OVARIAN CHANGES DURING AND AFTER LONG TERM STEROID CONTRACEPTIVE THERAPY

by

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It is customary nowadays to see pill users with long history of three or more years continuous therapy and to be confronted with so many important and yet not definitely answered questions such as :

1. Does this continuous therapy produce any dilitereous effect on future ovarian function ?

2. Must we discontinue therapy every now and then to allow resumption of normal ovarian activity ?

3. Is it safe to give long term oral contraception to newly married women ?

4. If any changes do occur after therapy, is it reversible ?

5. Has oral contraceptive therapy got any place in the treatment of sterility, i. e. through rebound ovulation ?

Studying ovarian histopathology during and after therapy will definitely throw some light and pave the way to a better and acceptable answers to such questions.

MATERIAL AND METHOD

Ovarian wedge biopsies were taken from five patients undergoing a laparatomy for tubal sterilization. Their ages ranged between 30 to 37 years and their parity was higher than five.

— One case was under Lyndiol 2.5 (2.5 lynestrenol + 0.075 mestranol) for 3 years.

— One case was under Gynanovlar 21 (3 mg. norethisterone acetate + 0.05 mg. ethinyl estradiol) for 1 year.

— One case was uder Deladroxate monthly injections. (150 mg. 16, a 17 a dihydroxyprogesterone acetophonid + 10 mgm. estradiol enanthate) for 1 year.

— One case was under Lyndiol 2.5 for 5 years and therapy stopped 2 months before operation.

— One post-cessation case for 5 months. Rheumatic heart, pregnant 3 months, to whom therapeutic abortion was performed.

Endometrial biopsy taken at the same time was sectioned and stained with haematoxilin and eosin. (H. E) Serial ovarian sections were stained with H. E. and Van Gieson Stain.

For comparative purposes two ovarian biopsies taken during ceasarian section from normal full term pregnancies, and one case of Stein Leventhal ovaries were included in the study.

RESULTS

Our results are presented in Table 1. and figuers 1 to 6. The results show the following points :

1. Naked eye picture : Ovaries were pale grey yellow puckered and showed cystic follicles in 3 cases, not more than 1 cm. in diameter.

2. The process of follicular development and maturation has proceeded normally till the stage of follicular maturation. Only in case No. 1 under lyndiol was there evidence of absence of such follicles in the specimen examined.

3. There was evidence of thickening of the tunica albugenia more than that observed in full term pregnancy ovaries but less marked than in Stein-Leventhal ovaries.

4. Cystic follicles were present in cases 1 & 2 under pills.

5. Evidence of complete regression of changes in case No. 5 after five months and of incomplete regression in case No. 4.

