

Effectiveness of an Oral Contraceptive

Effects of a progestin-estrogen combination upon fertility, menstrual phenomena, and health.

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In previous papers we described the effectiveness of certain 19-nor steroids, when orally administered, as inhibitors of ovulation in animals (1) and man (2). Subsequent studies demonstrated that the combination of a small amount of estrogen with these progestins permitted the regular, repeated induction of artificial menstrual cycles in women taking the medication from the 5th to the 25th day of the cycle (3, 4). This property of maintaining normal menstrual cyclicity along with repression of ovulation led to the experimental testing of a norethynodrel-estrogen combination as an oral contraceptive, and reports of the first 18 months of a study made in San Juan, Puerto Rico, have been made (4, 5). After our initial experience in San Juan, two projects were initiated in Humacao, Puerto Rico, and one in Port-au-Prince, Haiti. We have recently collected and analyzed the data (to November 1958) from these four projects (6) and present here the outstanding findings derived from these data; 830 subjects took the medication for a total of 8133 menstrual cycles, or 635 woman-years.

The same regimen of tablet-taking was followed in all projects—namely, one tablet a day (10 mg of norethynodrel plus 0.15 mg of ethinyl estradiol 3-methyl ether) from the fifth through the 24th day of the menstrual cycle. Regu-

lar visits were made to each subject, and a record was kept of the length of each cycle, the nature of the menstrual flow, the occurrence of "side reactions," the frequency of coitus, the number of days of tablet-taking that were missed, and any other noteworthy phenomena.¹ In addition, physical examinations of representative samples of each group were made from time to time, and in October 1958, data were obtained for over one-third of the women in each project from pelvic examinations, two liver-function tests (thymol turbidity and cephalin flocculation), endometrial biopsies, and vaginal smears.

Sixteen certain and one probable pregnancy occurred in women taking the medication; this represented a rate of 2.7 pregnancies per 100 woman-years and a 96-percent reduction in the pre-medication rate of 61.2 pregnancies per 100 woman-years. In Table 1 we present the distribution of these pregnancies according to the number of days of tablet-taking that were missed in the cycle in which conception occurred. It is clear that if the regimen is followed faithfully, practically 100-percent contraception occurs; it is also clear that the rate of conception is proportional to the number of tablets missed. Analysis of the data indicates no habituation to the medication—that is, pregnancies occurred at about the same rate in long-term users as in short-term users.

Among the menstrual-cycle phenomena recorded we observe the following: (i) a mean cycle length of 28.6 days with a normal frequency distribution; (ii) the occurrence of flow during

the course of medication (breakthrough bleeding) in 2 percent of the cycles; (iii) a temporary amenorrhea in 0.8 percent of the cycles, with regular withdrawal bleeding in 99.2 percent; (iv) a reported increase of menstrual flow in 6 percent of the cycles, no change in 46 percent, and a decrease in 48 percent; (v) no significant change during medication cycles in the reported incidence of pain associated with menstruation.

Side Reactions

"Side reactions," such as nausea, headache, dizziness, vomiting, gastralgia, and malaise, were reported in 10.9 percent of the 4988 cycles in San Juan, in 6.3 percent of the 1410 cycles in the first Humacao project, in 18.3 percent of the 658 cycles of the second Humacao project, and in 7.3 percent of the 1077 cycles of the Port-au-Prince project. In each instance the largest percentage of these reactions was reported in the first cycle of medication and declined to low levels thereafter. The similarity of reactions to those common in early pregnancy and their subsequent subsidence is noteworthy. Similarly, the frequency of breakthrough bleeding was highest in the first medication cycle.

These data suggest an accommodation to the medication, probably involving uterine response to the level of the stimulation established by the drug. However, interesting results were found in a double-blind study of placebo versus true medication effect in which women continuing to use conventional contraceptives were given either a placebo or the true drug. In 41 cycles of 15 women taking the placebo, breakthrough bleeding occurred in 4.9 percent, suggesting that medication was not responsible, and reactions were reported in 17.1 percent of the cycles, suggesting a psychogenic factor; in 30 cycles of 13 women given the true medication, a higher incidence of breakthrough bleeding (16.7 percent) and of reported reactions (23.3

Table 1. Pregnancies according to number of tablets missed.

No. of tablets missed	No. pregnant	Rate per 100 woman-years
0	1 ?	0.2
1-5	5	7.7
6-19	11	43.3

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percent) occurred, but these values are not significantly higher on a statistical basis. Furthermore, in 48 cycles of 15 women (separated by a great distance from the others) who were given the medication with no admonition as to possible reactions or menstrual irregularity, the frequency of breakthrough bleeding was 2.1 percent and that of reactions, 6.3 percent.

