# ENDOMETRIAL BIOPSIES IN WOMEN ON ORAL CONTRACEPTIVES

by

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*Introduction*

The endometrium is our most sensitive and easily available indicator for judging the levels and proportions of the sex hormones in the blood. The histological changes found in the endometrium after use of contraceptive agents are informative for many reasons. On the one hand, the changes give us unique insight into how normal and abnormal endometrium react to hormones; on the other hand, the changes show us what the limits of these reactions are. In healthy women the endometrium responds to exogenous hormonal therapy by very definite histological changes. We were interested to see whether the endometrium in the later half of the cycle differs in any way with the duration of O.C. Pills and the type of change the endometrium undergoes in the first and second part of the so called luteal phase in these women.

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*Material and Methods*

This is a prospective study of the endometrial morphology obtained by biopsy from the women on combination type of pills. The duration of pills varied from a few months to 8 years. A total of 201 biopsies were collected; however, in 9 cases the report was not available. Thus 192 biopsies were studied. Out of these, 187 were done in the later half of the cycle i.e. from the 16th day onwards upto the 37th day but before the patient had her menstrual period. Biopsies on the 16th to the 22nd day of the cycle and those taken from the 22nd to 37th day of the cycle (1st and 2nd half of the luteal phase), were further analysed. Five more biopsies were studied in the proliferative phase of the cycle.

*Results*

Table I indicates the morphology of the endometrial glands in women on O.C. according to the duration of the pills. The biopsy was taken from the 16th to 22nd day of the cycle. A total of 55 biopsies were studied.

It can be seen that in 20 of the cases (36.3%) the endometrium was in the proliferative phase, whereas in 19 women (34.5%) the endometrium was in the secretory phase and in 13 cases (23.6%) the endometrium was in the mixed phase.

TABLE I

*Endometrial Glands in Relation to the Duration of Oral Contraceptives 16th to 22nd Day*

| Duration of Pills | Total Cases | Secretory Phase | | | | | |
|---|---|---|---|---|---|---|---|
| | | Proliferative | Mild | Moderate | Good | Mixed | No material |
| Upto 2 years | 37 | 15 | 7 | 5 | 1 | 9 | Nil |
| 2 to 5 years | 13* | 5 | 2 | 2 | Nil | 3 | 1 |
| More than 5 years | 4 | Nil | 2 | Nil | Nil | 1 | 1 |

* The fourteenth patient in this series had products of conception.

In the remaining 3 cases, the endometrium was probably very atrophic in 2 and 1 patient showed the products of gestation in her biopsy slide. There was no correlation between the duration of O.C. and endometrial glandular morphology.

Table II shows the morphology of the endometrial stroma in these patients.

Table III indicates the endometrial morphology in women on O.C. when the biopsy was collected in the second half of the luteal phase i.e. between 23rd to 37th day of the cycle but before the onset of menstruation. Table IV reveals the morphology of the endometrial stroma in the same women. It is seen that among the

TABLE II

*Stroma in Relation to the Duration of Oral Contraceptives 16th to 22nd Day*

| Duration of Pills | Total Cases | Secretory Phase | | | | | |
|---|---|---|---|---|---|---|---|
| | | Proliferative | Mild | Moderate | Good | Mixed | No material |
| Upto 2 years | 37 | 9 | 0 | 6 | 22 | Nil | Nil |
| 2-5 years | 13* | 4 | Nil | 2 | 5 | 1 | 1 |
| More than 5 years | 4 | Nil | Nil | Nil | 2 | 1 | 1 |

* The fourteenth patient in this series had products of conception.

In 37 women or 67.2%, the stroma was in secretory phase as against 34% of women having the endometrial glands in the secretory phase. In 23% of the cases the stroma was in the proliferative phase and in only 3.6% the stroma was in the mixed phase as against 23.6% of the women with the endometrial glands in the mixed phase. Again there is not much co-relation between the duration of cycle and the stromal picture.