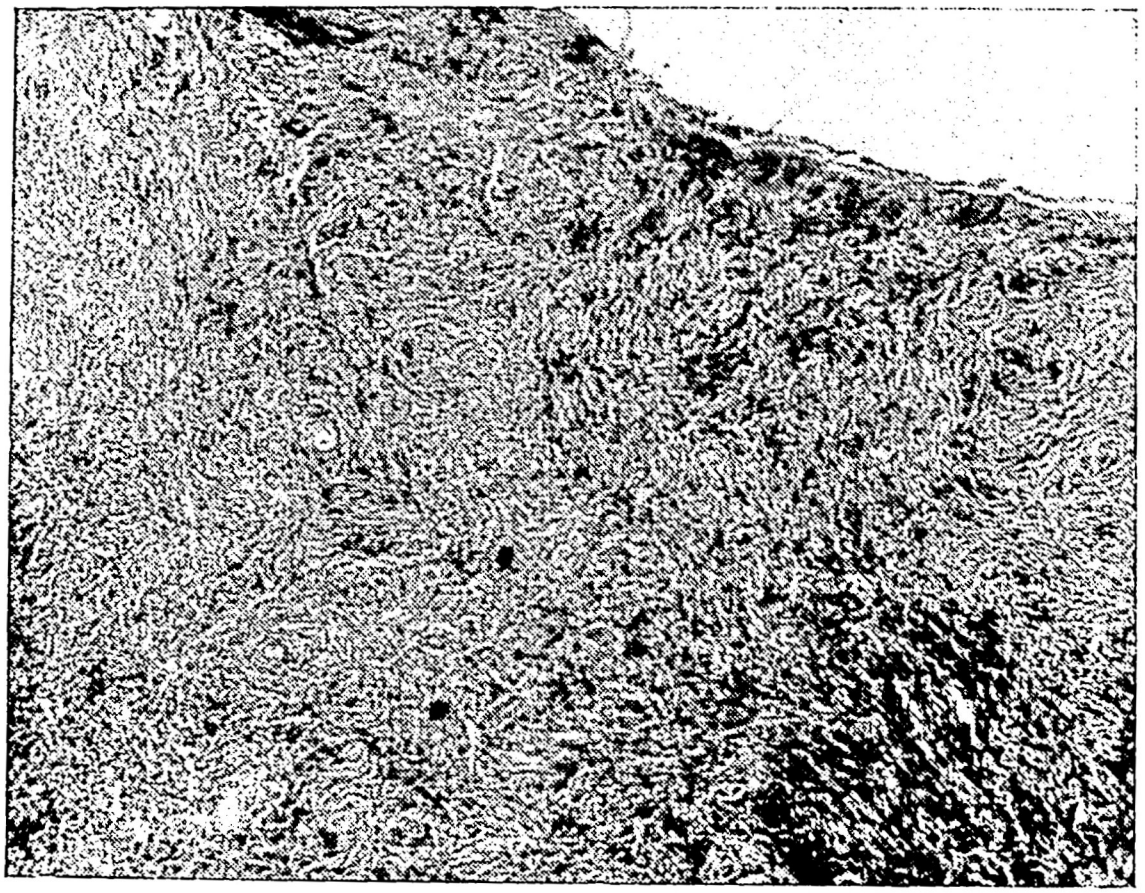
TABLE I

Ovarian Changes after Prolonged Use of Contraceptive Steroids and in Comparable Pattients

	Case 1	Case 2	Case 3	Case 4	Case 5	F.T. 1	F.T. 2	St. Lev.
Contraceptive used	Lyndiol 2·5	Gynanovlar	Deladroxate	P.C. 2m.	P.C. 5m.	F. T.	F. T.	
Ovarian Biopsy	20th. day	7th. day	20th. day	22nd. day	Preg. 12 w	—	—	—
Endometrial biopsy	—	Prolifration	Scanty	—	—	—	—	—
Primordial follicles	—	+	—	—	+	+	+	+
Developing follicles	—	+	+	—	+	+	+	—
Maturing follicles	—	+	+	—	+	+	+	—
Follicular cysts	+	3& 6	+	—	+	+	+	++
Corpus luteum	—	—	—	+	+	+	—	—
Corpora albricans	++	+	++	+	+	+	+	—
Atretic follicles	+	—	+	++	——			
Intra-follicar and perifollicular haemorrhage		—	—	—	+	—	—	—
Thickened tunica albuigenia	++	++	+	++	—	+	+	+++
Stromal fibrosis	++	+	+	+	—	—	—	+
Thick-wall stromal arteroiles	++	++	++	++	+	++	++	++

6. No evidence of hyperthecosis.

7. Fibrotic and cystic changes did not reach the extent seen in Stein-Leventhal syndrome.



Case No. 1.—Showing thickened tunica albugenia and focal stromal fibrosis with absent developing follicles.

DISCUSSION

Little is yet known regarding the possible effects of long-term steroidal ovulation suppression on the pituitary ovarian function. It is rather amazing how a prolonged interference with such a vital function of human biology should cause little damage.

