ENDOCRINE ASPECTS OF JUVENILE METROPATHIA

by

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My previous speakers Prof. DeSa DeSouza and Prof. Purandare, from their extensive experience of many years, have borne out what Sutherland (1949) has said that this condition is indeed not frequently met with in patients under the age of 20 years. It is, therefore, obvious why many workers have not discussed the question of this disorder in young patients or have a large series of such cases investigated during one's own life time.

Although this condition is not frequently met with in patients under the age of 20 years, nobody in this audience would deny that this disorder, when it occurs, represents one of the most formidable problems in gynaecological practice. Before any rational basis for the therapeutic implications with the various hormones in the management of dysfunctional uterine bleeding is discussed, the knowledge of the physiological processes underlying the maturation of the hypothalamic-hypophyseal system and of the basic hormonal findings in cases of dysfunctional uterine bleeding is essential.

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The occurrence of the menarche, as you all know, represents a long step towards the attainment of sexual maturity which, according to the recent experimental data, is dependent upon the maturation of the hypothalamus (Harris & Jacobsohn 1952). The factors conditioning maturity of hypothalamus are poorly understood at present. However, it is presumed that under normal conditions, with the maturity of hypothalamus, there is secretion and release of both FSH and LH in optimal ratio, with the result that the initial, infrequent anovulatory menstrual cycles are changed to regular ovulatory cycles. The duration of "physiological" type of anovulatory menstruation during adolescence is not fixed but appears to range from 2-3 years after menarche. Occasionally, however, the physiological transference from anovulatory cycles to ovulatory ones, like any other transference, is not smooth, and in such instances, one of the ways in which this disturbance gets manifested is by abnormal uterine bleeding. Although the actual mechanism for such bleeding is anybody's guess today, the recent evidence by Brown and his coworkers indicates that such bleeding shows no correlation between the daily urinary oestrogen levels and the bleeding dates (Keller et al. 1959). Furthermore because there is no dramatic drop in the circulating

oestrogen level, complete desquamation of the endometrium fails to occur and therefore the bleeding is not self-limiting as it happens in a normal anovulatory menstrual period. This dysfunctional "flow" occurs when the endometrium is build up to a point beyond which the oestrogen level is unable to support its continued growth. The unopposed prolonged or excessive oestrogen is believed to be due to the dysfunction of the hypothalamic hypophyseal system. Thus we have achieved some insight into the nature of the disturbance and we hope, with the development of precise methods to quantify FSH and LH separately, more useful information in this respect would be collected for the normal physiological function of the ovary and for the altered ratio during dysfunction of the hypothalamic-hypophyseal system.

One other factor, viz. impairment of nutrition, may be pertinent by affecting the pituitary gonadotropic function (Johnston 1948). It is necessary to emphasise that the protein requirement of the puberal girls is about three times that of the adult and unless adequate intake is assured, gonadotropic secretion is bound to suffer. And finally the clinical experience of every day gives an insight into close relation between emotional system and menstrual disorders. It cannot be therefore overemphasised that any such patient is not wholly composed of endocrine glands and an obvious corollary therefore is that before any hormone therapy is thought of, one should try to estimate the possibility of a relation between the abnormal bleeding and the patient's exposure to malnutrition and all sorts of stressful situations leading to emotional disturbances. I am quite aware that I am now treading on the path which Dr. Vahiya should, and therefore will restrict my remarks to the processes related to the hormonal control of menstruation.

The usual question whether one should insist on the histological examination of the endometrium in every case of abnormal uterine bleeding belonging to this age group may be partly answered from the findings in Table 1. This presents the histological findings of the endometrium in Sutherland's 200 cases and in our 20 cases under the age of 20 years having abnormal uterine bleeding. Sutherland's series is perhaps the largest ever recorded and it represents the cases investigated during the last 10 years (Sutherland 1953).

TABLE 1

Endometrial Histology in Abnormal Uterine Bleeding (Age group under 20 years)

	Number of cases	Endometritis	Tuberculosis	Atrophy	Hyperplasia	Proliferative	Secretory
Sutherland (1953) ..	200	10	8 (4%)	4	31 (15.5%)	75 (37.5%)	72
Present series ..	20	—	2	—	4	14	—

It is evident here that the large majority of his cases viz., 73.5%, had

normal looking endometrium and more than 50% had anovulatory menstrual bleeding. It is interesting to mention that contrary to the common impression, only 15.5% of his cases had hyperplasic endometrium and 4% had tuberculosis of the endometrium. Our small series have comparable findings except that all our patients were having anovulatory cycles and the incidence of tuberculosis appears to be high. It is quite probable that with a large series, our figures for tuberculosis would come down and remain comparable to those of Sutherland's series. However, both these studies highlight many issues for diagnostic and therapeutic implications — one of these being the necessity for routine histological examination of the endometrium in every case of abnormal uterine bleeding of considerable duration. We preach and practice that it is absolutely essential to carry out the diagnostic procedure irrespective of the age or other considerations. Two of our 20 patients had histological evidence of tuberculous infection. It is necessary to re-emphasise that if this was not done, the unrecognised endometrial tuberculosis will end up in permanent amenorrhoea in due course of time. We believe that if the instruments used are small and if one is gentle, one can certainly obtain sufficient endometrial tissue without producing much damage. Such a policy also helps to examine these patients under anaesthesia to exclude local pathology of uterus or ovary — though rare in this age group.

