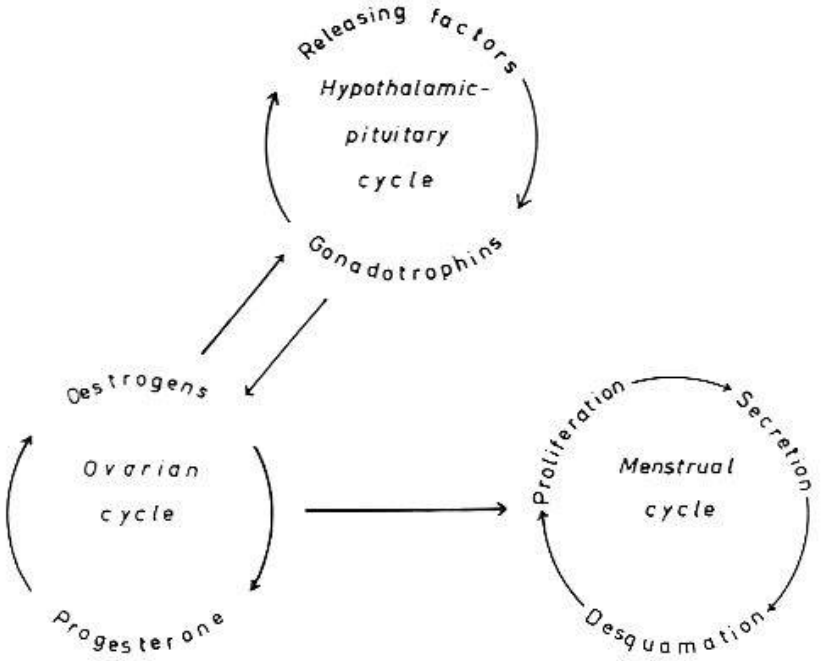

Fig. 1. The female cycle.

spontaneously, and assured that treatment to stimulate follicular growth and ovulation may be postponed until they wish to become pregnant and that the chance for success at that time will be the same. This is a kind of psychotherapy which may be further extended with the help of social workers and psychiatrists who can evaluate and treat social and emotional factors which, according to our experience, are of great importance in the development of secondary amenorrhoea and other functional disturbances. We feel that it is highly doubtful whether treatment with estrogens, progestogens, gonadotrophins, clomiphene, Sexovid, etc., will give these patients spontaneous menstruations earlier than when no such treatment is given. It may even be so that in some cases administration of estrogen-progestogen combinations for months or even years – a treatment schedule frequently used – may delay the appearance of spontaneous menstrual periods.

Progestogens as a tool to regulate disorders of the female cycle are mainly used in two ways, either to substitute for the lack of ovarian progesterone production in anovulatory conditions or to supplement a low postovulatory progesterone production. However, even other modes of action of the progestogens can be utilized therapeutically (e.g. an action on the hypothalamic level or an eventual direct action on the ovaries), but these latter methods are so far of minor clinical value.

Anovulatory conditions may appear under fairly different clinical pictures such as secondary amenorrhoea, oligomenorrhoea[1] and metropathia. Progestogens given to a woman with a secondary amenorrhoea generally induce a withdrawal bleeding only if the endogeneous estrogen production is high

[1] Amenorrhoea = at least 6 months since the last spontaneous menstruation. Oligomenorrhoea = from 42 days to 6 months between menstruations.

enough to prime the endometrium (i.e. capacity to bring about proliferative changes). That fact is often used to evaluate whether or not such a prerequisite is present in amenorrhoeic patients – the so-called "progesterone test". Some give an injection of 50 mg of progesterone but others use instead oral progestogens for 5–10 days.

Secondary amenorrhoea and oligomenorrhoea, whether anovulatory or ovulatory, I seldom treat with progestogens alone. Treatment follows the principles mentioned earlier. If, for some reason, a decision is made to induce for some time artificial cycles, the contraceptive pills of the 15/5 sequential type are preferred. In cases of amenorrhoea of ovarian origin (e.g. cases of gonadal dysgenesis or castration) artificial cycles with p-pills are induced in most patients, but it is not uncommon that women with gonadal dysgenesis after one or two years wish to stop the treatment which they consider laborious and unnecessary since they observe no other differences than the appearance of menstrual bleedings. So far, I have not met with any convincing argument to justify continued treatment.