133 cases studied, in only 10% biopsies the glands were in the proliferative phase. In other 45 biopsies (33%), the endometrial glands were in the mixed phase. In 61 biopsies (46%) secretory phase was seen. On the other hand, the stromal morphology reveals that the proliferative phase was present in 6% only and the secretory phase in 80% and the mixed phase was seen in only 3% as against 33% showing the glands in the mixed

TABLE III

*Endometrial Glands in Relation to the Duration of Oral Contraceptives*
*23rd to 37th Day*

| Duration of Pills | Total Cases | Secretory Phase | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Proliferative | Mild | Moderate | Good | Mixed | No Material | Atrophic |
| Upto 2 years | 92 | 7 | 22 | 20 | 4 | 34 | 3 | 2 |
| 2 to 5 years | 28 | 4 | 3 | 5 | 3 | 9 | 3 | 1 |
| More than 5 years | 13 | 2 | 2 | 2 | Nil | 2 | 2 | 3 |

TABLE IV

*Stroma in Relation to the Duration of Oral Contraceptives*
*23rd to 37th Day*

| Duration of Pills | Total Cases | Secretory Phase | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Proliferative | Mild | Moderate | Good | Mixed | No material | Atrophic |
| Upto 2 years | 92 | 4 | 3 | 28 | 48 | 4 | 3 | 2 |
| 2 to 5 years | 28 | 2 | 1 | 7 | 14 | Nil | 3 | 1 |
| More than 5 years | 13 | 2 | 1 | 1 | 4 | Nil | 2 | 3 |

phase. The endometrial picture does not differ according to the duration of O.C. but atrophic endometrium is more common in women on O.C. for more than 2 years.

Five more biopsies were studied in the first half of the menstrual cycle. Four out of these 5 were done on women on O.C. upto 2 years. The endometrial glands were proliferative in 2 cases, secretory in 2 cases, mixed in 1 and no material was obtained in 1 of the biopsy.

Table V reveals the dissociation between the endometrial glands and the endometrial stroma in 86 biopsies. In other 101 cases there was a co-relation between the glandular and the stromal picture. The dissociation was seen in 40% and 35% of biopsies taken from women on O.C. for less than 2 years, between 2 to 5 years and more than 5 years respectively. The commonest type of dissociation was when the glands were in mild or moderate secretory phase or in mixed phase, the stroma was in good secretory phase. There is no co-relation between the duration of O.C. or the phase in which the biopsy is taken and the type of dissociation.

Among all these biopsies, 7 women were complaining of scanty menstruation after starting O.C. and in 6 of them the stroma was in good secretory phase and the glands were in the mixed phase in 4 biopsies, mild to moderate secretory phase in 2 biopsies. Thus there was no definite co-relation with the menstrual history. Only one patient had continuous vaginal bleeding prior to biopsy and the

TABLE V

*Dissociation between Glands and Stroma*

| Type of Dissociation | | Duration of O.C. | | | | | |
|---|---|---|---|---|---|---|---|
| Glands | Stroma | Up to 2 Yrs. | | 2-5 Yrs. | | Above 5 Yrs. | |
| | | 16-22 | 23-32 | 16-22 | 23-32 | 16-22 | 23-32 |
| + | +++ or ++++ | 4 | 10 | 2 | 2 | 1 | 1 |
| ++ | ++++ | Nil | 2 | Nil | Nil | Nil | Nil |
| — | +++ | 6 | 1 | 1 | 1 | Nil | Nil |
| — | ± | Nil | 1 | Nil | Nil | Nil | Nil |
| ± | ++ or +++ | 8 | 31 | 2 | 7 | 1 | 1 |
| Others | | — | — | — | 2 | 1 | 1 |
| Total | 36 | 18 | 45 | 5 | 12 | 3 | 3 |

Note: + Mild, ++ Mod, +++ Good } Secretory change—Proliferative phase

Others include 2 cases of atrophic glands with Stroma compatible with good secretory activity and 2 cases of glands in secretory phase with mixed stromal reaction.

endometrium was in good secretory phase.

*Discussion*

Hissaw has expressed that endometrium has a memory like an elephant that is it never forgets previous hormone therapy and reacts later accordingly (quoted by Dallenbach-Helweg).