On being questioned at the October examinations, approximately 55 percent of the subjects reported weight increases occurring during medication, 25 percent reported no change, and 20 percent reported weight decreases. Similar ques-

tioning concerning general health disclosed that 39 percent felt an increase, 10 percent a decrease, and the balance no change, in well-being. Concerning libido, 20 percent reported an increase, 22 percent a decrease, and the balance no change. However, the data on frequency of coitus disclose that increasing frequency was reported by approximately 50 percent, decreasing frequency by 40 percent, and no change by 10 percent.

The data on over 200 pelvic examinations disclose: (i) a restoration of involuted *postpartum uteri* to normal size but not to hypertrophy even after 30 or

more cycles of medication; (ii) an inconsistent change in the degree of cervical erosion; (iii) no pathological changes in the adnexae or vagina. No pathological breast changes were seen, and all vaginal smears were negative by Papanicolaou stain. Among the 148 liver-function tests, one was positive with respect to liver-tissue damage, a frequency consistent with the occurrence of this condition in the general population of these areas.

Efficacy

In San Juan 86 women who withdrew from the project after 1 to 20 cycles of medication were observed further, and the occurrences of pregnancy were noted. The data, presented in Table 2, indicate no impairment of fertility in those not regularly using other means of contraception, and no tendency toward impairment in long-term as compared with short-term users. The mean conception rate of 193 per 100 woman-years of exposure is not significantly different from the premedication rate of 244 per 100 woman-years for the San Juan subjects prior to medication. The oral contraceptive would appear to be ten times as effective as the other contraceptives used.

For certain subjects who had been taking the standard dose of the drug, the dosage was halved in 224 cycles and quartered in 46. Relevant data presented in Table 3 indicate no significant difference between the efficacy of norethynodrel at the 10- and 5-mg levels, but indicate a tendency toward shorter cycles and an accompanying increased frequency of premature bleeding at the 2.5-mg level. Since we have previously shown (3) that adequate endometrial sustainment requires a level of the ethinyl estradiol methyl ether at least double that (0.037 mg) present in the quartered dose, the possibility of controlling breakthrough bleeding by means of higher estrogen dosage is being tested. It should be noted that no conceptions occurred at these lower dosage levels.

Acceptability

The acceptability of this method of contraception may be examined by listing the reasons given for withdrawal from each project. These are presented in Table 4. In three projects, 28.2 to

Table 2. Data for individuals who withdrew from the San Juan project.

No. of cycles prior to withdrawal	No. of individuals	Other contraceptives not used regularly*			Other contraceptives used regularly†		
		No.	Percent pregnant	Exposure (months)	No.	Percent pregnant	Exposure (months)
1-5	55	30	87	6.2	25	16	55
6-10	16	10	80	5.0	6	17	39
11-15	7	6	67	11.0	1	0	
16-20	8	8	88	4.2			
Totals	86	54	83	6.1	32	15	52

* The mean conception rate is 193 per 100 exposure years. † The mean conception rate is 27 per 100 exposure years.

Table 3. Effects of lowering dosages on menstrual-cycle phenomena.

Dose per day (mg)	No. of cycles	Mean length (days)	Subjects		
			With reactions (%)	With breakthrough (%)	With amenorrhea (%)
2.5	46	26.2 ± 0.51	8.7 ± 4.1	15.2 ± 5.3	2.2 ± 2.2
5.0	224	27.3 ± 0.20	12.5 ± 2.2	2.7 ± 1.1	2.2 ± 1.1
10.0	4718	27.9	10.9	2.0	2.2

Table 4. Reasons for withdrawal.

Reason	San Juan		Humacao-R		Humacao-P		Haiti	
	No.	%	No.	%	No.	%	No.	%
Reactions	64	28.2	5	41.8	10	32.3	3	7.3
Not interested	36	15.9	1	8.3	0	0.0	17	41.5
Pregnant	12	5.3	1 ?	8.3	1	3.2	3	7.3
Unrelated illness	16	7.0	0	0.0	0	0.0	2	4.9
Husband opposed	5	2.2	0	0.0	0	0.0	1	2.4
Moved	34	15.0	3	25.0	6	19.3	9	22.0
Sterilized ♂ or ♀	29	12.8	1	8.3	6	19.3	0	0.0
Separated	20	8.8	0	0.0	6	19.3	2	4.9
Miscellaneous	11	4.8	1	8.3	2	6.5	4	9.7
Total withdrawing	227		12		31		41	
Total No. of subjects	438		117		126		149	
Percent withdrawing	51.8		10.3		24.6		27.5	