In metropathia there are highly irregular, prolonged and often heavy bleedings which by their nature are estrogen break-through bleedings. The hormone treatment can be divided in two phases, one to stop the actual bleeding (haemostasis) and one to prevent further severe episodes of bleeding episodes (prophylaxis).

The best way to stop an estrogen break-through bleeding is to give estrogens, but some days afterwards a new bleeding starts – a withdrawal bleeding after the administered estrogens. Some progestogens can be used instead, but generally with less efficiency. The recommended treatment is a combination of estrogens and progestogens, in order to increase the estrogen level, to transform the endometrium into a secretory phase and to create, a few days later, an estrogen-progestogen withdrawal bleeding which desquamates the endometrium. The treatment schedule can be varied in several ways as long as the above-mentioned principle is followed.

New metropathia bleedings are generally prevented by regular administration of progestogens starting on the 15th–19th day from the onset of the previous withdrawal bleeding and continuing until day 25 or 26. In some older women near their menopause the estrogen level is not always high enough to prime the endometrium. In such cases some additional estrogen is given during the period of progestogen treatment.

Therapy to induce ovulation in anovulatory women we generally restrict to those who wish to become pregnant. Such treatment involves human gonadotrophins, clomiphene and Sexovid. Some attempts have recently also been made with progestogens, e.g. a retrosteroid[2], which has been reported useful. The whole mechanism of action when clomiphene, Sexovid and steroids are used is not fully understood, but influences on both the hypothalamic-pituitary and ovarian levels are quite possible.

[2] Ro 4-8347 from Hoffmann-La Roche & Co. Ltd.

Table I

Diagnose of "corpus luteum insufficiency" in non-pregnant patients

Methods	Degree of		Comment
	"patient effort"	reliability of method	
1. Basal body temperature	low	low	Screening method
2. Endometrial biopsies	moderate	high	So far the best
3. Determination of pregnanediol in urine	high, if serial	low	Wide variations
4. Determination of progesterone in plasma or blood	rather high	high(?)	Variation limits still unclear
5. Vaginal smears	low	moderate	Disturbed evaluation when infection, cytolysis
6. Cervical mucus	moderate	low	Limited possibilities for quantitation

Progestogens may also be used as a supplementation therapy in functional disorders of the female cycle. The indication for such a treatment should be a demonstrated underproduction of progesterone in ovulatory cycles. Because the investigation to establish an insufficient progesterone production is time-consuming and laborious, the documentation, according to my experience, is often omitted. The methods used to diagnose a corpus luteum insufficiency are compiled and commented in Table I.

The main group treated according to the supplementation principle consists of women with so-called unexplained infertility. Usually, progestogens are given from day 15 to 17 until menstruation starts or – if pregnancy is obtained – for 1–2 months. Since many progestogens have the ability to postpone menstruation, the treatment cycles may be prolonged. This disadvantage is less marked by some progestogens, dydrogesteron, for example, which we consequently prefer. Progestogens with androgenic properties ought to be avoided in these cases.

Progestogens in the treatment of functional menorrhagia may be included in the supplementation principle of therapy even if other modes of action may be involved. Using methods to measure the blood loss during menorrhagia the efficiency of several of the progestogens has been well demonstrated, found comparable to that of amino capronic acid and superior to ergometrin and related substances.

The choice of progestogen for the treatment of cyclic disorders according to the above mentioned principles must include the consideration that these substances may have other properties than the progestational (such as

estrogenicity and androgenicity) but also that some may influence liver function. Most progestogens raise basal body temperature, but e.g. dydrogesterone lacks thermogenicity which may be valuable if used under certain circumstances. I think it is advisable for the ordinary gynecologist to keep to a few progestogens in order to become more familiar with their properties and utility.

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