

The Food and Drug Administration  
Advisory Committee on Obstetrics and Gynecology

REPORT OF SUBCOMMITTEE MEETING

Place: Crystal Plaza Office Center, Arlington, Virginia

Date: February 25, 1966

Participants: Dr. Karlis Adamsons (Chairman), Dr. Henry F. Fuller,  
Dr. Robert Hodges, and Dr. Edward Ortiz

Agenda: Revision of the Preliminary Report pertaining to the  
Evaluation of the Efficacy of Oral Contraceptive Drugs  
Presented to the Advisory Committee on January 20, 1966

The following uses for which therapeutic efficacy has been  
claimed were reviewed:

- A. fertility control
- B. treatment of amenorrhea
- C. treatment of dysmenorrhea
- D. treatment of endometriosis
- E. treatment of functional uterine bleeding
- F. habitual abortion
- G. miscellaneous uses

Note: With the exception of subject A the comments pertain only to  
combination preparations containing a progestational agent and an  
estrogen.

A. Fertility Control

The efficacy of the older oral progestational agents in  
fertility control was considered exceptional when compared with

that of other therapeutic agents used in medical practice, such as antibiotics, analgesics and tranquilizers. Even when all contraception failures are considered to represent drug failure rather than patient failure in proper administration of the drug, the efficacy index in most series exceeds 99%. The more recently introduced sequential preparations were also found highly effective in controlling fertility, although to a slightly lesser degree than the progestational agents. The frequency of pregnancies occurring while patients were receiving sequential preparations averaged approximately 1.2 per 100 women years. It was considered that sufficient number of patients have been studied up to two and one half years to justify statistically valid conclusions. On the other hand, the group sizes representing patients that had been followed for up to 54 cycles were too small to offer anything more than general impressions. It is noteworthy that the frequency of pregnancies occurring while on medication remained unchanged over the two and one half year period, thus supporting the contention that tolerance to or escape from the medication does not occur. The committee commented on the terms "unwanted" and "unplanned" pregnancies used in the submitted material. Since the individual circumstances under which the pregnancies occurred did not appear to be known to the investigator, the use of these terms did not seem to be warranted. From the statistical point of view, difficulties were encountered in the interpretation of "woman years" since the value of large numbers observed for a short

period is not comparable to long term observations on a small sample. It was also pointed out that the high efficacy of oral contraceptives is not entirely due to suppression of ovulation but also to other mechanisms of action such as changes in cervical mucus, endometrium, and possibly on the development of the early embryo.

B. Treatment of Amenorrhea

The efficacy of oral contraceptives in the treatment of amenorrhea could not be readily determined by the material available to the committee because of the endpoint used. Successful treatment was considered one in which uterine bleeding was accomplished following cyclic withdrawal of the medication. It was the opinion of the committee that such an endpoint does not specifically measure the efficacy in treating amenorrhea, since cyclic withdrawal bleeding and menstrual periods are different biologic phenomena. If efficacy in the treatment of amenorrhea is being claimed it could be based only on evidence that menstrual cycles are established following discontinuation of drug therapy. Such information was not contained in the submitted material. However, it was pointed out that if the objective of the therapeutic effort is to produce cyclic withdrawal bleeding in the amenorrheic patient, the oral contraceptive drugs can be considered as efficacious since this endpoint was achieved in 80 to 90 percent of treated patients.

Additional information desired:

1. Follow-up data on amenorrheic patients after discontinuation of the cyclic therapy with oral contraceptives.

2. Comparison with the frequency of spontaneous resumption of menstrual periods in similar patient material.

C. Treatment of Dysmenorrhea

The comments pertaining to drug efficacy in the management of patients with dysmenorrhea were similar to those alluded to in the previous paragraph. The situation was even more complicated because of the difficulty to quantitate the principal variable. Dysmenorrhea is known to disappear spontaneously and relatively "high cure" rates have been obtained with placebo preparations. No follow-up data were available in the submitted material, and thus, in reality, the reports pertained to the evaluation of pain during cyclic withdrawal bleeding rather than during a menstrual period. The data suggests that in certain patients the progestational agent might be of value in the treatment of dysmenorrhea. However, additional information is required before the therapeutic efficacy can be considered as demonstrated.

