

ENDOMETRIAL BIOPSY

Its Diagnostic Value In Amenorrhoea

BY

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The term amenorrhoea denotes absence of menstrual flow. It is considered abnormal when it occurs within the limits of the reproductive period, in the absence of pregnancy or lactation. Diligent study and intensive therapy are often necessary if the reproductive life of a woman is to be salvaged. Primary amenorrhoea means that the woman has never menstruated, whereas if the menstruation ceases at some time after menstrual function is established, the term secondary amenorrhoea is used.

Sex physiology has for its ultimate purpose the procreation of the species. The purpose of the complex pituitary—ovarian—endometrial system is the cyclic maturation of a potentially fertile ovum and the preparation of the endometrium for nidation of the fertilised ovum. Menstruation per se may not serve any known useful physiological purpose but the presence or absence of ovulation is important physiologically. A defective link in this complex chain is likely to disturb menstruation. Special tests may be applied to each link in this chain and one or more defective links may be detected. The lowest link in the chain is the "Endometrium", hence endometrium is the first to be tested when any menstrual disturbance occurs. Ob-

viously if the uterus has been surgically removed, there will be no menstruation.

In amenorrhoea, the endometrium is often atrophic. This atrophy is usually ascribable to inadequate hormone stimulation, which in turn is due to deficient ovarian endocrine function. Such a disturbance may be due to ovarian disease or secondary to disturbance of the endocrine function of the pituitary. Due to insufficient gonadotrophic stimulation from the anterior pituitary or deficient reactivity of the ovary, a graafian follicle fails to mature and there is absence of ovulation. The rise and fall in the oestrogen level may fail to occur. There is no progesterone and so the normal oestrogen—progesterone withdrawal from the involuting corpus luteum is absent, hence menstruation fails to occur.

In some cases amenorrhoea occurs even when ovarian function is normal and the endometrium receives normal stimulus. This occurs when the endometrium is incapable of responding adequately to the stimulus from ovarian hormones. This may be due either to anomaly of the uterus or due to diseased condition of the endometrium.

The therapeutic approach to the problem of amenorrhoea is depen-

pain in the lower abdomen and dysmenorrhoea of 4 months' duration.

Previous history. She started her periods at the age of fourteen. The periods were regular and moderate 3/29. She was married 4 years ago and had a full-term breech delivery 3 years ago. The female child is living. Four months after delivery she began to menstruate on alternate months. In February '53 she missed her period and in June '53 she consulted a doctor who diagnosed a pelvic tumour. The rat-test was done and found to be positive. Amenorrhoea continued till September '53 without any signs of pregnancy. In September she went to her doctor for fever and pain in the left leg and he gave her some medicine. Next day she had profuse bleeding which lasted for 8 days. From the next month she had regular periods 3 to 4/28 to 30 but always accompanied by severe pain. She was admitted on 10th March 1954. L.M.P. was 8 days previous.

Vaginal examination revealed cervix directed downwards and forwards. Uterus was small and deviated to the right. On the left side of the uterus was felt a tender firm mass, the size of an orange. Subserous fibroid. She was operated on 11-3-1954 under spinal anaesthesia.

Uterus with enlarged rudimentary

horn and haematosalpinx on the left side was plainly visible. There was no recto-vesical peritoneal fold. The size of the rudimentary horn was equal to that of the uterus. Its junction was clamped and it was excised. On incising it, a brownish dirty macerated material with foetal bones was discovered. After compressing the isthmus of the uterus and the left fallopian tube, saline was injected into the body to see whether it would leak through the connecting stump which was released from the previously applied clamp. No water leaked out showing that there was either no connection between the main uterine body and the accessory horn, or it had become obliterated.

