subnormality and were at local health authority training centres, in subnormality hospitals, or at home. And, for good measure, it must be mentioned that in 1965 1,172 girls under the age of 16 years had an illegitimate baby; 190 boys and girls under the age of 16 years were treated at venereal diseases clinics, but very few of them were known to be at school; about 63,000 of those under 17 years of age were found guilty of indictable offences (mainly larceny and breaking and entering); and almost 70,000 of those under the age of 18 years were in the care of local authorities on 31 March 1967.

They add up to a formidable total, and present educational, medical, and social problems of greater or less degree; their management depends on a close working partnership between education, medicine, and the other social services. They are the very stuff of present-day paediatrics and will be the subject of my second lecture. But we must keep all this in perspective and remember that although many schoolboys and schoolgirls have defects and disabilities that retard their development and education, and some are permanently incapacitated, the big majority are healthy, without handicap of any kind, and are well-behaved; and this I emphasize. There always have been those who have criticized the younger generation, and so it is today; but I am not of their company. In my opinion the present generation of children and young people compare favourably with their predecessors and I believe that our society will be safe in their hands.

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[The second lecture will appear in next week's issue.]

Antifertility Effect of Continuous Low-dosage Oral Progestogen Therapy

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Inhibition of fertility with progesterone and 19-norsteroids was first reported by Pincus *et al.* (1958); it was evident that progestogens in adequate dosage inhibited ovulation. The use of injectable long-acting progestogens without oestrogens for fertility control was reported by us in 1965. It was shown that medroxyprogesterone acetate 250 to 500 mg. intramuscularly induced ovulation inhibition for a period of at least six months (Zañartu and Navarro, 1965; Zañartu *et al.*, 1965). However, it was soon observed that in subjects receiving one single injection fertility was still inhibited for two or more months even after ovulation was re-established, as shown by the existence of corpus luteum under macroscopic and microscopical examination of the ovaries (Zañartu *et al.*, 1965). It was felt that the effect of injected progestogens induced the inhibition of fertility during this period by modifying other factors more sensitive to lower doses (endometrium, cervical glands, etc.).

The observations reported by Martinez-Manautou *et al.* (1965, 1966, 1967a) and by Rudel *et al.* (1965) of inducing contraception with daily microdoses of progestogen have opened a new approach to fertility control without interfering with the hypothalamic-pituitary-ovarian axis, at least in respect of ovulation. From a historical viewpoint it is interesting to note the gradual reduction in the steroid dosage required to obtain fertility inhibition in women. The initial pioneering clinical work from Pincus *et al.* (1958) used 10 mg. of norethynodrel with 150 µg. of ethinyloestradiol 3-methyl ether, compared with the progestogen microdosage (0.5 mg. of

chlormadinone acetate) now being reported as successful in inhibiting fertility.

The continuous "non-stop" form of administration may be particularly acceptable and be easier to follow in subjects from low socio-economic and educational levels. The low cost and easy handling of the treatment is also attractive for family planning purposes in this population. The present report therefore attempts to explore the acceptability and clinical effectiveness of the therapy in fertile healthy young women from low socio-economic and educational levels as compared with a group of well-to-do educated subjects.

Material and Methods

From 1965 to March 1967 390 fertile healthy young women from two different socio-economic and educational groups were studied. Forty-five were educated and came from families with an above-average income. The remaining 345 were from low-income groups. Chlormadinone acetate 0.5-mg. tablets were given daily without interruption. The therapy was offered to women when conventional combined or sequential

TABLE I.—Age and Fertility Before Treatment

Age	Group A	Group B	Fertility (No. of Pregnancies)	Group A	Group B
16 to 20 years	26	—	1 to 4 ..	146	23
21 " 30 "	199	23	5 " 8 ..	124	20
31 " 40 "	117	21	9 " 12 ..	58	2
41 or more "	3	1	13 or more ..	17	—

Group A = 345 clinical patients. Group B = 45 private patients.

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prisingly well accepted by these women as well. Most of them (40) had previously received conventional combined or sequential therapy; they reported better tolerance, which was very welcome. Only two women from group B discontinued the method because of menstrual disturbances, while 12 required accessory oestrogen therapy.

Discussion

It has been shown by urinary pregnanediol excretion and culdoscopy that continuous oral low-dosage chlormadinone acetate does not consistently interfere with the hypothalamic, pituitary, and ovarian relations conditioning ovulation, but that ovulation often persists. It was suggested that changes in the endometrium and/or the receptivity to sperm of cervical mucus were significant (Martinez-Manautou *et al.*, 1965, 1966; Rudel *et al.*, 1965, 1966).