From the statistical point of view the submitted material was considered unsatisfactory because of the small number of patients in the individual series. It was surprising to find that a very small sample had been utilized in the study of such a common phenomenon. The members were cognizant of the difficulties in designing controlled studies, since placebo preparations do not provide contraception, a fact that cannot be left undisclosed to the patient.

Additional information desired:

1. More data with expansion of the individual series with suitable controls.

D. Treatment of Endometriosis

In evaluating the material in which the diagnosis of endometriosis was established by histologic examination, the committee finds a high therapeutic value of continued and prolonged (6 to 12 months) progestational therapy in either conservative management or pre- and postoperative treatment of the affected patient. In the well documented cases it is reasonable to anticipate a favorable response in 75 to 90 percent. It must be, however, pointed out that recurrence might be expected in an appreciable proportion of patients after secession of medication.

In contrast, the therapeutic efficacy in subjects in which the diagnosis of endometriosis had been made on grounds of physical examination or history only, was uncertain. Undoubtedly, this population contains a variety of disease entities such as residual pelvic inflammatory disease, adnexal pathology of noninflammatory nature, etc., which are not expected to improve during therapy with progestational agents.

The committee recommends that in future studies, only those patients are included for evaluation in whom objective criteria for the presence of endometriosis can be provided.

E. Treatment of Functional Uterine Bleeding

The claims for therapeutic efficacy in treatment of functional uterine bleeding were met with similar criticism that applied to dysmenorrhea and amenorrhea. The committee finds the pooling of a

variety of conditions summarized under the heading of "Functional Uterine Bleeding" inappropriate because the individual disease entities have specific and different etiologies. Thus, an overall efficacy index might not reflect the favorable results achieved in certain categories or vice versa, and create the impression of therapeutic merit for disease entities which are not susceptible to therapy.

Irregular menstrual periods are expected to respond in a high percentage of cases to therapy if cyclic withdrawal bleeding is made synonymous to a menstrual period, whereas metrorrhagia might be and appears to be considerably more resistant to the advocated therapy. Difficulty in constructing a meaningful endpoint for the various categories was apparent since most of the functional bleeding abnormalities are known to be self limiting.

Additional information desired:

1. Data on patients in whom oral contraceptive drugs were used to control acute bleeding episodes.

F. Habitual Abortion

The Committee found no data which would indicate that any of the oral contraceptives are effective in favorably altering the natural history of patients with habitual abortion. Although the reasons for habitual abortion are not known, it appears that in a considerable percentage of cases it is due to a genetic defect in the embryo. These cases, in all certainty, would not

benefit from steroid therapy. It was pointed out that clear distinction should be made between synthetic progestins, some of which have known androgenic properties, and the native product progesterone when their use in the therapy of threatened abortion or habitual abortion is considered.

G. Miscellaneous Uses

The value of oral contraceptives in the treatment of conditions such as acne, chronic vulvar infections, psychotic and emotional disorders could not be ascertained at present because of the preliminary nature of the available reports.

Summary

The efficacy of the older progestational agents in fertility control is exceptional and approaches unity. The more recently introduced sequential preparations are also highly effective in reducing the incidence of pregnancies although with not quite the same degree of certainty as the progestational compounds. Regarding other uses, the efficacy is less certain. Most studies lack control and follow-up data and, consequently, it is difficult to determine whether drug treatment resulted in a significant departure from the course expected from the natural history of these frequently self limiting disorders. Consistently the phenomenon "cyclic withdrawal bleeding" is confused with menstrual period which is unwarranted. Pelvic endometriosis, however, represents a notable exception. In this disorder, prolonged therapy appears to offer excellent palliation and occasionally even disappearance of endometrium from abnormal sites.

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