41.8 percent of those withdrawing did so because of reactions; in the fourth project, lack of interest was the prime cause of withdrawal. Between them, these two reasons account for 32 to 50 percent of the withdrawals. Since the reactions are in large measure psychogenic, means for dealing with them may be devised. We have, in fact, shown that an antacid, or even a placebo, pill will relieve up to 90 percent of these reactions (4, 5). The lack of interest is due chiefly to lack of motivation among an economically low-level group. The actual rate of withdrawal was highest for the first year of operation of the San Juan project, in which 50 percent of the subjects who started had withdrawn by the end of the year. In contrast, in the Humacao-R project, 11 percent of those who started had withdrawn by the end of the year. We believe these high withdrawal rates for the San Juan project to be due to the following factors: (i) the availability of sterilization for contraception as well as the availability of other means economically practical; (ii) frequency of moving, chiefly to the

continental United States; (iii) improvement in economic situation, which makes larger families less undesirable; and (iv) difficulties attendant upon initiating and testing this new method of contraception. Actually, among those starting the second year of medication, the withdrawal rate fell to 30 percent, and in Humacao-R, to less than 1 percent. In the latter project is a stable group of very poor women who are highly motivated, and in this project, begun a year after the one in San Juan, the supervisor had full knowledge of the difficulties encountered during the first year in San Juan. It is perhaps significant that in Haiti, where the population is also quite poor but where it is less stable, the first year's rate of withdrawal for all causes was 34 percent.

Questions and Answers

For the period studied, the foregoing data appear to us to answer the following questions, in the manner indicated: (i) Is the method contraceptively effective?

yes; (ii) does it cause any significant abnormalities of the menstrual cycle? no; (iii) does it adversely affect the reproductive tract and adnexae? no; (iv) does it have physiologically adverse effects generally? no; (v) does it affect the sex life of the subjects adversely? no; (vi) does it impair fertility upon cessation? no; (vii) may a low dosage level of the drug be used? yes; (viii) is the method acceptable? yes, but to an extent which varies with motivation, economic situation, and other factors (7).

References and Notes

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J. P. Greenstein, Biochemist and Investigator of Cancer

The sudden death of Jesse Philip Greenstein on 12 February 1959 ended a career of outstanding achievement. Dr. Greenstein had achieved eminence in his extensive work on the chemistry of amino acids, peptides, and proteins, and on the biochemistry of cancer.

He was born in New York City on 20 June 1902 and did his undergraduate work at the Polytechnic Institute of Brooklyn, from which he was graduated in 1926 with honors in chemistry. He then went to Brown University, where he worked with C. A. Kraus and P. H. Mitchell. His Ph.D. thesis dealt with electrometric determinations of the dissociation of glycine and certain simple peptides; its character foreshadowed much of his later work. In 1930–31 he

was a National Research Council fellow at Harvard, under Edwin J. Cohn, where he continued and extended his studies on the ionization constants of peptides. This was followed by a year's work in Dresden under Max Bergmann, who was just developing the carbobenzoxy method of peptide synthesis. Greenstein's experience in Bergmann's laboratory profoundly influenced his subsequent career. With Bergmann and Zervas he was the first to apply the new methods to the synthesis of lysylglutamic acid and lysylhistidine, and he developed a mastery of both organic and physical chemistry, particularly in relation to the study of peptides and proteins, which was exceptional among the biochemists of his generation.

After a year in Berkeley in the laboratory of C. L. A. Schmidt, he returned to Harvard for six years (1933–39). During this period he was active as a tutor in biochemical sciences at the college and was also research associate at Harvard Medical School, in Cohn's laboratory. His zeal and enthusiasm for both teaching and research, and his extraordinary energy and enthusiasm, were strikingly displayed then as later. As tutor in biochemical sciences he looked after a larger number of students than any other member of the board has ever been responsible for, and served as an inspiring and effective teacher in frequent personal conferences with students. He also served as head assistant to L. J. Henderson in the latter's course in biological chemistry; indeed, as Henderson's major interests were shifting from biochemistry toward sociology, Greenstein for several years was largely responsible for the general management of the course. At the same time he was astonishingly productive in research. He continued to synthesize new peptides and to study their ionization constants and correlate these with their structure, and, in collaboration with J. Wyman and T. L. McMeekin and others, he studied