A STUDY OF THE ENDOMETRIUM AND CYTOHORMONAL PATTERN IN FUNCTIONAL UTERINE BLEEDING*

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Functional uterine bleeding is one of the commonest conditions met with in the gynaecological service of any hospital. On account of its doubtful aetiology, the literature on this vexed subject is voluminous. Yet published data in this country were comparatively few (Agarwal and Saxena, 1961; Upadhyay and Mishra, 1963) until recently, when following the symposium on functional uterine bleeding in 1963 a series of papers were published (J. Obst. Gynae. India, 1964). Little new light has been thrown on the pathogenesis of this condition and this aroused the interest of the present authors in attempting a detailed study of the endometrium and the ovary in so-called functional uterine bleeding. The present paper is a preliminary report describing the histology of the endometrium and vaginal cytology in 50 cases of functional uterine bleeding.

Material and Methods

The material consists of clinically diagnosed cases of functional bleeding admitted consecutively over a period of eight months in the gynaecological department of the S.S.K.M. Hospital, Calcutta. It includes cases with suspected pelvic pathology, but those with history of recent abortion, nonspecific and specific infection like pelvic tuberculosis or recent surgical interference such as endometrial biopsy have been excluded. Similarly, cases with history of hypo-or hyperthyroidism and blood dyscrasias, if any, have been excluded. Also the adolescent group of cases in whom hysterectomy was not performed have been left out. The clinical history of each case was carefully recorded in detail. Specimens were collected, preserved, processed and stained as described previously (Ghosh *et al*, 1965).

Results

Clinical features

Cases were divided into four groups according to age as shown in Table I.

TABLE I

Age distribution

Age group	Age in decades.	No. of cases
I	Upto 30 years.	2
II		
III		

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The youngest subject was 25 and the oldest was 55 years old. The highest incidence was in group III. Forty-three patients belonged to the reproductive phase of life, while 6 were premenopausal and 1 postmenopausal. Except two all were married and 4 of them were nulliparous. Menarche occurred between 11 and 16 years. Menstruation was more or less regular in only 19 cases. The date of the last menstrual period (LMP) was recorded whenever possible. Abortion or stillbirth occurred in 10 cases, more than 2 years previously in all instances. There were 2 cases each of primary infertility and sterility.

Curettage was done in 16 cases, cervical biopsy in 2, tubal ligation in 5, removal of polyps in 2, myomectomy in 1 and partial resection of ovary in 1 case. Apparently, none of these procedures could influence the course or character of the bleeding.

An analysis of the bleeding episodes showed the following characteristics:

		Cases
Pattern:	Menorrhagia	19
	Menometrorrhagia ..	11
	Irregular	17
	Continuous	3
Duration:	Less than 1 year ..	9
	1- 5 years	28
	6-10 years	10
	More than 10 years ..	3
Amount:	Excessive	20
	Profuse	25
	Moderate	5

Abnormalities of bleeding phase

Even when the cycle was compa- [illegible]rrhagia, va- [illegible]ration rhagia, bleeding was more irregular with shorter cycles. In irregular bleeding, all possible varieties of irregularity of frequency, duration and amount were observed. In continuous bleeding, the bleeding phase was the only phase met with.

Intermenstrual bleeding was present in 7 cases.

Two patients had diabetes for the last 10 and 18 years respectively which was controlled. Oestrogen and progesterone were given in 4 cases 2½-3 years before admission and androgen in 1 during stay in hospital. Moderate obesity was present in 3 cases (2 diabetic) and mild hirsutism in 1 case (biochemical findings within normal limits).

Psychological background was noncontributory.

Vaginal cytology

The cytohormonal pattern observed in the vaginal smears in the different age-groups is shown in Table II.

The mean maturation index in gr. I was 0-35.8-64.2; in gr. II 0.3-43.4-56.3; in gr. III 0.3-48.2-51.5 and in gr. IV 2.6-59.8-37.6. One case in gr. II with history of almost continuous bleeding for about 6 months prior to hospitalisation and another in gr. III with history of androgen therapy were excluded. The rightmost index i.e. the percentage of superficial cells showed a gradual progressive decline with the advance of age from 64.2 in gr. I to 37.6 in gr. IV, the range of variation being about 26. The percentage of intermediate cells showed a corresponding gradual rise from about 35 in gr. I to about 60 in gr. IV. The trend of variation in these two

TABLE II

State of endometrium and vaginal cytology in functional uterine bleeding.