With almost all combination preparations the proliferative phase of the first few cycles is characteristically shortened. Failure of glands and stroma to develop completely, premature appearance of persistently deficient secretory changes in the glands and stroma and remarkable intermingling is common. This is due to premature interruption of oestrogen stimulation by gestogen inducing early arrest of growth and differentiation of the glandular epithelium.

According to Maqueo *et al* (1970) the effect of combination pills on endometrium is gradual change from early secretory to irregular secretory to suppressed appearance.

The spotty oedema of the endometrial stroma is striking. The ratio of glands and stroma is shifted in favour of the stroma. Marked decidual changes of stroma is striking (Song *et al*, 1970; Maqueo *et al*, 1963). Shedding of these decidual casts can give rise to break-through bleeding.

Accurate dating of the endometrium is impossible (Dallenbach-Helweg, 1975). The prolonged use of contraceptive agents results in further histological changes. The abortive secretory change gradually subsides from cycle to cycle and finally disappears (Azzopardi and Zayid, 1967). The endometrium atrophies with its sparse and tiny glands. It is indistinguishable from that of a non-treated castrated woman (Sheffield *et al*, 1969; Charles, 1964). The stroma becomes poor in cells consisting primarily of collagenous fibres. A protracted breakthrough bleeding may supervene in these atrophic endometria probably from the walls of blood vessels.

According to Pincus *et al* (1958) no distinction could be made between endometrium from short term and long term treated patients.

Atypical endometrial hyperplasia associated with contraceptive pills has been reported with increasing frequency in recent years (Song *et al*, 1970). They also stress the importance of different response in different individuals; the multi potential stroma reacting in a variety of ways to different stimuli.

When progesterone effect predominates continuosly the action of oestrogen is persistently blocked and the endometria eventually undergo irreversible atrophy. If oestrogen predominates (those of the patient + supplied by contraceptives) then the endometrium will proliferate, unopposed. Glandular proliferation also develops when endometrial sensitivity to oestrogen only has persisted (Dallenbach-Helweg, 1975). Apart from sequential agents such glandular proliferation occurs after metabolic conversion of gestogens into compounds with oestrogenic action (Charles, 1964; Goldfarb). Atypical and precancerous hyperplasia of the endometrial glands with papillary proliferation is described after long term treatment with lyndiol (Schmidt). This explains the proliferative phase of the endometrium in 17% of the biopsies in this series. Similarly the predominance of gestogenic component also results in a pseudosarcomatous appearance of the stroma. More frequently a nodular stromal hyperplasia may be found in patients on O.C.

Maxwell (1975) divides the response of contraception according to whether the

cycles were ovulatory or anovulatory. Ovulatory cycles with O.C. were difficult to distinguish from non-treated cycles on biopsy. However, early secretory change and more extensive decidua like response were characteristic. In anovulatory patients the endometrial picture is primarily dependent on the aetiology of the interruption of hypothalamo-pituitary ovarian function and overall pattern was that of endometrial suppression and focal patchy predecidual reaction.

Ober (1966) has summed up the effects of combined pills as:

(i) Hyperinvoluted glands
(ii) Prominent decidual reaction (inert stroma)
(iii) Suppressed arterioles (also reported by Maxwell and Dallenbach-Helweg, 1975).
(iv) Dilated venules.

According to him the inhibition of spiral arterioles is the common denominator in all progestogen-oestrogen regimen. He also emphasises that the glandular change with combination pills is an indirect effect, whereas its role in the development of decidual like change is the direct effect of these pills.

*Summary*

1. One hundred and ninety two biopsies were studied from women on combination type of Oral Contraceptive Pills.

2. The proliferative phase of the endometrium in 17% of the biopsies in the second half of the cycle is explained.

3. A dissociation between the glandular and stromal morphology was found in 45% of endometrial biopsies.

4. No consistent change was found in women complaining of hypomenorrhoea after the usage of Oral Contraceptives.

5. There was no definite co-relation between the endometrial picture and the day of the biopsy in relation to the cycle or to the duration of Oral Contraceptive Pills.

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