PAPERS AND ORIGINALS

Relations between bleeding pattern, endometrial histology, and oestrogen treatment in menopausal women

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Summary and conclusions

Vacuum curettage was performed on 348 women who had received various regimens of oestrogen treatment for an average of 9·7 months for climacteric symptoms. In 62 cases (18%) the specimens were unsatisfactory for histological assessment; among the remainder, however, they showed a normal endometrium in 257 cases (90%), cystic hyperplasia in 21 (7%), adenomatous hyperplasia in 7 (2%), and endometrial adenocarcinoma in one. Cyclical unopposed oral oestrogen treatment (98 cases) was associated with a 12% incidence of endometrial hyperplasia, but among those given an additional five-day course of progestogen in each cycle (37 cases) the incidence was only 8%. No case of hyperplasia occurred among 102 women taking regimens including 10 or 13 days of progestogen. Among women treated with subcutaneous oestradiol implants and monthly five-day courses of oral progestogen (50 cases) there was a 28% incidence of hyperplasia including the one case of carcinoma, though some of those with hyperplasia may not have taken the full course of progestogen. Regular withdrawal bleeding during treatment was associated with a lower incidence of endometrial hyperplasia (6%) than unscheduled breakthrough bleeding (28%), but the one patient with carcinoma had experienced regular bleeding only.

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The risk of developing endometrial carcinoma from oestrogen treatment may be reduced by avoiding the use of unopposed oestrogen regimens, the addition of more than five days' treatment with a progestogen, and recognising that a regular bleeding response to oestrogen is no guarantee of a healthy endometrium.

Introduction

The part played by oestrogen treatment in the development of endometrial adenocarcinoma remains uncertain despite several retrospective studies[1-3] and close scrutiny of the findings by later workers.[4-6] This is of great importance for the many menopausal women being given oestrogens, but final clarification may not be possible until larger, better controlled, and possibly prospective studies are completed; these will necessarily be of long duration.

We therefore report, as part of a continuing prospective study, our observations on the effect of various regimens of hormone treatment on the endometrium of menopausal women and the incidence of abnormal endometrial histology, with particular reference to differences in their bleeding patterns.

Patients and methods

The 348 women studied had been receiving oestrogen treatment for 4-42 months (mean 9·7 months) at the Menopause Research Clinic, the Birmingham and Midland Hospital for Women; and, under the care of one of us (JWWS), at King's College and Dulwich hospitals, London. Treatment consisted of one of the following regimens.

Cyclical oral oestrogen for three weeks out of four—(*a*) Piperazine oestrone sulphate 3 mg (Harmogen); (*b*) conjugated equine oestrogens 0·625 or 1·25 mg (Premarin); (*c*) oestradiol valerate 2 mg (Progynova).

Continuous oral oestrogen (as above) with additional oral progestogen for five days each month, either (*a*) norethisterone *BP* 5 mg (Primolut N) or (*b*) ethynodiol diacetate 0·5 mg (Femulen) or (*c*) medroxyprogesterone acetate 10 mg (Provera).

Oral sequential oestrogen-progestogen—(*a*) Oestradiol valerate 2 mg alone for 11 days, then with addition of DL-norgestrel 0·5 mg for 10 days, followed by seven tablet-free days (Cyclo-Progynova); (*b*) mestranol in graded doses of 12·5-50 μg for 15 days, then with addition of norethisterone *BP* 0·75-1·5 mg for 13 days (Menophase).

Subcutaneous implant—Oestradiol *BPC* 50 mg with or without testosterone *BP* 100 mg (Organon Laboratories Ltd) but with additional oral norethisterone 5 mg for five consecutive days each month.

Endometrial specimens were obtained by vacuum aspiration curettage using either the Rolon curette (Rocket Ltd) or the Vabra aspirator (Lewis Laboratories Ltd). Curettage was attempted when possible before treatment started but was done routinely after six months and thereafter yearly while treatment was continued. Curettage was performed during the last week of a cycle, before any withdrawal bleeding.