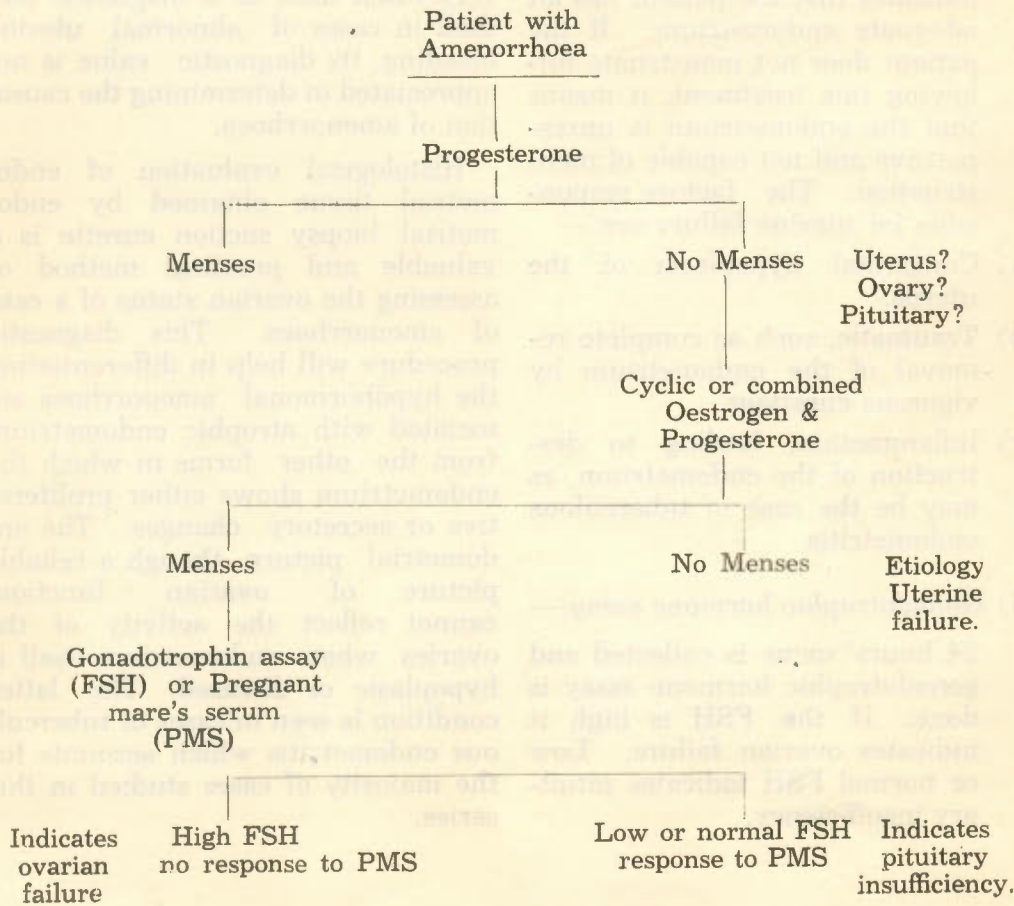
The stump was ligatured and the appendix was removed. She made an uneventful recovery.

Comment. She had one full-term normal delivery. Taking for granted that there was no connection between the well-developed accessory horn and the main uterus, the pregnancy in the horn must have occurred by external wandering of the fertilised ovum or the sperm. The accessory horn responded well by hypertrophy but a missed abortion took place, there being no outlet, and the well-formed foetus with bones underwent mummification.

dent on the cause of this menstrual disturbance. It is therefore important that a correct appraisal of the etiologic factor be made before any extensive therapy is instituted. Treatment of amenorrhoea in a number of cases is expensive and often ineffective. The facilities for laboratory tests for diagnosis of amenorrhoea are not always available, hence the clinician is tempted to treat the patient with hormone preparations, though often with inadequate dosage. The treatment in such cases is often given without adequate knowledge of the underlying pathology.

