An Oral Contraceptive

A 4-Year Study of Norethindrone

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In 1956, the Los Angeles Planned Parenthood Center initiated a study of the more potent synthetic progestins as oral contraceptives. The initial phase of the study was largely exploratory from the standpoint of selection and number of cases, but in a short time it seemed clear that an extensive study was indicated. In reporting the results of the first 2 years of this investigation at the American Medical Association meeting in June 1958, we noted that the synthetic progestins were effective ovulation inhibitors and could be used for contraceptive purposes. Since that time, our study progressed substantially. The main purpose of this report is to summarize the data pertaining to the effectiveness of norethindrone as an oral contraceptive. In addition, we wish to present some of the data being accumulated in a long-range study of possible side effects or more serious long-term consequences of norethindrone dosage.

MATERIALS AND METHODS

As of Sept. 1, 1960, a total of 570 patients had received norethindrone, the oral progestin used most widely in our study, for contraceptive purposes in our clinic, and 337 patients were actively using this drug. We maintain a relatively constant number of patients on this medication and try to keep the figure at 350 for reasons relating to available supplies, nursing supervision, etc. rather than patient interest (there is a waiting list of several hundred patients who would like to use the tablets).

Patients were selected from the general clinic population. The chief criteria for inclusion in the study were proved fertility and history of no obvious illness that would preclude the use of a systemic medication. Detailed medical histories were taken and pelvic examinations were performed on all patients before norethindrone administration was started.

We administered norethindrone in 10-mg. doses, instructing the patients to take 1 tablet daily from Days 5 to 25 of the menstrual cycle. Patients were to await bleeding after Day 25 and to resume medication on Day 5 of the following cycle. In a separate group, to be reported later, we used reduced dosages.

Vaginal and cervical smears were taken from each patient at half-year intervals, and endometrial biopsies were obtained once, and often twice, a year. These pathologic studies, supervised by Drs. L. Zeldes and D. Moyer of the Department of Pathology, are the subject of a separate report. Patients were also selected at random for additional clinical pathologic studies such as cephalin

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flocculation tests, determination of Bromsulfalein excretion, complete blood counts, and assay of 17-hydroxycorticoid and 17-ketosteroids excretion.

At each bimonthly visit, the patient's weight was recorded, and periodic breast examinations were made. The nurse supervising the study routinely questioned the patient to determine whether she had been consistent in the use of the method as well as to elicit possible complaints. Every half year the data collected were tabulated so that at these intervals adequate summaries of the progress of the study could be obtained.

One of the major considerations in any program involving the prolonged use of a systemic agent is that of side effects. In an attempt to be completely objective, we noted every complaint volunteered by the patient, and in certain instances leading questions were asked. Admittedly, this technic would make for a falsely high reporting of side effects, but we thought it desirable to err in that direction. Furthermore, since major differences were noted with respect to various progestins used at the clinic, we believe this technic to be valid. Before Sept. 1, 1960, we reviewed the bimonthly record of all patients in detail and tabulated the occurrence of nausea and other side effects, including weight changes, bleeding, amenorrhea, and the like.

RESULTS

Effectiveness

The 570 patients who had received norethindrone as of Sept. 1, 1960, represented a total of 7194 patient-cycles and included a substantial number of long-term users.

A number of patients discontinued the method, for the following reasons:

Reason	*No. of patients*
Moved from area	77
No reason given	53
Side effects	18
Planned pregnancies	15
Private physician's advice	15
Lack of confidence in agent	13
Weight gain	10
Divorce	8
Hysterectomy	6
Unplanned pregnancies	6
Vasectomy	5
Religious reasons	5
Failure to get supplies	5
Husband's objections	3
TOTAL	239

Only six unplanned pregnancies occurred. On the basis of thorough questioning of these patients, we concluded that five of these were definitely related to incorrect use of the method: 3 patients failed to obtain new supplies of medication, 2 used it irregularly, and 1 claimed to have used the drug constantly.