All the histology was reported on by a single observer (TW-E). For ease of presentation the histological findings are classified as (*a*) normal—that is, indistinguishable from normal proliferative or secretory endometrium, menstrual or atrophic; (*b*) abnormal—namely, cystic hyperplasia, adenomatous or atypical hyperplasia of whatever grade, or frank adenocarcinoma; or (*c*) unsatisfactory—that is, insufficient material for examination.

Particular note was made of any bleeding during treatment. Withdrawal bleeding starting either during a tablet-free week or after the completion of a course of progestogen was classed as "scheduled" bleeding, whereas bleeding that started at any other time was classed as "unscheduled" bleeding.

Results

Table I summarises the results of curettage in all the patients according to treatment, bleeding, and histological findings. Most of the women (73·6%) received either Premarin (with or without additional progestogen) or Menophase or implant. For further analysis we placed the patients into three broad treatment groups (table II)—namely, oral oestrogen alone; oral oestrogen plus oral progestogen, given as either five-day courses or for the 13 or 10 days provided in the sequential preparations Menophase and Cyclo-Progynova; and implants.

Bleeding (table III) was experienced by all 59 women in the implant group and in all but one of the 151 who had oral oestrogen and progestogen; in these groups 39 (66%) and 145 (96%) respectively had scheduled bleeding. Thirty-three women did not have bleeding; of these, 32 were in the group receiving oral oestrogen alone and constituted 23% of all the women in that group.

Vacuum curettage failed to produce a specimen suitable for histological assessment in 62 cases (18%). In some this was due to technical difficulties, but in others failure probably reflected the small amount of endometrium present, either because it had been little stimulated or because there had been recent breakdown or regeneration, particularly when unscheduled bleeding was being investigated. In a pilot study in which we looked into the possibility of serial examination before and during treatment, worthwhile specimens were obtained before treatment from only 7 (12%) out of 57 women. (This agrees with the findings of a much larger series,[7] in which satisfactory specimens were obtained by formal curettage from only 13% of 1521 post-menopausal women.) The success rate among the treated women varied with both the bleeding pattern and treatment: specimens were obtained from only 13 of the 33 who had no bleeding, but from 220 of the 250 with scheduled withdrawal bleeding and 53 of the 65 with unscheduled bleeds; in the treatment groups curettings were obtained from 98 (71%) of the women given oral oestrogen alone, 50 (85%) treated with implants, and 138 (91%) given oestrogen and progestogen.

Tables II and IV exclude the women whose specimens were unsuitable for histological assessment and give the results in the remaining 286. Among these the highest proportion with abnormal histology was found in the implant group (28%) and the lowest in the group given oral oestrogen and progestogen (2%). Those given oral oestrogen alone occupied an intermediate position (12%). Although in this last group oestrogenic stimulation was intermittent, 10 (10%) of the women's specimens showed the pattern of cystic hyperplasia; somewhat surprisingly the proportion in the implant group was twice this (20%; 10 cases), even though most of these women had taken the progestogen that had been prescribed.

TABLE II—*Summary of incidences of normal and abnormal endometrial histology among the menopausal women receiving oestrogens. (Women with specimens unsatisfactory for histological assessment excluded)*

	Total No of patients	No with normal histology	No with abnormal histology			
			CHE	AHE	CA	Total
Unopposed oral oestrogen	98	86	10	2		12 (12%)
Oral oestrogen + progestogen	138	135	1	2		3 (2%)
Implant + progestogen	50	36	10	3	1	14 (28%)
Total	286	257	21	7	1	29 (10%)

CHE = Cystic hyperplasia. AHE Adenomatous hyperplasia. CA = Adenocarcinoma.

