

FOOD AND DRUG ADMINISTRATION
BUREAU OF MEDICINE
SIXTH MEETING
OBSTETRICS AND GYNECOLOGY ADVISORY COMMITTEE

May 18 and 19, 1967

Arlington, Virginia

Crystal Plaza Office Center

Members of the Committee Present:

Dr. Karlis Adamsons (first day only)
Dr. Elsie Carrington
Dr. Philip Corfman
Dr. Eleanor Delfs (first day only)
Dr. Nicholson Eastman
Dr. Henry Fuller
Dr. Roy Hertz
Dr. Schuyler Kohl (second day only)
Dr. Alfonse Masi
Dr. Philip Sartwell
Dr. Roger Scott
Dr. Christopher Tietze

Consultants to the Committee Present: Dr. Sheldon Segal

Chairman: Louis M. Hellman, M.D.

Executive Secretary: Edwin M. Cortiz, M.D.

PROCEEDINGS

Dr. Hellman opened the meeting.

Prospective Study:

Dr. Ley introduced Dr. Anderson for his report on the feasibility of a collaborative study on the adverse effects of contraceptive drugs. Dr. Anderson heads a pro tem task force which has investigated the problem from the standpoint of methodology. It would take several years for the evaluation of carcinoma associated with oral contraceptives, about 3 or 4 years for the study of thromboembolic phenomena, while the study of carbohydrate and other metabolic effects could be resolved in a much shorter time. The studies could be either prospective or retrospective. The drugs are either combination or sequential, and in each category there are several brand names with different chemical composition. Dr. Anderson stated that in order to conduct an adequate study using several study centers, the protocols must be standardized and the forms and procedures must likewise be very similar in all centers. A very high degree of monitoring is required. He stated that the only realistic hope for obtaining useful

information from a collaborative study is to closely monitor a long-range study of quite limited scope.

His recommendation was for FDA to locate responsibility for the pursuit of this matter in one unit created for the purpose and to staff realistically in accordance with the degree to which it was decided to press on. To continue as in the past would not produce, he stated.

Dr. Lay stated that a cooperative study is almost doomed, since we are almost obligated to use the available facilities. Dr. Hellman pointed out certain difficulties associated with the use of the facilities of Kaiser Permanente. Dr. Anderson noted that the purpose of the existing Kaiser contract with FDA is to extract from the hospital records information of value for adverse drug reactions. He stated that the new contract is aimed at collecting information from the inpatient records, outpatient records, pharmacies and house calls. This information will be in one information system in order to try to correlate the occurrence of certain diagnoses with the use of certain drugs. It will take approximately one and half years to get going on this study, which includes oral contraceptives but is not specifically aimed at this drug category any more than any other category.

He referred to the need for two types of studies with respect to contraceptive drugs.

1. Specific laboratory-oriented studies requiring limited numbers of subjects.
2. Epidemiologic studies of broader nature requiring large numbers of subjects.

Dr. Corfman agreed with this analysis and stated that some studies of both types are currently contracted for by NIH.

Dr. Anderson suggested the formation of HEW policy requiring the cooperation of NIH, the FDA and the Children's Bureau and any other part of HEW funding birth control programs in assuring the collection and submission of certain information as part of any such program receiving Federal support.

Dr. Hellman mentioned the necessity of a protocol to study congenital malformations in children born to women previously on oral contraceptives.

Dr. Segal noted that the Population Council supports studies, and some investigators might alter the design of their studies to suit the FDA needs if we let them know what we are interested in. At present the Population Council has three grants on carbohydrate and lipid metabolism and that there is also a study in progress of the possible lack of resistance to tuberculosis in women on oral contraceptives.

Dr. Tietze stated that in view of the difficulties associated with setting up prospective studies we should consider some retrospective studies similar to the reports currently available from the United Kingdom on vascular disease. He remarked that all three studies were done retrospectively and

one of those studies is almost identical to the current study sponsored by the FDA.

British Report:

Dr. Ley mentioned the possibility of a representative from Great Britain discussing the British findings with the Obstetrics and Gynecology Advisory Committee. He stated that Dr. Cahal is to come to Canada in June and asked the Committee if they would be interested in meeting with Dr. Cahal and possibly Dr. Witt.