In addition to the unplanned pregnancies, data were obtained on 15 planned pregnancies. The distribution of the number of pregnancies according to the length of time norethindrone was used was as follows:

Months of use	*Patients*
27	1
16	1
15	1
13	1
12	2
11	2
8	2
7	1
5	1
4	1
3	1
1	1

There were undoubtedly many more planned pregnancies, but despite our insistence that patients report back routinely to the clinic after discontinuing the method, a number of them failed to do so. Follow-up visits were often made, but many patients had left the area.

Side Effects

Since the occurrence of side effects has been an issue in these programs, we present our experiences in considerable detail. It is our impression that the usually encountered side effects, because of their relatively low

incidence and lack of serious consequences, do not significantly limit the usefulness of norethindrone as a contraceptive agent.

NAUSEA. One of the side effects encountered with progestin products in contraception is nausea and other gastrointestinal complaints. Fifty-six of 570 patients given norethindrone reported the occurrence of nausea at one time or another. Of 5432 cycles studied, nausea was noted in only 59, or 1.1 per cent. As most patients continued taking the medication despite the single episode or two of nausea, it must be concluded that it did not present a significant problem. Most instances of nausea were reported in either the first or second cycle. One would question the significance of nausea reported for the first time after the drug had been taken for some time.

WEIGHT GAIN. Weight gain has been mentioned as a side effect in the oral contraceptive programs. As norethindrone and related compounds were reported to have anabolic properties, we kept detailed records of weight changes. Certain patients had weight problems before starting norethindrone, and a considerable number of control patients similarly had weight problems. The distribution of weight change was as follows:

Weight range (lb.)	*No. gaining weight*	*No. losing weight*
7–10	66	5
11–15	30	12
16–20	19	6
21–25	4	2
26–30	1	2

MENSTRUAL IRREGULARITIES. One of the major considerations in the cyclic use of progestins for contraception is the maintenance of a regular menstrual schedule. Therefore, we paid particular attention to any changes from the premedication menstrual pattern.

In a previous report we indicated that bleeding on days other than regular menstrual days ("breakthrough" bleeding) and intermenstrual spotting were commonly reported. There was more breakthrough bleeding and intermenstrual spotting during the early phase of the study. The incidence was reduced considerably by adjusting the estrogenic component, as described below.

There were 87 patients who had breakthrough bleeding or intermenstrual spotting. Of a total of 4939 cycles evaluated in detail, breakthrough bleeding occurred in 281 cycles and intermenstrual spotting in 139 cycles, a combined incidence of approximately 8 per cent.

Amenorrhea presents a problem in the use of oral progestin medication in that failure to obtain withdrawal bleeding disturbs the patient and can be confused with an indication of pregnancy. If withdrawal bleeding fails to occur, the patient is told to resume medication 8 days after taking the last tablet of the previous cycle. We believe that the recommendation is warranted, because as long as the medication is taken the chances of pregnancy are extremely remote.

Fifty patients missed their periods during the period covered by this report. The total number of periods missed was 282, out of the 4939 cycles studied, or approximately 6 per cent.

Another change in menstrual function was the tendency of patients to develop a reduced quantity of menstrual flow during cyclic therapy. Fourteen patients reported 52 cycles with increased flow, whereas 70 patients reported 230 cycles with decreased flow. Thus, decrease in flow occurred about 6 times more frequently than increase in flow. This finding did not appear to be of any particular importance. Many patients preferred having less bleeding during their periods, and once they were reassured, the relative decrease in flow was looked upon as a positive factor rather than as a side effect.

LIBIDO AND MISCELLANEOUS SIDE EFFECTS. Findings relating to changes in libido, dysmenorrhea, headache, and breast tenderness are extremely difficult to evaluate because the psychic factor is so variable.

Eighty-nine patients reported an increase in libido during 128 cycles, whereas 17 reported a decrease during 18 cycles. Eighteen women stated that they had headaches during 20 cycles. Twenty-eight mentioned soreness of the breasts during 36 cycles. Finally, 209 patients noted that their menstrual pain was diminished, whereas 142 reported it to be increased.

Early in the study, a small percentage of patients reported a definite decrease in libido that appeared to be related to use of the medication. This was of some concern, but as the study progressed it became clear that the number remained small and also that some patients were reporting increased libido. In view of the substantially increased amount of patients reporting greater libido this finding could very well be significant. It is very possible that a major reason for increase in libido was a feeling of security based on the knowledge that intercourse would not be associated with the occurrence of an unwanted pregnancy.