The procedure of identification of the organ responsible for amenorrhoea is based in principle on the methods used in qualitative chemistry for identifying an unknown compound. The patient may be subjected to various tests, on which positive and negative results are obtained. Herbert S. Kupperman and his colleagues from the departments of therapeutics and obstetrics and gynaecology, New York University Bellevue Medical Centre, New York, have suggested the following schematic diagram of the various diagnostic procedures applied to patients with amenorrhoea.

Fig. 1. Schematic diagram of the various diagnostic procedures applied to patients with amenorrhoea (Kupperman et al. Courtesy of Paul B. Hoeber, Inc).



(1) *The use of progesterone:—*

If menstruation occurs following administration of progesterone it is apparent that the amenorrhoea is not due to serious defect of pituitary, ovary or endometrium. It indicates that the patient must have adequate ovarian function to produce sufficient amount of oestrogen which primes the endometrium for progesterone to have its effect. If menstruation does not occur then the second test is done.

(2) *Cyclic or combined oestrogen and progesterone:—*

If menstruation does occur, it indicates that the patient has an adequate endometrium. If the patient does not menstruate following this treatment, it means that the endometrium is unresponsive and not capable of menstruation. The factors responsible for uterine failure are:—

- (a) Congenital hypoplasia of the uterus.
- (b) Traumatic, such as complete removal of the endometrium by vigorous curettage.
- (c) Inflammation, leading to destruction of the endometrium, as may be the case in tuberculous endometritis.

(3) *Gonadotrophic hormone assay:—*

24 hours' urine is collected and gonadotrophic hormone assay is done. If the FSH is high it indicates ovarian failure. Low or normal FSH indicates pituitary insufficiency.

(4) *Administration of potent gonadotrophins such as pregnant mare's serum:—*

This contains follicle stimulating hormone predominantly. The best guide to the effectiveness of PMS therapy is the changes in the vaginal smear. If there is no response to PMS, it is indicative of ovarian failure, whereas response to PMS indicates pituitary insufficiency, because PMS acts directly on the ovaries.

It is quite clear from this diagram that endometrial biopsy has not been used as a routine study in the diagnosis of amenorrhoea. Whereas endometrial biopsy or curettage is very often used as a diagnostic method in cases of abnormal uterine bleeding, its diagnostic value is not appreciated in determining the causation of amenorrhoea.

Histological evaluation of endometrial tissue obtained by endometrial biopsy suction curette is a valuable and practical method of assessing the ovarian status of a case of amenorrhoea. This diagnostic procedure will help in differentiating the hypohormonal amenorrhoea associated with atrophic endometrium from the other forms in which the endometrium shows either proliferative or secretory changes. The endometrial picture though a reliable picture of ovarian function, cannot reflect the activity of the ovaries when endometrium itself is hypoplastic or diseased. The latter condition is seen in cases of tuberculous endometritis which accounts for the majority of cases studied in this series.

During the past 22 months, all cases of sterility attending the gynaecological out-patient's department were referred to the sterility clinic for investigation and treatment. Practically all patients suffering from amenorrhoea in the childbearing period reported to this clinic. The symptom of amenorrhoea was associated with a desire to have children. Obviously these patients presumed that if amenorrhoea is treated, the chances of conception will be improved. Every case in the clinic has a routine endometrial biopsy done with the object of detecting evidence of ovulation. In the cases of amenorrhoea, the common physiological causes of the condition were ruled out by general physical and gynaecological examination. It is difficult to say when it is proper to make the diagnosis of amenorrhoea. If the menarche has not been instituted by the eighteenth year, the diagnosis of primary amenorrhoea is made. If cessation of menstruation has occurred for six months or longer in a woman who has menstruated before, the diagnosis of secondary amenorrhoea is made.