TABLE III—*Bleeding patterns and oestrogen treatment in all 348 menopausal women studied*

	Total No of patients	No bleeding		Scheduled bleeding		Unscheduled bleeding	
		No	%	No	%	No	%
Unopposed oral oestrogen	138	32	23	66	48	40	29
Oral oestrogen progestogen	151	1	0·7	145	96	5	3·3
Implant progestogen	59			39	66	20	34

Table IV gives the relation between the bleeding pattern and histological findings. Only 13 of the 33 women in the no-bleeding group produced satisfactory specimens, but all of these were normal. The proportion with abnormal histology was highest (28%) among the women with unscheduled bleeding, though among those with scheduled bleeding the proportion was still 6%, which included the one case of carcinoma.

TABLE IV—*Summary of bleeding patterns and endometrial histology in the menopausal women. (Women with specimens unsatisfactory for histological assessment excluded)*

	Total No of patients	Normal histology		Abnormal histology	
		No	%	No	%
No bleeding	13	13	100		
Scheduled bleeding	220	206	94	14	6
Unscheduled bleeding	53	38	72	15	28

TABLE I—*Bleeding pattern and endometrial histology in 348 menopausal women receiving oestrogen*

	No bleeding					Scheduled bleeding					Unscheduled bleeding					Total
	N	U	CHE	AHE	CA	N	U	CHE	AHE	CA	N	U	CHE	AHE	CA	
Harmogen 3 mg	4	4				4		1				1				14
Premarin 0·625 mg		4				5	3				4	1	1			18
Premarin 1·25 mg	7	6				38	7	3			20	7	3	1		92
Progynova 2 mg	2	5				2	1	2				1		1		14
Harmogen 3 mg + progestogen						2										2
Premarin 1·25 mg + progestogen		1				26	8	1	1		2			1		40
Progynova 2 mg + progestogen						3										3
Cyclo-Progynova						10										10
Menophase						90	4				2					96
Implant + progestogen						26	7	3	2	1	10	2	7	1		59
Total	13	20				206	30	10	3	1	38	12	11	4		348

N = Normal histology. U = Unsatisfactory for histological assessment. CHE = Cystic hyperplasia. AHE = Adenomatous hyperplasia. CA = Adenocarcinoma.

Discussion

The part played by oestrogens is the question of greatest practical importance among the many remaining unanswered about the aetiology of endometrial adenocarcinoma. That such hormones cause cystic hyperplasia is incontrovertible, so that the simple hyperplasias can virtually be defined as the endometrial states resulting from prolonged oestrogenic stimulation, but the relation between cystic hyperplasia and adenocarcinoma is not understood.

Although steady oestrogenic stimulation plays a part in the genesis of some of the other endometrial lesions classified as hyperplasia, their investigation is hampered by a lack of agreed definition for the histological terms used and the subjective nature of their diagnosis. Without doubt some carcinomas develop from endometria in which glandular growth exceeds stromal—that is, from adenomatous hyperplasias—particularly when there is epithelial "atypia," in the severe or atypical forms, but what proportion do so remains unknown. Furthermore, it is difficult to find objective criteria for deciding when a complex hyperplasia has passed the point at which it will regress when any known cause is removed or when it can be modified by other stimuli such as progestogens.

Cyclical unopposed oral oestrogen, usually with a tablet-free week, is the most widely prescribed treatment of climacteric symptoms. It has been assumed to be safe because it allows the stimulated tissue either to regress or to break down and be shed, so avoiding a cumulative effect of oestrogen. These assumptions, however, were not supported in an earlier report of ours[8] and are strongly contradicted by our present results.

For the pattern of cystic hyperplasia to develop, oestrogen stimulation must be continued for many weeks or some months, and we find that 10% of women given cyclical oral oestrogen have this pattern after a few months, though higher incidences have been reported with longer durations of treatment.[9] Although the relation between cystic hyperplasia and carcinoma is uncertain, at least the former lesion indicates prolonged oestrogenic activity, and it seems wise, while doubt remains about the long-term importance of such stimulation, not to use regimens that lead to its occurrence.