DISCUSSION

With more than 4 years' experience, we have become increasingly impressed with norethindrone as an agent for conception control. Of several methods of contraception now available at our clinic, the oral method is the most popular with patients. The method is undoubtedly effective; even if we were to consider all unplanned pregnancies as method failures, the six conceptions in 7194 cycles would give a pregnancy rate (number of pregnancies $\times$ 1200, divided by number of months of use) of approximately 1. This pregnancy rate is better than the most commonly reported figure for the diaphragm-and-jelly method. As a substantial number of patients admitted incorrect use, particularly in the first cycle, the effectiveness and corrected pregnancy rate would be even better. Moreover, our data indicate that pregnancy is readily achieved after discontinuance of norethindrone administration.

Since our studies have indicated that certain side effects are not infrequently associated with this method of oral contraception, the physician must be in a position to evaluate them properly. In brief, the side effects enumerated above were generally not troublesome enough to interfere with the use of the method. Earlier in our study, we reported that side effects were a relatively frequent reason for changing to other methods of contraception because both physician and patient had much less confidence in the oral method and much less information as to what to expect. As our study progressed, our clinicians have been increasingly favorably impressed, and word-of-mouth information concerning the lack of seriousness of the commoner side effects has spread from patient to patient. The knowledge that most side effects were temporary has led many of our later patients to accept certain annoyances that previously might have been considered as an indication for changing the method.

The data serve to emphasize that such side effects as menstrual disturbances and gastrointestinal symptoms, the commonest side effects, generally occurred in the first few cycles and then tended to disappear. The reasons for the development of this tolerance are obscure, but there is definite evidence that the estrogen content of the compound is of considerable importance. In the usual manufacture of norethindrone, the 3-methyl ether of ethinyl estradiol appears as a contaminant in quantities up to 0.6%. During the course of this study, the manufacturer attempted to eliminate as much estrogen as possible, so that some lots contained more of it than others. It was observed that increased incidences of bleeding irregularities occurred with certain lots. Although the mechanics of correlating each cycle of use with each specific lot would be overwhelmingly difficult, it is our impression that the batches with very low estrogen content were associated with cycles of increased bleeding

irregularities. This is corroborated by the fact that when the estrogen concentration was fixed at 0.6%, the incidence of breakthrough bleeding became much lower than the general 4-year average.

In connection with side effects, it should be emphasized that the incidence of problems will vary with the preparation, the dosage, and the characteristics of the patient groups.

The question of long-term use of these progestational steroids has in part been answered by the approval of Food and Drug Administration of the claim of contraceptive effect for norethyndrel, a substance almost identical to norethindrone. However, the F.D.A. ruling limits contraceptive use in any one person to a period of 2 years.

Until further data on systemic effects are available the 2-year restriction is justified. Most of our patients have used these compounds for about 2 years, and the number of longer-term users has not approached the number in the 2-year group. As we continue to acquire more 3-, 4-, and 5-year users, we will be able to report with more assurance on longer-term use. In this connection, we are trying to obtain more data concerning subsequent reproductive activities in these patients, as well as the nature of their ovarian function following cessation of therapy and effects on other endocrine glands. We are also trying to obtain data concerning the status of infants born of women who have used this method of contraception.

It is important to note that the patients in our series are generally women of fairly good educational backgrounds. This is undoubtedly of importance in relation to effective use of these compounds. On the other hand, it should be noted that a relatively small group of patients, generally those with lesser degrees of education, have difficulty following the instructions for proper use of the method. The significance of this is obvious in relation to the international population problem. Whether this method can be successfully taught and employed on a large scale in overpopulated, underdeveloped areas in which education is inadequate, is an important question that requires an answer. Other studies now in progress elsewhere may help provide this information, for one factor seems increasingly evident: In birth control studies it is not routinely possible to transpose results pertaining to acceptability, tolerance, and the like from one population group to another.

CONCLUSION

Norethindrone given in a dose of 10 mg. per day on 20 days of the menstrual cycle is very effective for contraception and can be prescribed for at least 2 years with assurance as to its probable safety.

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