In 12 patients under treatment ovulation and corpus luteum formation were investigated by direct gross and microscopical examination of the ovaries at laparotomy. Sperm penetration and ascent, and endometrial morphology were also investigated. These findings have been reported in part elsewhere (Zañartu, 1964, 1967; Zañartu *et al.*, 1965, 1967; Rosenberg and Zañartu, 1967), and are described in the paper which follows (Zañartu *et al.*, 1968).

Huhner-Sims post-coital tests performed from 2 to 12 hours after coitus in fertile healthy women receiving 0.5 mg. chlormadinone continuous therapy have shown that this dosage induces changes in mucous viscosity and leucocyte content, and also impairs fern crystallization and decreases sperm mobility. However, some tests performed between the 10th and 20th days of the cycle revealed sperm motility described as "fair" and "good" (Zañartu, 1964, 1967). Mucous hostility to spermatozoa was therefore not consistently affected in subjects under this therapy. Studies on the effect of progestogens in the biochemical composition of the cervical mucous are needed for better understanding of this mechanism.

Endometrial histology was evaluated by biopsies performed at different weeks of the menstrual cycle, particularly at the premenstrual period. Morphology similar to the patterns found in normal non-treated ovulatory women were observed. However, subjects with prolonged or irregular uterine bleedings had signs of inactive endometrium (Rosenberg and Zañartu, 1967). There was considerable individual variation of response.

Twelve subjects had their ovaries, Fallopian tubes, and uterus examined at surgical operation. Ovulation, as shown by the presence of a corpus luteum and urinary excretion of pregnanediol, had evidently occurred in six. Antioviulatory effects were apparent in the remaining subjects. Flushings from Fallopian tubes removed a few hours after coitus did not contain sperm, though there is as yet no information available about whether this therapy was responsible.

The studies suggest an interference with cervical glands, endometrium, and possible sperm transport, but with ovulation frequently preserved.

Advantages of this Therapy

The first advantage to be mentioned is the ease of management. With simple instructions therapy may be started immediately after initial examination and at any moment post partum or during the menstrual cycle. There has been no deleterious effect when the patient inadvertently received this progestogen while already pregnant. This occurred in three women without evidence of damage to the newborn.

Secondly, if properly used, the method is effective, though our failure rate seems somewhat higher than those reported by others (Martinez-Manautou *et al.*, 1965, 1966, 1967b); Rudel *et al.*, 1965).

Thirdly, tolerance to the drug is good. Most of the women in the present study had already shown intolerance to other forms of oral contraception. Their tolerance of this method is therefore particularly noteworthy. Irregular bleeding or amenorrhoea, or both, can be corrected by means of accessory oral oestrogens during few cycles if desired. The incidence of these complaints seems higher in women who had irregular uterine bleeding before marriage.

Fourthly, lactation is apparently not interfered with; occasionally it is increased by oral or injectable progestogens, when used without oestrogens (Gomez-Rogers *et al.*, 1967).

Fifthly, ovulation and endocrine ovarian function are usually preserved. Presumably the hypothalamic-pituitary axis is less disturbed.

Sixthly, recovery of fertility is almost immediate, either in the first or second cycle after discontinuation of therapy.

Seventhly, severe side-effects are the exception. In our experience specialized medical care was seldom required because of complications. In young healthy subjects medical examinations do not seem necessary more than once a year.

Eighthly, the low cost of the therapy is most important for developing nations with limited resources for family planning.

Finally, recent observations (Orellana-Alcalde and Dominguez, 1966, 1968) on subjects who have suffered from idiopathic jaundice or intrahepatic cholestasis during their pregnancy should be noted. These symptoms relapsed while combined or sequential oral contraception was used. Under chlormadinone acetate therapy, however, results of liver-function tests (serum bilirubin and transaminases, bromsulphalein excretion) have remained within normal values.

Disadvantages of Therapy

The disadvantages should also be listed. Firstly, it is an oral method. Illiterate subjects or women from low educational levels of the population have a higher incidence of not taking their tablets. Undesired pregnancies follow, often resulting in induced abortion. Secondly, even when the method is properly used effectiveness is not total. Failures seem to occur in subjects changing to this method after the use of sequential oral contraceptives.

