THE USE OF HORMONES IN ABNORMAL MENSTRUATION

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Attention has frequently been drawn to disorders of menstruation associated with gross and readily demonstrable pathology. Benign and malignant tumors of the reproductive organs and abnormalities of early pregnancy serve to illustrate these examples of organic bleeding. Fifty years ago Hitschmann and Adler discovered that the endometrium undergoes cyclic change. The subsequent recognition of the function of the endocrine glands concerned in the control of menstruation has so helped our understanding of the phenomenon that we can now also talk with certainty about functional disturbances.

The term functional implies a disturbance of physiological mechanisms and when referring to uterine bleeding is known by a variety of names. The commonest of these is Functional Uterine Bleeding. Others use Dysfunctional Uterine Bleeding and, at Dalhousie, Benign Uterine Bleeding has been a popular term for many years. These terms refer to a group of disturbances resulting from endocrine dysfunction, but in dealing with individual patients, it is usually desirable to seek more specific diagnoses so that treatment can be logically planned.

The presently accepted view of the hormonal control of menstruation is, that the anterior pituitary secretes follicle stimulating hormone (FSH) which caused the Graafian follicle to ripen and secrete increasing amounts of Estrogen prior to ovulation. Luteinizing hormone (LH) from the anterior pituitary causes the actual act of ovulation, while luteotrophic hormone (LTH) maintains the function of the corpus luteum with its cyclic output of progesterone. Prior to ovulation then, the endometrium is influenced by Estrogens alone, while after ovulation by both Estrogen and Progesterone. A fall or imbalance in these leads to menstruation.

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At one time, the disorders of menstruation were classified into simple groups. Since the menses were thought to follow the cycle of the moon and occurred every twenty-eight days, it was obvious that some disturbance was present when they appeared at shorter or longer intervals (polymanorrhea and oligomenorrhoea), were scanty or profuse (hypomenorrhoea or menorrhagia), were absent altogether (amenorrhoea) or were unduly painful (dysmenorrhoea).

Based on the knowledge of the known events in the menstrual cycle, the specific defects in most cases of functional uterine bleeding have been worked out. Most functional excesses occur from proliferative or estrogenic endometrium; that is, there is a lack of progesterone effect. It is rare to have excessive bleeding from a full-blown, normally differentiated, progestational endometrium in the absence of organic disease. To all intents and purposes, the only hormone being produced in most cases of functional bleeding is estrogen. When the estrogen level rises, bleeding stops; when it falls, bleeding occurs. The rise and fall of estrogen is controlled by the relationship between the graafian follicle and the output of FSH by the pituitary. There is usually a time lag of two to five days in the estrogen and bleeding relationship. An effective rise in estrogen stops bleeding within two to five days, and conversely, an effective fall in estrogen results in bleeding within two to five days.

What causes the upset in the pituitary, ovarian and endometrial functions is really not known. Perhaps one or more of the following may happen: -

1. A failure of the late menstrual rise in estrogen may result in prolongation of what would otherwise have been a normal period.
2. An extremely rapid fall in estrogen may induce excessive bleeding.
3. Prolonged bleeding may result from

estrogen levels that teeter at critical depressions for prolonged periods of time.

4. Prolonged and unopposed estrogen stimulation of the endometrium may produce endometrial hyperplasiasia, providing periods of endometrial growth followed by excessive bleeding.

We do know that in most cases ovulation does not occur, and if it does occur, the production of progesterone is poor.

A distinction must be made between normal and abnormal menstruation. The features of abnormal menstruation are: -

1. Prolonged bleeding - lasting 8 days or more.
2. Bleeding too often - 23 days or less from the beginning of one period to the beginning of another.
3. Excessive bleeding - more than a moderate increase in a specific patient's normal amount of flow.
4. Continuous bleeding - which might be more or less daily spotting or moderate or profuse flow.

These descriptive terms are more meaningful than the words menorrhagia, metrorrhagia, etc. and it is important to take an accurate history.