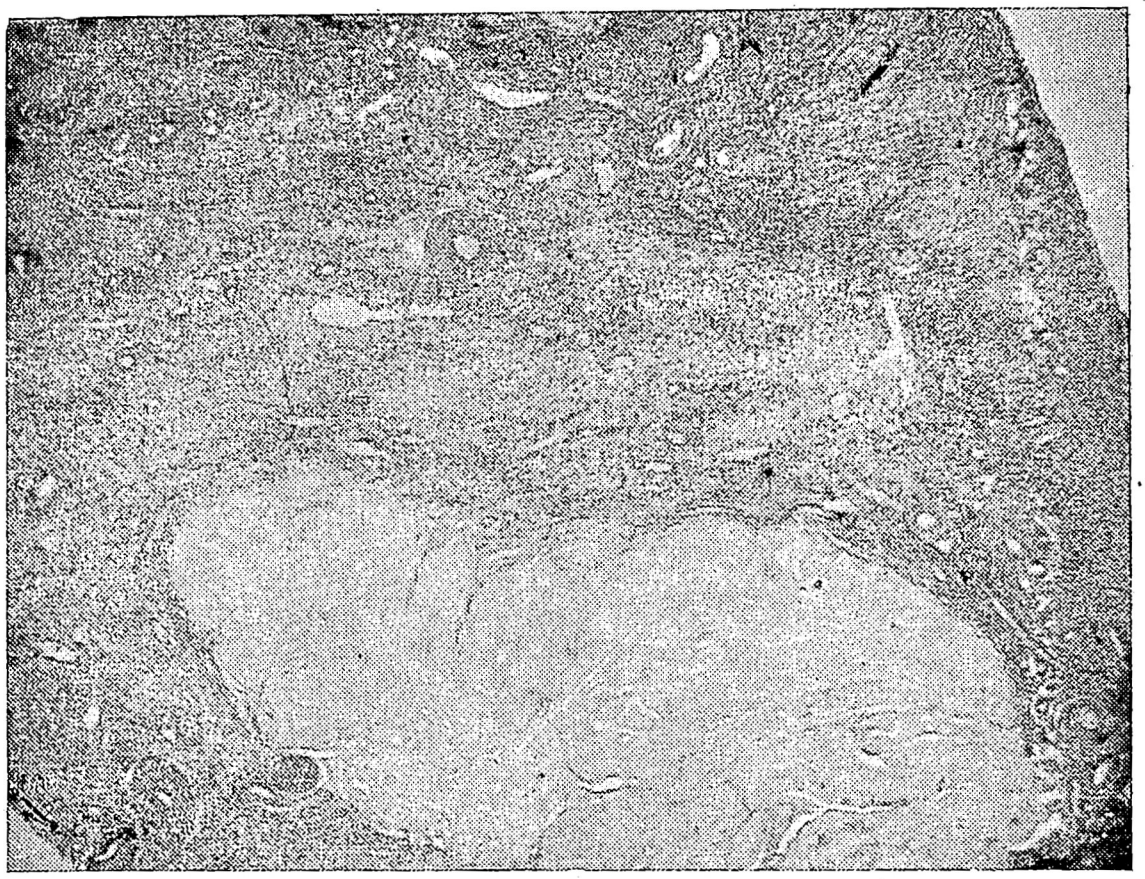
Most of the publications concerned with ovarian changes after long-term oral contraception point to the fact that there is no interference with the process of follicular development and maturation (Plate 1968). This was also our finding except in the two cases receiving lyndiol.

Case No. 2.—Cystic follicles, thickened tunica albugenia.

Hyperthecosis (Plate, 1968 ; Puga et al. 1967), hypertrophy of theca interna and haemorrhages in theca interna which may invade the lumen of the follicular cyst are indications that F. S. H. and L. H. activities are still in action and that ovulation inhibition is the only result of such therapy (Plate 1968).

Cystic follicles were also reported by many authors (Plate, 1968 ; Matsamoto, et al. 1960 ; Lauwerijns and Ferin 1964 ; Ryan et al. 1964 and others). This was also noticed in our cases.

On the other hand, Mall-Haefsli et al. (1965) and Garcia et al (1967) observed a juvenile or menopausal appearance of the ovaries and interpreted it as indicating inactivity. The extensive thickening of the tunica albugenia and focal stromal fibrosis noticed in our cases were also described to occur in most of the specimens reported by Zussman, Carcia, Plate and others. Plate (1968) in addition, demonsrated follicles completely embedded in connective tissue. On the other hand, Linthorst (1966) examined 20 such ovaries without finding any demonstrable thickening of the tunica, this was also the finding of Zanartu (1966).



Case No. 3.—Compressed and compact stroma, thickened tunica and fibrosed corpora albicans.