Case No.	Age in yrs.	Days L.M.P.	Days bleeding	State of endometrium	% sup. cells.
25	28	33	x	Prolif	52.2
46	25	6	x	HNE	76.2
1	40	x	4	HNE	55.0
4	40	28	x	Prolif	50.2
6	40	20	x	HNE	39.4
10	35	14	x	HNE with stromal prolif. & few subnuclear vacuoles.	64.4
11	39	32	x	Secretory	22.4
13	36	29	x	,,	20.3
14	35	22	x	,,	24.5
18	39	27	x	,,	37.2
30	40	x	19	Cystic	77.0
31	40	9	x	HNE	75.8
32	38	x	35	Cystic	70.8
38	40	6	x	HNE	44.8
*43	40	x	180	,,	17.8
47	40	11	x	,,	46.8
58	40	23	x	Cystic	38.6
3	43	8	x	Prolif.	32.4
5	45	8	x	,,	45.2
7	44	x	25	Cystic	41.6
8	45	20	x	HNE with stromal prolif.	81.2
9	48	14	x	HNE	63.6
16	43	28	x	,,	34.6
17	41	x	25	Cystic	33.0
19	46	16	x	HNE stromal prolif. ..	73.0
20	50	90	x	,,	60.6
21	45	14	x	HNE	65.8
22	46	19	x	Prolif. with pseudodecidual change.	77.2
23	48	21	x	HNE	41.6
24	43	84	x	,,	68.6
27	43	18	x	Prolif.	46.0
28	50	x	28	Cystic	37.4
34	42	23	x	HNE	40.6
36	49	38	x	Prolif. with oedematous stroma	35.6
**41	47	27	x	HNE	8.8
50	42	24	x	,,	65.2
51	43	19	x	,,	66.6
52	48	x	30	,,	46.8
55	41	11	x	,,	28.0
56	42	x	48	Cystic	48.2
2	55	120	x	Atrophic	20.4
12	51	45	x	Prolif.	38.4
15	52	18	x	Pseudomalig.	53.4
33	54	19	x	HNE	27.8
35	51	24	x	,,	61.4
37	52	26	x	Cystic	54.4
40	53	x	19	Prolif.	21.2
42	51	90	x	HNE	54.8
49	52	120	x	Prolif.	11.0
54	54	55	x	HNE	30.6

* Almost continuous bleeding for about 6 months.

** Androgen therapy. HNE-hyperplastic non

cell types was thus parallel but inverse. The leftmost index, i.e. the percentage of parabasal cells was significant only in gr. IV. An interesting finding in this last group was that the rightmost index of 37.6 was rather higher for this age-group since Masukawa's (1960) figure was only 14.0 for the age-group 50-54. The general character of the smears was found to be usually clean in most of the cases.

The endometrium

All endometria were studied from hysterectomy specimens. Their histological appearances are summarised below:

Hyperplastic nonsecretory (HNE)	22
Cystic	8
HNE with stromal proliferation	4
Pseudomalignant	1
Proliferative	10
Secretory	4
Atrophic	1

It was observed that 35 cases exhibited hyperplasia of different grades and forms, while 10 were proliferative, 4 secretory and 1 atrophic. Table II shows that all categories of hyperplasia had fairly high maturation index except the cystic ones in gr. III. Out of 4 cases in this category, 2 were examined on the 25th. day and 1 each respectively on the 28th. and 48th. day of bleeding. This migh have influenced the vaginal cell population. All the other varieties of endometria showed fair correlation with their respective vaginal cytologies.

Associated pathology

Out of a total of 50 cases examined, organic lesions were detected in 33. Their distribution and endometrial patterns are given in Table III. It was seen that hyperplasia accounted for the majority of cases, only 10 being proliferative.

Discussion

In selecting cases for the present study, the presence of coexistent pelvic pathology was ignored since the controversy about the definition and scope of functional uterine bleeding has not been finally set at rest. According to Brewer and Jones (1948) it can occur irrespective of the presence or absence of any associated gross pelvic lesion. Comparing endometria of cases of functional uterine bleeding with those of 'organic' uterine bleeding, Sutherland (1957) concluded that the picture in the two groups was essentially similar. He remarked "it is difficult to be sure that associated gross pelvic lesion bears a causal relationship to the abnormal

TABLE III

Distribution of organic lesions and their endometrial patterns

Type of lesion	Number	Type of endometrium		
		HNE	Cystic	Prolif.
Adenomysis	15	5	5	5
Adenomyosis with fibroids	8	5	1	2
Fibroids	10	7	X	3
.. .. ..	33	17	6	10

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uterine bleeding, especially since these lesions are found in patients who have normal menses."

Functional uterine bleeding can occur from any type of endometrium, both normal and abnormal (Sutherland, 1957). In the present series, endometrium was found normal for the day of cycle in 10 cases (20%) and abnormal in 40 (80%). The percentage of normal endometrium appears to be too low, probably because the number of cases examined was small.

In categorising abnormal endometrium, one group was labelled as hyperplastic nonsecretory endometrium (HNE) according to the criteria laid down by Lloyd (1951). This type of nonsecretory endometrium was found in 44% of cases and constituted the largest single entity. Along with other types, hyperplasia was observed in 70% of cases. A perusal of some of the reports recently published in this country on the incidence of endometrial hyperplasia revealed that there could be a wide variation between one report and another e.g. 8.1% (Wagh & Swamy) and 61.9% (Kanakadurgamba & Rao). The present finding of 70% is near to that of the latter workers but disagrees with those of others. As is well-known, hyperplasia by itself is not responsible for bleeding, but bleeding is caused from such endometria by sudden fluctuation (drop) in the level of systemic oestrogen.

