

FOOD AND DRUG ADMINISTRATION
ADVISORY COMMITTEE ON OBSTETRICS
AND GYNECOLOGY

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MINUTES

THIRD MEETING
April 7 and 8, 1966

Bureau of Medicine
Arlington, Virginia

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COMMITTEE MEMBERS:

Dr. Karlis Adamsons
Assistant Professor of Obstetrics and Gynecology
Columbia University

Dr. Elsie R. Carrington
Professor of Obstetrics and Gynecology
Women's Medical College - Philadelphia

Dr. Eleanor M. Delfs
Professor of Obstetrics and Gynecology
Marquette University - Milwaukee, Wisconsin

Dr. Henry F. Fuller
Clinical Associate Professor of Obstetrics and Gynecology
University of North Carolina

Dr. Louis Hellman, Chairman
Professor of Obstetrics and Gynecology
State University of New York

Dr. Roger B. Scott
Professor of Obstetrics and Gynecology
Western Reserve University

Dr. Christopher Tietze
Director of Research
National Committee on Maternal Health

CONSULTANTS TO THE COMMITTEE:

Dr. Philip Sartwell
Professor of Epidemiology
Johns Hopkins University

Dr. Schuyler Kohl
State University of New York

SPECIAL GUEST:

Dr. Philip Corfman
National Institute of Child Health
and Human Development

FOOD AND DRUG ADMINISTRATION STAFF:

Dr. James L. Goddard, Commissioner
Dr. Robert J. Robinson, Acting Director
Dr. Paul A. Palmisano, Acting Deputy Director
Dr. Jean D. Lockhart, Assistant for Medical Resources and Liaison
Dr. Clem O. Miller, Coordinator of FDA Committees
Dr. William J. Evans, DMR
Dr. Ralph G. Smith, DMD
Dr. Donald G. Levitt, DMI
Dr. Robert M. Hodges, DMD
Dr. James W. Long, DMD
Dr. Adrian H. Gross, TE
Dr. Jule K. Lamar, TE

EXECUTIVE SECRETARY:

Dr. Edwin H. Ortiz, DMR

Dr. Hellman called the meeting to order and introduced Dr. Goddard, Commissioner of the Food and Drug Administration. Dr. Goddard thanked the Committee for meeting and promised to furnish support in handling the problems with which the Committee is presented.

Ethynerone

Dr. Hodges stated that this drug, investigated by eight United States and two foreign investigators, has three times the progestational activity of Mesthynodrel. Huntington Laboratories in England conducted a study in beagles which received up to 25 times the human dose. The animals on the low dose showed mammary hyperplasia while the dogs on the high dose, when sacrificed at 52 weeks, showed carcinoma in situ with early invasion, carcinoma in situ, atypical hyperplasia, and benign intraductal papilloma.

Dr. Adrian Gross presented color slides of the microscopic sections to the committee.

Dr. Adamsons remarked that malignant changes in animals brought about by medication can often be reversed after discontinuation of treatment.

Dr. Hellman pointed out that the dose seemed quite high and wondered if too much weight can be placed on this data.

Dr. Hertz stated that this effect has been described in animals when these types of compounds are used. He said there was no reason to single out any particular drug because of these results.

It was also pointed out by committee members, that experiments of this sort may give us proof of toxicity of the drug rather than predictable results, and that similar studies done in currently marketed products may yield the same results.

Dr. Kohl's Survey

Dr. Schuyler G. Kohl reported the findings of his survey of deaths reported by all the oral contraceptive drug manufacturers. His personal inspection of the records of each company yielded 110 deaths reported on patients who were taking oral contraceptives, of which 65 were due to "idiopathic" thromboembolic phenomena. He remarked that the yearly number of deaths reported has not increased through the years, even though the number of patients taking these drugs has multiplied.

Drs. Kohl, Hertz, Tietze, Goddard, Hellman, Sartwell and Fuller discussed the need for a good nationwide surveillance system. The pros and cons of different systems were discussed, and most committee members felt that a Government sponsored system would be preferable.

Dr. Kohl indicated that two thirds of the deaths occurred in patients who had taken the medication for less than four months, and that 25% of the patients were

taking the drug for an indication other than contraception.

Dr. Kohl, and the committee members thought that this survey was a good source of information, although they realized that the figures were not significant from a statistical point of view.

Dr. Tietze mentioned the yet unpublished reports of GAF (Growth of American Families). This survey, conducted on married women living with their husbands will indicate that 6 to 6.5 million women have at one time or another taken oral contraceptives and 3.5 to 4 million women are currently taking these drugs. This study was based on a survey of approximately 6 thousand persons.

The committee agreed not to release any of the information obtained from Dr. Kohl's survey until it is incorporated in the final report to be drafted at the next committee meeting.

Dr. Sartwell's Report

Dr. Sartwell presented a preliminary report intended to be submitted to Dr. Eastman, who is chairman of the subcommittee on Thromboembolic Phenomena. Several steps have been taken towards starting the pilot study at Johns Hopkins. They include: a search of the literature, a review of hospital records of patients discharged with a diagnosis of thrombophlebitis (the "idiopathic" cases amount to about 10), and the preparation of an interview form. There is a possibility that the Mayo Clinic may be used in the pilot phase of the study, and a preliminary conference has been held with Dr. Virgil N. Slee regarding the cooperative effort with his organization, the Commission of Professional and Hospital Activities.

Dr. Sartwell and Dr. Long presented to the committee, and the committee discussed, several problems involved in the selection and matching of patients.