Figure 1 shows the instruments we use for removal of sufficient endometrial tissue without dilating cervix

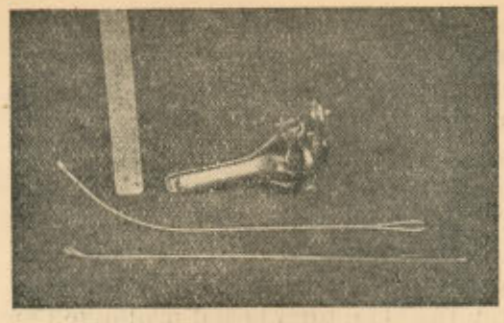

Fig. 1

in our young unmarried girls.

Once the organic lesion is excluded by pelvic examination and endometrial study, the theoretical basis for the hormonal therapy consists in the first instance of the knowledge that the pathological physiology hinges on the constant influence of solely oestrogenic hormone in absence of progesterone. Consequently, on sound physiological basis, this condition should be treated either by progesterone substitution, or by stimulation of the ovary to produce progesterone endogenously or by inhibition of oestrogen production or neutralisation of the oestrogen formed.

Secondly, successful treatment is dependent upon a correct appraisal of the degree of oestrogenic effect. Study of vaginal cytology in our hands, has been most helpful in this age group for quantitation of circulating oestrogen (Shah & Dave 1959). Elaborate investigations like hormone assays of blood and urine or thyroid function tests have little usefulness in clinical management of these patients.

The practical aspects of this problem are two — (1) emergency establishment of haemostasis, (2) establishment of regular cycles and eventually ovulation.

The treatment in our cases could be grouped under 2 series: (A) Constituting those treated before the development of potent oral progestational agents. (B) Those treated after oral progestational agents were made available to us. I may add here that the development of potent orally active progestational steroids recently introduced a new era in the hormonal treatment of dysfunctional uterine bleeding.

There are several different orally active progestational compounds available but we have experience with only two, viz. Norethynodrel and Ethynodiol Diacetate — popularly known as Enovid and SC11800 respectively. The latter compound is 5 times more potent than Enovid per mg. to mg. and is extremely well tolerated. Both these oral pills contain 0.1 mg. of added mestranol which is a potent oestrogen. These combinations are very good in ridding the uterus of a proliferative or hyperplasic endometrium and have found their most striking usefulness in dysfunctional uterine bleeding both for haemostasis as well as for establishment of regular cycles (Shah 1963).

Fig. 2 summarises the therapeutic regime used in the first series of our patients. For emergency establishment of haemostasis we have used testosterone propionate parenterally with consistently beneficial results. The total dosage usually employed is 150-250 mg. spread over 2-4 weeks. Once the bleeding is stopped, cyclic treatment with ethinyl oestradiol and parental administration of progesterone in oil is advised for 6 cycles. From the seventh cycle onwards pro-

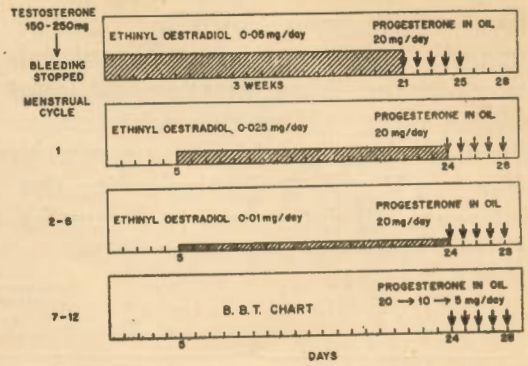

FIGURE 2

gesterone alone is administered during the last 5 days of the cycle for another six cycles when each patient is advised to maintain Basal Body Temperature chart. In this series, patients are followed for 12 months starting from the seventh cycle.

For haemostasis in the second series of our patients we have been using Enovid in 10 mg. doses twice or three times a day for a couple of days when bleeding invariably stops. After bleeding stops these compounds are given at reduced dosage and the treat-

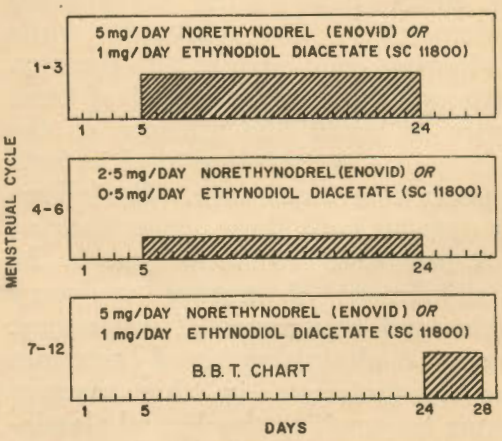

FIGURE 3

ment is continued for a total of 20 days. Withdrawal bleeding, unlike medical curettage with parenteral progesterone, is not profuse and lasts for 1-4 days. After this withdrawal bleeding cyclic treatment is given as shown in Figure 3. In this series, the follow-up till date is up to 9 months starting from the seventh cycle.

TABLE 2

Results of Treatment

Series	Therapy given	No. of patients	No. of patients with regular cycles	No. of patients with ovulatory cycles	No. of patients pregnant
A	Testosterone + cyclic oestrogen & progesterone	10	9	5	4
B	Oral progestational steroids	8	8	5	1
	Total	18	17	10*	5

* Eight married.

Table 2 summarises the results of treatment in our two series. Of the 20 cases, two having tuberculous endometritis are omitted while evaluating the results of therapy. Although the number in each of these series is small the efficacy of the therapeutic regime employed in both appears to be impressive. The follow-up data on both these series indicate that prognosis is good as regards the establishment of regular ovulatory cycles and occurrence of pregnancy. Repeated administration of oestrogen and progesterone in this manner seems to sensitize the hypothalamic-hypophyseal system leading to ovulation frequently. Once the therapy is stopped after several months of artificial menstrual periods, it is quite likely that occurrence of continued spontaneous cycles is probably due to a "maturing" effect on the central nervous system.

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