Summary

Chlormadinone acetate 0.5 mg. was given daily as a continuous "non-stop" oral contraceptive to 390 young fertile healthy women during 3,400 months. Tolerance was good, systemic side-effects being infrequent. Uterine bleeding, menstrual cycle disturbances, and amenorrhoea were the main complaints against the method, but were seldom severe. In 47 women accessory oral oestrogen therapy was added to the daily progestogen to correct these alterations.

The method can be started at any time after parturition or abortion; it does not interfere with lactation. Its use is simple and does not require complicated instructions. The method seldom interferes with ovulation. In a few of the 12 subjects who underwent surgery while under therapy, fresh corpora lutea were observed. Urinary excretion of pregnanediol also indicated progesterone secretion.

Studies have suggested possible interference with sperm ascent. No sperms have been recovered from the fluid flushing from Fallopian tubes obtained a few hours after coitus.

Fertility is re-established immediately after therapy is discontinued, either in the first or the second cycle.

Twenty-four undesired pregnancies have been observed during this period. They were due to improper use of the

method in 11 women; in 13 subjects who claim they used the method correctly apparently the method failed.

The method is well tolerated and accepted by subjects who had experienced previous intolerance to conventional oral combined or sequential therapy. Its low cost and ease of administration makes it of interest to developing countries with limited resources for family planning.

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Effect of Oral Continuous Progestogen Therapy in Microdosage on Human Ovary and Sperm Transport

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Therapy with oral continuous progestogens in microdosage is an effective and simple contraceptive steroidal method (Martinez-Manautou *et al.*, 1965, 1966, 1967; Rudel *et al.*, 1965). However, its mechanism of action has not yet been fully clarified. It has been claimed that ovulation is usually preserved, and eventually the main factors conditioning the contraceptive effect are the changes induced on the secretion of the cervical glands (Zañartu, 1964, 1967; Martinez-Manautou *et al.*, 1966, 1967).

This paper attempts to throw further light on the possible antifertility mechanism of this method.

Material and Methods

Twelve young fertile women underwent surgical operation while receiving oral continuous chlormadinone acetate 0.5 mg. contraceptive therapy for 4 to 19 months. Their ages ranged from 32 to 39 years (Table I).

Before surgery the antioestrogenic effect of the compounds was evaluated by serial vaginal cytology, cervical mucus tests (its tolerance to sperm as seen 6 to 12 hours after coitus), and endometrial histology in the same and/or preceding cycle to the operation. Vaginal smears and Huhner-Sims post-coital tests were done between the 7th and 10th, 13th and 16th, and 22nd and 26th days of the cycle. Endometrial tissue was obtained by biopsy around the 22nd to the 26th day (Noyes *et al.*, 1950). The 24-hour urinary pregnanediol excretion was studied between the 8th and 14th days and the 22nd and 26th days on those subjects with regular cycles (Sulmovici *et al.*, 1965).

Laparotomy was done on the 14th, 15th (four women), 16th, 17th, 19th, 21st, 26th, and 27th days of the cycle and in one

subject who was amenorrhoeic, the latter symptom persisting after lactation was discontinued. The object was tubal sterilization in 10 patients, and treatment of non-gynaecological conditions in two. Careful macroscopic examination of the uterus, Fallopian tubes, and both ovaries was carried out. Then a substantial wedge biopsy specimen was taken from an area of the gonad where there was definite evidence of some functional activity (mature follicle, cystic follicle, follicular cyst, corpus luteum, etc.). The ovarian tissue was processed for conventional haematoxylin-eosin and van Gieson staining methods in serial sections, as well as histochemical identification of carbohydrates and steroid-converting enzymes. For this purpose part of the biopsy specimen was immediately frozen and sectioned on a cryostat at -20°C , $16\ \mu$, and incubated at 37°C . Techniques were used for demonstration of lactic, succinic, glucose-6-phosphate, 3- β -hydroxysteroid, and 20- α -hydroxysteroid dehydrogenases. Some ovarian sections were also stained with Sudan black for total lipids (Pupkin *et al.*, 1966).

The appearance of both ovaries, particularly in respect of their size, aspect and number of cysts, signs of ovulation, and presence of corpora lutea, was carefully recorded. The germinal epithelium, ovarian cortex stroma, characteristics of follicles, cysts, with or without luteinization of the theca interna, were also studied histologically.

Follicles were classified as: "primary" (I), when the egg-cell was surrounded by a single layer of flat epithelium; "secondary" (II), if one or more stratified granulosa cell layers were present; "tertiary" (III) or vesicular follicles, with antrum and fluid; Graafian and "mature" follicles, containing numerous layers of granulosa cells, a developed, eccentric

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