Endometrial biopsies have been done on 68 cases of amenorrhoea who reported for investigation and treatment of sterility. It is usually presumed that by far the larger proportion of cases of amenorrhoea in clinical practice are associated with relative or absolute ovarian failure resulting in atrophic endometrium. Such patients often receive hormone therapy without investigations into the pathologic cause of amenorrhoea. When studying the histology of the endometrium, a large proportion of

cases of amenorrhoea were found to be suffering from endometrial tuberculosis. This diagnosis could never have been established with the help of the other diagnostic tests mentioned above. The endometrial histology showed:—

1. Endometrium showing secretory phase in 3 cases (as in fig. 2).
2. Endometrium showing proliferative phase in 8 cases (as in fig. 3).
3. Atrophic endometrium in 7 cases (as in fig. 4).
4. Endometrium showing evidence of tuberculosis in 50 cases, with almost complete loss of normal endometrial structure, endometrium being replaced by tuberculous granulation tissue (as in fig. 5).

By the detailed study of the endometrial histology the conclusions drawn are:—

- (1) The endometrium showing secretory phase may be due to persistent corpus luteum. Spontaneous regression of the corpus luteum will result in menstruation. Failing this, laparotomy may be done and corpus luteum can be excised and menstruation established.
- (2) If the endometrium shows good oestrogenic effect it is probable that administration of adequate dosage of progesterone would result in menstruation.
- (3) In atrophic endometrium, the endometrial glands may be very small or almost absent. Such an endometrium is not

likely to respond to any hormone therapy.

- (4) The endometrium may be replaced by tuberculous granulation tissue and may be associated with partial or complete loss of endometrial structure. Epithelioid cells, lymphocytes, giant cells and caseation may be present. The detection of tubercle bacilli with Ziehl Neelson stain and growth of tubercle bacilli by culture of endometrial tissue confirms the diagnosis of tuberculous endometritis.

The patient with amenorrhoea can therefore be treated after the pathologic cause of amenorrhoea is diagnosed. Of great importance is the diagnosis of endometrial tuberculosis in 73% of cases, suffering from amenorrhoea during the childbearing period, who reported to the sterility clinic. It is gratifying to be able to report that 7 cases of endometrial tuberculosis suffering from amenorrhoea of 1½-4 years' duration have started regular menstruation after treatment with antituberculous drugs. They have been followed for one year after cessation of therapy and are having regular ovulatory menstrual cycles. Whether conception will occur in these cases, only a careful follow up for several years will give the answer.

Data are available on the study of endometrial histology of 1,816 cases of sterility. 68 cases had amenorrhoea, and of these 50, i.e. 73% of the patients with amenorrhoea, showed evidence of endometrial tuberculosis.

The remaining 18 had amenorrhoea due to causes other than destruction of endometrium by tuberculous endometritis. Thus, less than 1% of cases of sterility investigated have amenorrhoea due to non-tuberculous lesions. Hormone imbalance as an etiologic factor of amenorrhoea seems to play but a minor part. Endometrial biopsy therefore is a valuable diagnostic aid in the study of pathologic causes of amenorrhoea. This should be the first test done in the investigations into the causes of amenorrhoea. The pathologic cause in the majority of cases would be missed without the use of this single simple test. Endometrial biopsy is therefore as important in study of amenorrhoea as it is indispensable in the diagnosis of abnormal uterine bleeding.

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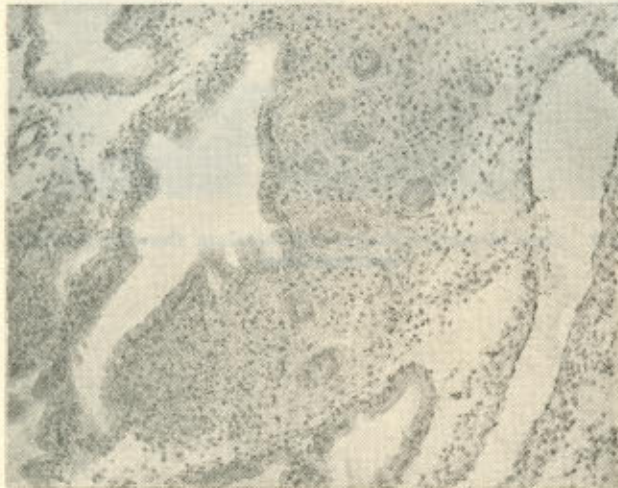


Fig. 2: Case of Amenorrhoea—Endometrium showing late Secretory Phase.