Of the 10 proliferative endometria, 5 were normal. Case no. 22 showed only patchy and incomplete secretory change on the 19th. day; similarly, the endometrium of case no. 27 remained proliferative on the 18th. day of the cycle. Whether the former was due to delayed and/or incomplete development of the ovarian cycle and the latter to 'late' ovulation (normal for this patient) or uniphasic cycle can be corroborated only by the study of the ovary in these cases. That will form the subject matter of a subsequent communication. The remaining 5 cases are apparently abnormal as these are either uniphasic (nos. 4, 25) or their cycles are grossly irregular nos. 12, 36, 40). Cases 4, 12 and 25 which showed a rather high maturation index could be included in the same group as HNE functionally though not morphologically.

A comparison of the status of each individual endometrium with the respective M.I. shows that 12 cases (nos. 6, 7, 16, 17, 23, 28, 33, 34, 54, 55, 56 & 58) have a relatively low M.I. In 4 cases (nos. 7, 17, 28 & 56) this may be, partly at least, explained by the state of prolonged bleeding but in the remaining 8 cases this is difficult to explain unless one accepts the postulate that during the bleeding phase the circulating oestrogen is at a comparatively low level and so unable to induce the necessary maturation changes in the vaginal epithelium. On the other hand, 3 cases (nos. 22, 25 and 27) show rather high M.I. without corresponding growth-effects on the endometria. It is possible that in these instances the endometria were relatively refractory to the usual hormonal stimulus.

The analysis of cases associated with organic pathology (fibroid and adenomyosis) revealed that there was hyperplasia of the endo[illegible] in 23 out of 33 [illegible] Chu[illegible]

thology in 11 out of 30 cases of functional bleeding undergoing hysterectomy. But, for a thorough and detailed histological examination, these would go undiagnosed and pass for functional bleeding. Joshi and Deshpande (1964) included enlarged uteri of 8-10 weeks' size which constituted about 30% of their cases. Among 79 cases subjected to hysterectomy, adenomyosis and fibroids were detected in 14.4% and 3.6% respectively. In the absence of histological examination, it is hard to believe that the rest of the enlarged uteri were all due to multiparity. Similarly, Wagh and Swamy (1964) found the incidence of adenomyosis and fibroids nearly 17% and 9% respectively in 101 cases of hysterectomy while Kanakadurgamba and Rao (1964) made no comments on their 18 cases of enlarged uteri. All these figures indicate that functional bleeding diagnosed clinically as well as with suitably timed endometrial biopsy always includes a significant number of cases with organic pathology. Removal of the uterus in all cases of functional bleeding is not warranted particularly in the younger group of patients. It is doubtful whether the simple presence of an intramural fibroid or an island of adenomyosis detected by such a drastic procedure can contribute significantly to the production of functional bleeding. Although fibroids may cause bleeding from the endometrium, it is the ovarian dysfunction in a large proportion of cases that is the responsible factor and this is suggested by the not infrequent existence of endometrial hyperplasia in myomatous uteri (Novak and Jones, 1961). Moreover, Beclere (1965) considers that uterine bleeding in association with a fibroid is also 'functional' since bleeding is not conditioned by the fibroid nodules and that both are independent consequences of the same oestrogenic hyperaction. Similarly, adenomyosis *per se* may cause menorrhagia on account of the increased amount of endometrium but is often due to the ovarian dysfunction so frequently associated. Moreover, the belief that adenomyosis is due to an endocrine dysfunction of the ovary has received considerable support, though experimental evidence is still incomplete (Novak and Woodruff, 1962). Marcus (1961) has suggested that in the interrelationship between adenomyosis, endometrial hyperplasia and endometrial adenocarcinoma, there was a common denominator which was probably hormonal. Hence, it seems more likely that the abnormal bleeding in the above 23 cases was 'hormonal' rather than 'organic'.

The cause of bleeding from the apparently normal endometria (5 proliferative, 4 secretory and 1 atrophic) remains obscure although Brewer and Jones (1948) and Jeffcoate (1955) thought that the fault lay with the corpus luteum in the cases associated with secretory endometrium and that in bleeding from the atrophic endometrium just enough oestrogen was produced to reach the critical level of bleeding but not enough to maintain endometrial growth. It is, therefore, intended to carry on further work at cellular level by the application of the newer techniques of histochemistry and cytochemistry in the hope of obtaining useful information for elu-

cidation of the cause of bleeding in these cases.

Summary and conclusions

Fifty cases of abnormal uterine bleeding were investigated. Histology of the endometrium and vaginal cytology demonstrated hyperplasia and moderately high M.I. in the majority of cases. The abnormal bleeding was considered to be dysfunctional in the majority. Organic pelvic lesions like fibroids and adenomyosis were probably responsible in the rest. Further study by more sophisticated methods are needed.

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