There are five common clinical varieties of functional bleeding that can be recognized, the first two of which accounts for the vast majority of cases. Briefly, they are: -

1. **Anovulatory Bleeding** - here there is a failure of ovulation and the endometrium is under the influence of estrogen alone. Frequently, there is a delay in the expected period date by one or two weeks and when it starts, it lasts well beyond the normal 8 days. It may also be profuse. This is common in adolescents and premenopausal women but may occur after a miscarriage or full term delivery.
2. **Endometrial Hyperplasia** - the end result of anovulatory bleeding where the glandular elements as well as the stroma become overgrown from prolonged estrogen stimulations lasting several months. Clinically, the bleeding is excessive and often continues for long periods of time.
3. **Irregular Shedding of the Endometrium** - here there is ovulation, but progesterone effect persists well into the bleeding phase of the cycle and produces bleeding for longer than normal. There may be excessive bleeding as well. The cycle interval is not changed. If curettage is done while bleeding, the usual normal microscopic picture of sloughing endometrium is not seen.
4. **Inadequate Luetal Phase** - here again, ovulation occurs, but there is either poor production or poor utilization of progesterone resulting in prolongation of the bleeding phase. Bleeding is not excessive. Once again the microscopic picture of the endometrium does not resemble the usual for any particular day of the cycle - it is rather poorly developed.
5. **Ovulation Bleeding** - bleeding (or spotting) on the day ovulation is seen in at least 10% of healthy women. Its cyclic recurrence helps to confirm the diagnosis. It usually requires no treatment.

The diagnosis of uterine bleeding must be approached with caution and reservation, for the foremost duty of the clinician is to rule out malignancy as the cause. Obviously, physical examination and pelvic examination with vaginal and cervical cytology are essential, but diagnostic D and Cs and vaginal examinations under anesthetic are not necessary on adolescents and young unmarried women. When curettage is done, it should be in the second part of the cycle to prove the absence or presence of ovulation. It is worth remembering that irregular shedding can be diagnosed only if the D and C is done on the 6th day or later of bleeding.

Since functional bleeding often runs a limited course, the clinician's therapeutic objectives are to combat depleting hemorrhages, treat anemia and to restore normal cyclic bleeding. From a practical point of view, modern treatment divides itself into hormone therapy and surgery.

The clinician not oriented along the lines of glandular physiology will resort to repeated curettage and then hysterectomy. The clinician who has used glandular therapy in a haphazard manner and, finding it wanting, decries its use. Others refuse to try hormones at all, asserting that their use is experimental or that they are carcinogenic.

It is possible, however, with knowledge

gained from the study of the physiology of menstruation, as previously discussed, to effectively apply hormones in the treatment of menstrual disorders. Of course, it is well known in medicine that menstrual irregularities can be caused by nutritional, nervous and psychogenic factors and these, when present, must be treated at the same time.

The hormones in current use for functional bleeding are estrogens, progesterone and the newer progestational agents, the 19 nortestosterone derivatives.

Estrogens

On the basis that an effective rise in estrogen will stop endometrial bleeding, they are commonly used in the management of functional bleeding at the menarche and at the menopause.

(1) **For rapid hemostasis** - Premarin 20 mgm. i.v. q 4-8 h. until bleeding is arrested, followed by Premarin 3.75 mgm. orally daily, reducing gradually to 1.25 mgm. a day and continued for 3 weeks. 2 to 5 (sometimes up to 8) days later, withdrawal bleeding will occur.

(b) **For less rapid hemostasis** - give Premarin orally in the dosage mentioned above, or stillesterol 5 - 10 mgm. at 4-hour intervals.

A complication of high dosage estrogen therapy is nausea. The errors that are most frequently made when employing estrogens are the use of inadequate dosages and the abrupt cessation of therapy when bleeding is arrested. Estrogens must be tapered off gradually, otherwise bleeding will always ensue. If one wishes to repeat the course in the next cycle, then start oral estrogens on the 2nd or 3rd day of bleeding and continue for three weeks.