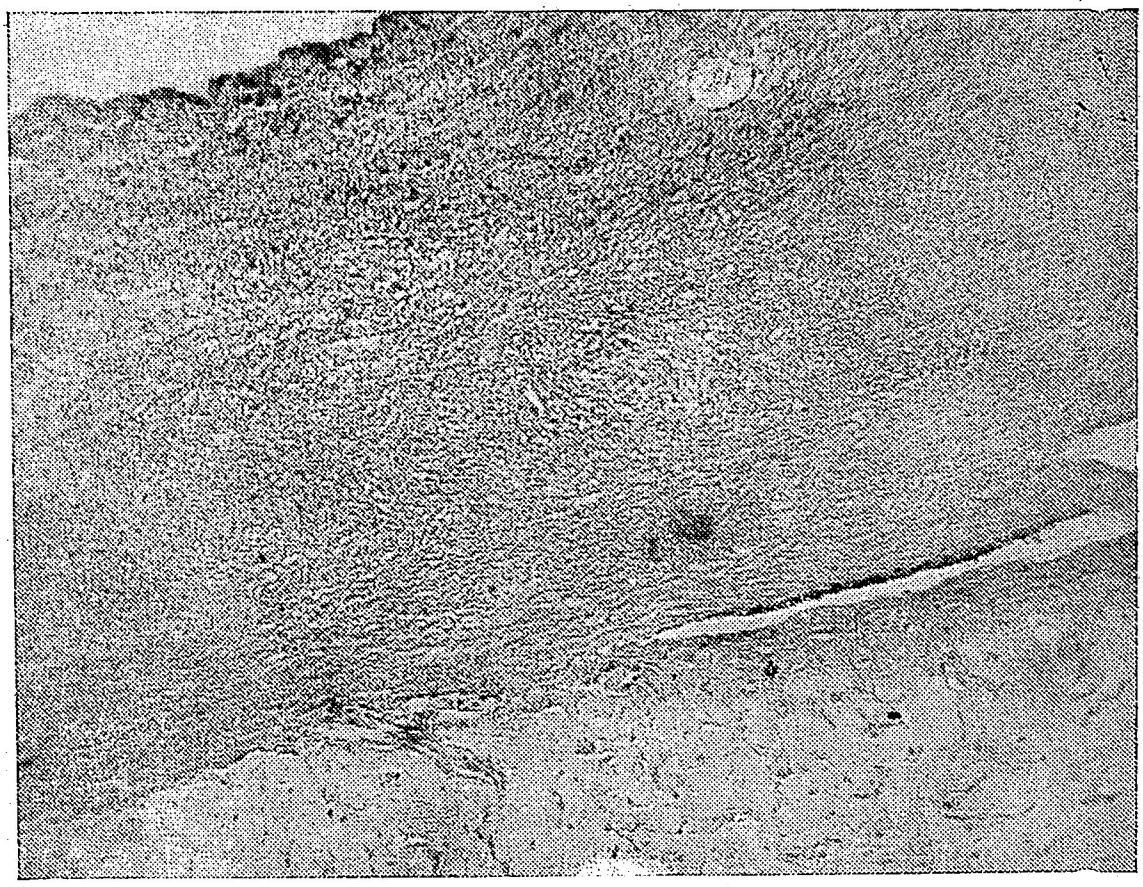
O'Neil (1965) observed a definite picture of Stein-Leventhal ovaries in the women under oral contraceptive pills. Graudenz & Beirao de Allmeida (1965) also reported one case simulating Stein-Leventhal ovaries. Reid (1964), in a discussion of Ryan's paper in 1964 stated that «one might speculate whether the individual destined to develop Stein-Leventhal syndrome might not do it earlier if she had been placed on these compounds.»

Evidence of such changes was not found in the present series.

Thickening of the tunica albugenia observed at full term pregnancy in this study, was also reported by Plate (1968).

Post-Cessation Status

It is well known that the majority of patients do return to normal cyclic ovulation and bleeding within the first 3 cycles. In the present



Case No. 5.—Normal tunica and corpus luteum of pregnancy.

series, 2 post-cessation subjects were studied, one case showed no ovarian changes and became pregnant after two months while the other still showed a moderate degree of fibrosis.

Weber 1969, examining post-cessation ovarian biopsies histologically found that ovarian changes completely disappear by the 2nd post-cessation cycle.

Frank et al. 1969, using steroid contraceptives directly after labour found that 80% of patients (20 out of 25) resumed cyclic withdrawal bleeding by the 2nd cycle.

Bell et al. 1967, studying urinary excretion of steroids, and gonadotrophins in 10 patients found low excretion levels of gonadotrophins in the first 2 cycles which subsided by the 3rd. cycle. This change was more pronounced the more estrogen used in the pill.

However, every gynecologist is confronted now and then with patients having anovulation and/or amenorrhea that persist for a variable length of time after cessation of contraceptive therapy.

Full term pregnancy ovaries moderate, thickening of tunica, developing, maturing and cystic follicles.

It is obvious that such cases are much higher than has been reported or suspected. However small the number of these patients is, they should not be overlooked.