Dr. Scott's Report

Carcinoma of the Cervix

Dr. Scott stated that the data available is difficult to analyze because of lack of completeness. He stated that if the recommendation that pap smears be done on patients receiving oral contraceptives every year is carried out, this will constitute a good preventive measure for invasive carcinoma of the cervix.

Carcinoma of the Endometrium

Dr. Scott stated that such a small percentage (5 to 8 per cent) of carcinoma of the endometrium occurs in patients under age 40 that the occurrence of the disease in patients on oral contraceptives will be very rare. He pointed out that numerous studies suggest a preponderance of estrogenic influence, either endogenous or exogenous, in women who subsequently develop endometrial adenocarcinoma.

Dr. Hertz stated that carcinolytic substances in man are known to be carcinogenic. Since we know that progesterone is carcinolytic, we would expect it to be carcinogenic also.

Carcinoma of the Breast.

Dr. Scott stated that he does not believe that the advent of estrogens has influenced the rate of breast carcinoma in humans. He mentioned that there is an increased amount of intra- and peri-lobular fibrosis in the breast in a study of a small amount of women on contraceptive pills.

Dr. Hertz stated that this study is inadequate, since the patients had only one year of maximum exposure. But some changes seem to be going on in the breasts of women taking oral contraceptives.

Dr. Hertz stated that there seems to be a different response to estrogens from young uterine tissue and from old uterine tissue.

Dr. Delfs remarked on the lack of concern of practitioners recently about postmenopausal bleeding. She stated that this trend should be reversed.

The committee then discussed the handling of the IUD for Ethynerone by The Food and Drug Administration and the role of the FDA in regulating the use of oral contraceptives.

Dr. Hertz summarized his views by stating that:

1. The Administration should exercise educational functions.
2. It should develop prospective studies designed so that further knowledge will be gained.

The Committee members then discussed the relative efficacy and ease of administration in clinic population of the different types of birth control measures.

Dr. Scott presented his recommendations to the Committee. He encouraged more extensive animal studies in several species, clinical trials in which significant data can be obtained pertaining to the relationship of oral contraceptives to the development of malignancy, and endorsement of the current statement in the labeling of oral contraceptives which states that these drugs are contraindicated in patients with previous history of breast or genital malignancy.

Dr. Delfs' Report

Pituitary, Adrenals, Thyroid and Pancreas

Dr. Delfs stated that studies indicate that the main action of the oral contraceptives is inhibition of ovulation at the pituitary level, with no demonstrable impairment of subsequent fertility. She also stated that there is

no definite evidence of clinical hazard on the pituitary, adrenal or thyroid function, although thyroid function tests must be interpreted with caution during the use of oral contraceptives and for a period of two months after cessation of medication. She stated that oral contraceptives should be avoided in women predisposed to diabetes until further research clarifies whether or not oral contraceptives may induce diabetes in normal women and convert preclinical diabetes to active diabetes in susceptible women. Dr. Delfs pointed out that some authors find a statistically significant increase in diabetes with parity.

Liver Function Test

Some women on oral contraceptives showed derangement of liver function tests, especially the BSP and transaminase. A few develop clinical jaundice and evidence of mild liver damage demonstrated by biopsy.

Effects on the Fetus and New-born

Dr. Delfs stated that oral contraceptives in high dosage may inhibit lactation. Studies in animals have shown that the hormones present in oral contraceptives have affected the male pattern or female pattern of the newborn and have rendered them sterile. Not enough time has elapsed in humans to adequately evaluate this effect. Dr. Delfs recommended that synthetic progestins should not be used in the treatment of threatened or habitual abortion. She also said that where the possibility of pregnancy exists, pregnancy tests are advisable before instituting or reinstating oral contraceptive routine.

Dr. Adamsons' Report

Dr. Adamsons stated that the oral contraceptives are highly effective when used for the purpose of contraception. The sequential preparations were found to be highly efficacious, although to a slightly lesser degree than the combination tablets.

Drs. Tietze, Hellman, Adamsons, and Scott discussed the significance of pregnancy rate, efficacy index, and the possibility of ovarian escape after several cycles of use.

Dr. Adamsons stated that in the treatment of amenorrhea and dysfunctional uterine bleeding the oral contraceptives may be effective in giving regular episodes of withdrawal bleeding. This does not necessarily mean that the patient will have normal menstrual periods after discontinuation of therapy.

Progestational agents may be useful in threatened and habitual abortion when hormonal deficiency is present. He also stated that in the treatment of endometriosis prolonged therapy with oral contraceptives appears to offer

deletion of endometrium from abnormal sites.

Dr. Tietze proposed that the committee check the death certificates of the patients reported by the drug manufacturers as having had "idiopathic" thromboembolic phenomena while on oral contraceptives and obtain a sample (of approximately 25%) at the National Office of Vital Statistics of death certificates of patients in the age range of 20 to 44 years who died of "idiopathic" thromboembolic phenomena. The cases in the second group can be traced back for evidence of a specific etiology for the thromboembolic phenomena.

The Committee members then briefly discussed the possibility of oral contraceptives as etiology for cerebral vascular accidents and eye abnormalities. They also discussed the possibility of removing the time limitations from the labeling of these drugs, but agreed that close surveillance is still necessary.

Mestranol

Dr. Hodges presented the result of animal findings on Mestranol acetate, which is marketed under the name of Volidan in England. Dogs treated with this drug developed thrombi in the right ventricle and pulmonary artery. Clinical trials with this drug have been discontinued in the U.S.

The committee will meet again in June to draft a report.

Respectively submitted:

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Executive Secretary
Advisory Committee on
Obstetrics and Gynecology
Bureau of Medicine