FERTILITY CONTROL BY ENDOCRINE AGENTS*

By

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Studies with representative steroidal hormones have demonstrated that ovulation inhibition in rabbits is most readily achieved with progesterone (pregn-4-ene-3,20-dione) and oestrogens, and that androgens and corticosteroids are relatively ineffective.

Assays have been made in the rabbit of the ovulation-inhibiting effect of a large variety of synthetic compounds related to the four major classes of hormonal steroids. The most effective ovulation inhibitors have proven to be a series of progestational compounds, and the ovulation-inhibiting potency on subcutaneous injection has roughly paralleled prostational activity as determined by the Miyake-Pincus modification of the Lutwak-Mann assay of carbonic anhydrase in the rabbit endometrium (Miyake & Pincus 1958 b). On oral administration, however, the ovulation-inhibiting potency has differed markedly from the uterine progestational effect; the most potent oral ovulation inhibitors are certain 19-nor-steroids either having both oestrogenic and progestational activity or being capable of at least partial conversion to oestrogen in vivo.

Investigations of the effects of a number of these oral progestins upon ovulation in normally cyclic, regularly ovulating women disclose also a maximal ovulation-inhibiting potency in the oestrogenic or oestrogen-convertible 19-nor steroids. Also, relatively low dosages of orally active oestrogens are quite effective ovulation inhibitors in women. Cyclic oral oestrogen administration is, however, accompanied by symptoms of hyperoestrinism and

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rather lengthy and heavy periods of menstrual flow following withdrawal. The cyclic administration of a progestin-oestrogen combination results in a succession of regular menstrual cycles with well-controlled menstrual bleeding and a minimum of oestrogenic side effects. Ovulation inhibition in women by such a combination has been demonstrated on laparotomy.

The contraceptive action of a 19-nor-steroid – oestrogen combination [nor-ethynodrel (17α-ethynyl-oestra-5(10)-ene-17β-ol-3-one) plus the 3-methyl ether of ethinylestradiol (17α-ethynyl-oestra-1,3,5(10)-triene-3,17β-diol)] has been tested since early 1956 in San Juan, Puerto Rico, and in three other areas in the West Indies since 1957.

Each woman volunteering for the study has been given a vial containing 20 tablets of the steroid mixture and has been instructed to take one tablet a day beginning on day 5 of the menstrual cycle. Each month at about the time of the expected withdrawal menstruation the volunteer is visited by a nurse who delivers another 20 tablet vial and who at the same time elicits information on menstrual history, alleged reactions, and so on. At intervals of six to eight months samples of the population of volunteers are given a physical examination and certain blood and urine tests are performed.

To October 1959, approximately 16,250 cycles of medication have been undertaken, amounting to 1,250 woman-years of experience. The most used daily dose of the medication has been 10 mg (in 10,300 cycles), but extensive trial has been made also at 5 and at 2.5 mg. With each of these dosages complete contraceptive action occurs when the medication regime is faithfully followed. The number of conceptions occurring is proportional to the degree of departure from the regime (i.e. the number of days of tablet taking missed), but even with such departure (occurring in 5% to 15% of the medication cycles) fertility is markedly inhibited. The overall reduction in fertility has been 96% to 99%. Among the subjects discontinuing the medication after periods ranging from one month to three years, and using no other method of contraception, there occurs a prompt return of normal or somewhat greater than normal fertility. Examination of a number of ovarian sections from control and medicated subjects disclosed no significant change with medication in the number of oocytes. Examination of the children conceived either during or within a few months after medication has disclosed no abnormalities, nor has any abortifacient action of the medication occurred.

The results of approximately three hundred regular examinations of volunteer subjects compared with 45 non-medicated controls are as follows: (1) no significant alteration in the frequency of irregularities in the introitus, vaults and adnexae, fundus and ovaries; (2) a small decline in the frequency of breast abnormalities (e.g. cystic mastitis); (3) a somewhat higher incidence (13% to 27%) particularly of minimal cervical erosions in the medicated subjects, but no significant difference in the incidence of ectropion; (4) no
significant alterations in liver function as judged by tests of cephalin flocculation or thymol turbidity; (5) no significant change with time in blood haemoglobin concentration or in bleeding and clotting times; (6) a small tendency for a reduced incidence of urinary infection, but no significant change in the white blood cell count; (7) a significantly higher average blood concentration of total and protein-bound iodine in medicated subjects which is constant regardless of the duration of medication and which declines to pre-medication levels on cessation of medication; (8) a reduced urinary excretion of corticosteroids, accompanied by an increased blood concentration of free corticosteroids and a decreased blood concentration of conjugated corticosteroids, suggesting an increase in cortisol-binding protein in the blood and its expected sequelae.

Upon questioning of the subjects at examination the following data were elicited: (1) the amount of the menstrual flow remains unchanged in approximately 46°/0, is increased in 8°/0, and is decreased in 46°/0; (2) 60°/0 to 70°/0 of the subjects reported a greater or lesser degree of dysmenorrhea preceding medication, and this incidence was reduced to 33°/0 to 49°/0 during medication; (3) no significant trend in breast-size changes was reported, 70°/0 to 90°/0 reporting no change, 0°/0 to 20°/0 reporting increases, and 4°/0 to 15°/0 reporting decreases; (4) 79°/0 to 88°/0 of the subjects reported no change in libido, 5°/0 to 6°/0 an increase, and 7°/0 to 11°/0 a decrease; (5) an average tendency for weight increase was reported; (6) no significant changes in overall well-being occurred.

The medication was rejected because of alleged "reactions" by 5°/0 to 20°/0 of the volunteers in the first year, by 0°/0 to 6°/0 in the second year, and by 0°/0 to 4°/0 in the third year. Otherwise, acceptability was quite high. Reducing the medication dosage led, on the average, to a corresponding reduction in "reactions" but to a somewhat increased incidence of short menstrual cycles.

It is evident that a safe, extremely effective contraceptive has been evolved from the study of steroids inhibiting ovulation.

REFERENCES

Miyake T. & Pincus G.: Endocrinology 65 (1959) 64.