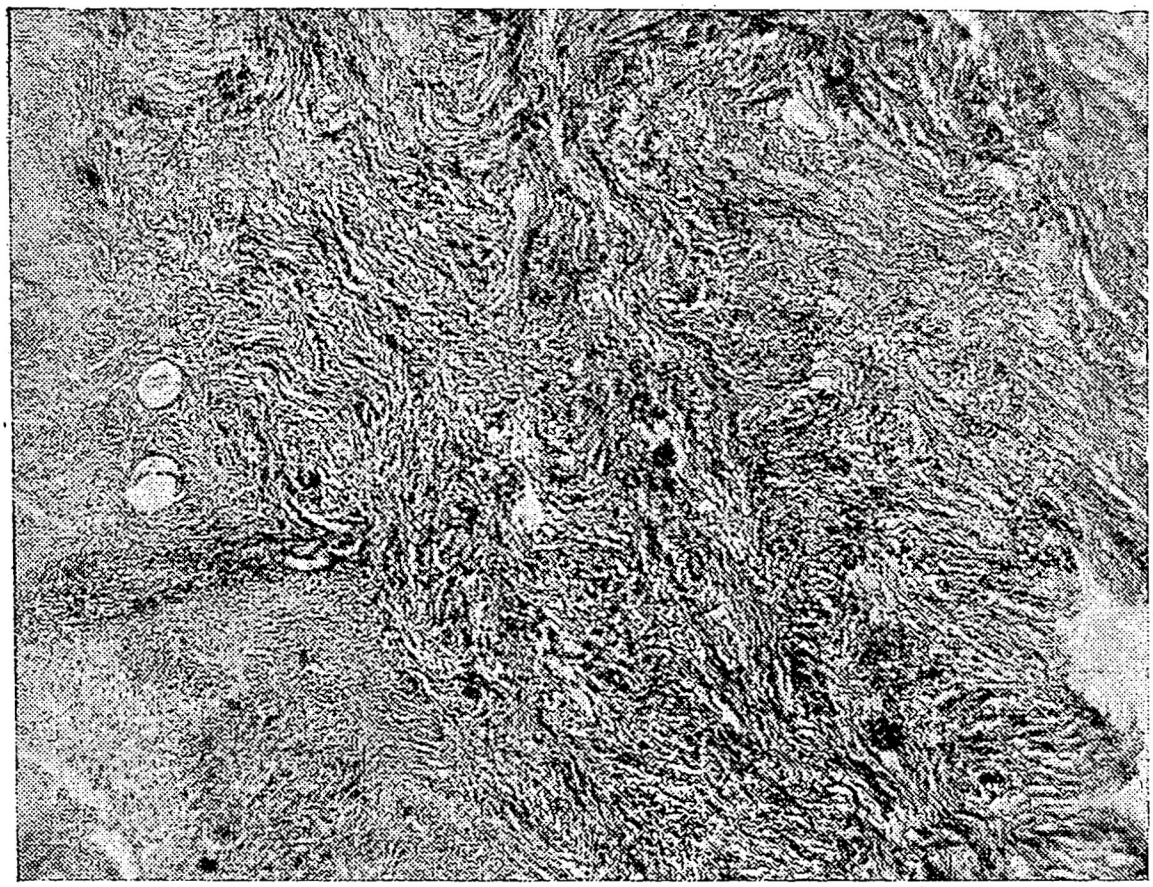
Recent articles appeared dealing with the treatment of such cases with prednisone, clomiphene, perganol or conservative expectant therapy with variable degrees of success.

This may direct our attention to the fact that the primary damage after long term contraceptive therapy is located at a higher station than the ovary and that such ovarian changes are but secondary in nature.

COMMENT

After this preliminary study, certain impressions should be stressed.

1. Long term contraceptive therapy should not be given freely to young nulliparas.



Stein-Leventhal ovary : Thick tunica albugenia, dense fibrosis of stroma and cystic follicles.

2. It is advisable to give interrupted courses, i. e. 1—2 years followed by a period of rest of 1—2 ovulations.

3. Patients with oligo-ovulation and oligomenorrhea should seek other kinds of contraception.

4. Oral contraceptive pills should not be used as a treatment of sterility.

5. Type and course of therapy should be individualized according to the subjects premedicational endocrine status.

Hewever, further studies should be carried along this line to clarify these impressions if the pills are alone distributed in a national family planning program.

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