In contrast, when oral progestogen had been added to oral oestrogen only one out of 138 women had this pattern, and four patients who had cystic or mild adenomatous hyperplasia of the endometrium during unopposed oestrogen treatment were found to have normal endometrial patterns after two months of Menophase treatment.

An even higher incidence of cystic hyperplasia was found in patients with implants than among those given unopposed oral oestrogen, even though they had been prescribed additional oral progestogen. This, however, suggests that a five-day course of norethisterone 5 mg is insufficient to modify the endometrium after stimulation by sustained circulating oestrogen concentrations produced by implanted oestradiol.[10]

Adding a course of progestogen to oestrogen treatment has been advocated for many years[5 6 11-13] but at present it is incorporated in about only 6% of prescriptions for menopausal oestrogen treatment in the United Kingdom.[11] Our findings show the value of additional progestogen and that it is probably the duration rather than the total dosage of progestogen that is important in producing a protective effect on the endometrium.[15 16] Those women who received a total of 25 mg norethisterone over five days in addition to either oral or implanted oestrogen were not so well protected from hyperplasia as the women given a total of 15 mg norethisterone over 13 days from Menophase treatment.

For most menopausal women receiving hormone treatment vacuum curettage is not readily available, so it would be reassuring to be able to exclude endometrial abnormalities by clinical findings alone. While the proportion of patients with abnormal histological findings was, as expected, greatest among those with unscheduled or breakthrough bleeding (28% of all those from whom adequate specimens were obtained), 6% of specimens from those with scheduled bleeding were also abnormal. Only a few of those with such a bleeding pattern who were having combined oral progestogen and oestrogen had lesions (1·5%), but the proportion rose to 12% among those having unopposed cyclical oestrogen, and to 18% among those with implants. Clearly the pattern of bleeding does not exclude abnormality, and the one case of carcinoma was associated with regular scheduled bleeding.

We believe that already the results of this study have important implications for the routine management of women with climacteric symptoms and that the potential risk of endometrial carcinoma from oestrogen treatment may be reduced by wider adoption of the following measures: (1) avoiding the use of unopposed oestrogen treatment; (2) adding more than five days and probably at least 10-13 days of a progestogen; (3) regular endometrial curettage of patients who are not receiving adequate additional progestogen; and (4) recognising that a regular bleeding response to oestrogen treatment provides no guarantee of a healthy endometrium.

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References

1 Smith, D C, *et al*, *New England Journal of Medicine*, 1975, **293,** 1164.
2 Ziel, H, and Finkle, W, *New England Journal of Medicine*, 1975, **293,** 1167.
3 Mack, T M, *et al*, *New England Journal of Medicine*, 1976, **294,** 1262.
4 Studd, J W W, *British Medical Journal*, 1976, **1,** 1144.
5 Greenblatt, R B, in *The Menopause*, ed R J Beard, p 247. Lancaster, MTP, 1976.
6 Lauritzen, Ch, *Clinics in Obstetrics and Gynaecology*, 1977, **4,** 145.
7 McBride, J M, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1954, **61,** 691.
8 Sturdee, D W, *et al*, in *Endometrial Cancer*, ed M G Brush, R J B King, and R W Taylor. In press.
9 Whitehead, M I, *et al*, *Acta Obstetricia et Gynecologica Scandinavica*, 1977, suppl No 65, p 91.
10 Hunter, D J S, in *The Menopause*, ed R J Beard, p 203. Lancaster, MTP, 1976.
11 Gambrell, R D, jun, *Journal of the American Geriatric Society*, 1974, **22,** 337.
12 Wilson, R A, *Journal of the American Medical Association*, 1962, **182,** 327.
13 Kistner, R W, *Obstetrics and Gynecology*, 1976, **48,** 479.
14 Bye, P, *Postgraduate Medical Journal*. In press.
15 Delforge, J P, and Ferin, J, *Contraception*, 1970, **1,** 57.
16 Vanderick, G, *et al*, *Contraception*, 1975, **12,** 655.

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