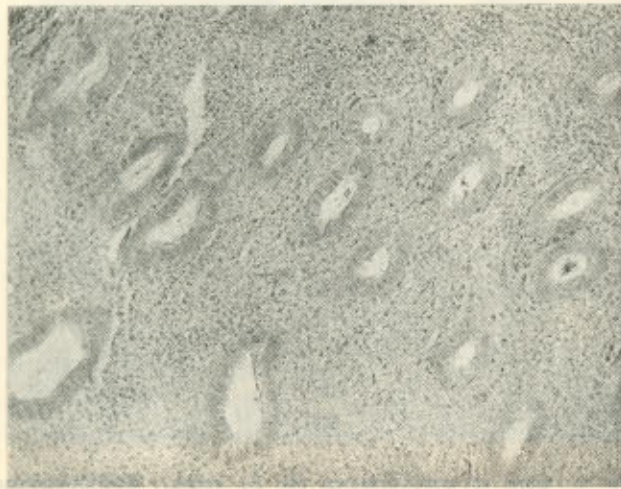


Fig. 3: Case of Amenorrhoea. Endometrium showing proliferative Phase.

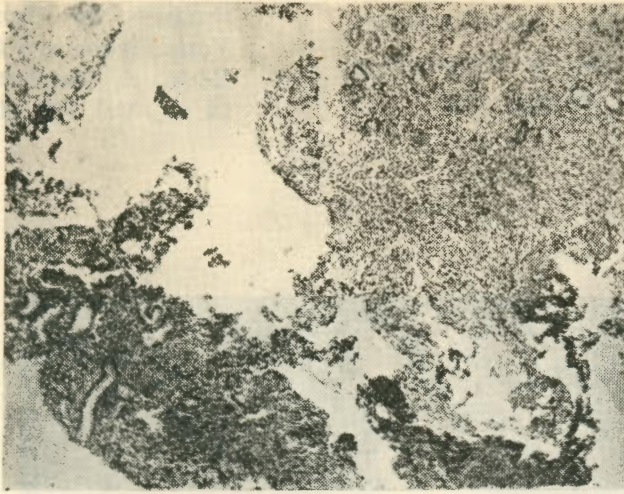


Fig. 4: Case of amenorrhoea-endometrium showing atrophic endometrium.

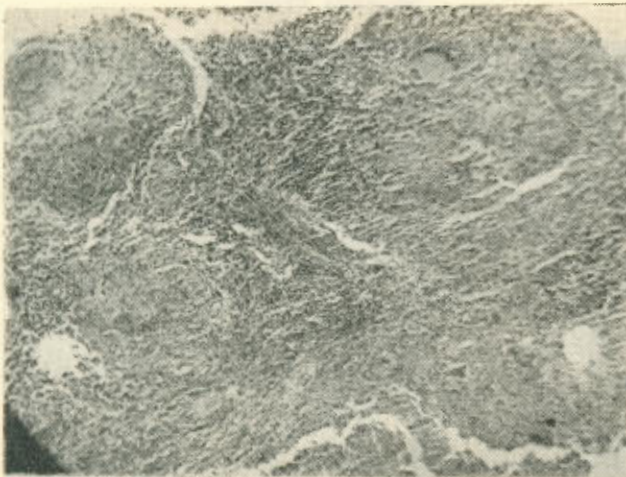


Fig. 5: Case of amenorrhoea for 2½ years. Endometrium showing tuberculous endometritis. Menstruation commenced 3 months after cessation of therapy with iso-nicotinic acid hydrazide.