Progesterone

This is a desquamative hormone. It increases the desquamation of the endometrium and therefore enhances shedding. Progesterone induces a "medical curettage". If properly employed it is the most effective single therapeutic agent available for treatment of irregular and profuse bleeding.

It is very important to remember that in adequate doses it will slow down and stop uterine bleeding, but that 2 to 10 days after it is withdrawn, bleeding will invariably follow. The interval depends on the agent used.

(a) **Progesterone 10 mgm.** i.m. daily for 5 consecutive days or 50 mgm. given in one dose i.m., will not stop bleeding completely and in 5 - 8 days will induce withdrawal bleeding. This method is not recommended since better doses and drugs are available.

(b) **Progesterone in Oil** 100 mgm. i.m. will stop bleeding in 2 - 3 days and 5 - 8 days later will induce withdrawal bleeding. This is a good way to insure that the patient gets the medication and the most suitable product is Proluton (Squibb) containing 50 mgms. Progesterone in Oil per cc.. To ensure regular cyclic bleeding give 100 mgm. i.m. every 25 - 28 days for 3 months. Progesterone is not effective orally.

Progestational Compounds

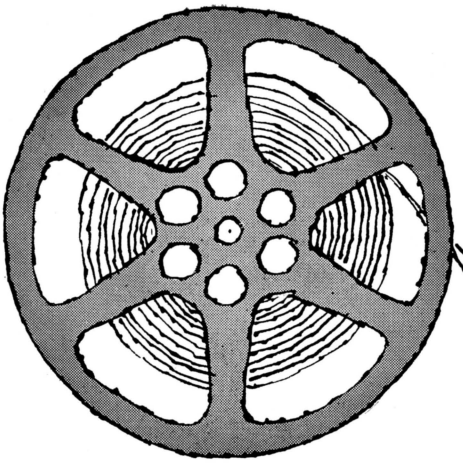
(a) 17 hydroxyprogesterone caproate (Delalutin) - this is a potent progestational agent for i.m. use and when given in 20 mgm. doses will arrest bleeding in 24-28 hours. Withdrawal bleeding usually occurs 7-10 days later.

(b) **19 - Nortestosterone Derivatives.** Norethindrone (Norlutin) and Norethynodrel (Enovid) are examples of very potent progestational agents. Each tablet contains a small quantity of estrogen since it is known that estrogens enhance the effectiveness of progesterone.

In functional bleeding, for example, 30 mgm. of Enovid will arrest bleeding in almost every case within 24 hours. For women when the loss of blood is heavy, the dose may even be doubled, but once the drug is given it must be continued, otherwise withdrawal bleeding will occur in 2 - 4 days. A practical plan would be to continue on a dose of 10 - 20 mgms. a day for a month, adjusting the dose up or down to keep patient from having breakthrough bleeding. In the meantime, appropriate iron therapy is given. If one wishes he may postpone the withdrawal bleeding (period) for 30, 40, 60 days or longer, if he wishes to give the hemoglobin a chance to approach normal.

A course of 2 - 3 months on 5 - 10 mgms. a day from the 5th to the 24th day of the cycle will give a regular cycle of 27 - 28 days.

Another way these agents may be used is to give 5 or 10 mgms. daily from day 17 in the cycle for one week to encourage development of a well differentiated endo-



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metrium and more effective shedding of the endometrium, especially in inadequate luteal phase and hyperplasia.

It is important to explain to the patient to expect withdrawal bleeding, otherwise she will feel the treatment has failed.

In the use of hormones in the control of functional bleeding, the arrest of bleeding is only a stop gap mechanism without assurance against recurrence. However, in girls and young women especially, cyclic treatment will often bring about cyclic menstruation with ovulation (or it may occur spontaneously) and one needs to go no further with treatment.

The clinician not orientated along the lines of glandular physiology will resort to repeated curettage and hysterectomy in an effort to help these distressed women, but these measures should be reserved for patients nearing the menopause or past their reproductive period. However, hormone therapy must be based on physiological grounds if it is to be used to best advantage in abnormal menstruation.

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