Dr. Tietze stated that Dr. Cahal has some information not yet published in the BMJ. He expressed agreement with the editorial.

Dr. Tietze stated that even though the oral contraceptive users are young middle class women, in whom the mortality is very low, you come out ahead on oral contraceptives. There are certain risks from anything and contraception is no exception.

Dr. Tietze added that we need to get detailed information before it appears in the press. Dr. Hellman remarked that the British have concluded part of the study and their conclusions are not different from those of the Sartwell report.

Dr. Tietze suggested the use of the National Office of Vital Statistics to gather some information on mortality.

Dr. Ley remarked that there is a long lag in reporting, as long as two years.

Dr. Sartwell stated he agrees with Dr. Anderson about a cooperative prospective study. He stated that they look better than they turn out.

After a brief discussion the members of the committee decided to meet with a representative from the United Kingdom even if it doesn't coincide with the next scheduled meeting on devices.

Pincus-Rutstein Study:

Dr. Corfman introduced the study by saying that it is based on experience in Puerto Rico and Haiti and stated that Dr. D. Siegel of NICHD will give more information on the subject.

Dr. Siegel said that 12,000 patients were followed up in 3 clinics in Puerto Rico. Six thousand patients were on oral contraceptives and 6,000 patients served as controls. The main interest of the study was the effect of oral contraceptives on breast and cervical carcinoma. He mentioned that the study has been quite unsuccessful in adequate follow-up of the patients. Approximately one-third of the patients never came back after the initial examination. He stated that the organizers of the study would like to see a physician come in and follow the patients.

Dr. Tietze stated that the study is not suitable for the study of thromboembolic phenomena. He said that a thromboembolic phenomenon is a sudden occurrence. Unless the group is under constant medical supervision it is not feasible to conduct such a clinical trial. He stated that Planned Parenthood only gives contraceptive advice and is therefore not a good group to use.

Dr. Masi thought that some money could be allocated for a Puerto Rico type follow-up and that the study could be started with Dr. Pincus' sample and then enlarged.

Dr. Tietze stated that if a large sum of money was involved you would need a quasi-captive population. He stated that the population in Puerto Rico is difficult to deal with from that standpoint. An alternative solution would be to persuade the Department of Defense to allow the study of dependents and military personnel for that purpose.

Dr. Corfman stated that Dr. Rutstein would like to have a physician come in and examine the patients and conduct the clinical evaluation.

In answer to Dr. Hallman's question, Dr. Corfman replied that Dr. Rutstein lacks the time and money necessary for adequate follow-up.

Dr. Tietze then stated that the only advantage of the Puerto Rico study is the observation of the survivors of a long range treatment with oral contraceptives.

Depo-Provera for Contraception:

Dr. Armstead presented a preliminary medical officer's report of the use of Depo-Provera for contraception. After presenting the animal toxicity data and the human pharmacology studies he summarized the efficacy data obtained to date. Depo-Provera has been used as an injectable female contraceptive agent in dosage regimen of 150 mg. every 3 months in 1320 patients who completed 3,760 patient months of treatment. Of these 288 completed 11 months. The study was performed by 10 investigators in clinics and by 32 physicians in their private practices.

Four patients became pregnant while on the drug, three within 60 to 85 days after receiving the initial injection and a fourth about 45 days after receiving a second injection. This represents 0.55 pregnancies per 100 women years. Eight pregnancies were reported following discontinuation of treatment. They occurred from four and one half to 14 months after the last injection.

A total of 356 subjects have dropped from this study for all reasons, for a dropout rate of 27.8 percent. The major reason for drop out was bleeding, which accounted for 8.6 percent of the subjects. During the course of the study 96 to 99 percent of the women had bleeding and or spotting on one or more days during their time in the study. Laboratory studies were fairly well within normal limits.

Dr. Tietze called this a heroic method of contraception and this study shows lack of statistical sophistication. Specifically, when the drug is listed as being discontinued due to "other reasons" these add up to 10 percent and this should be broken down further. In the instance of quoting pregnancies from treatment it should be specified if the patients were post partum. The fact that "some" women became pregnant on discontinuation of treatment only proves that "some" women are able to conceive. It should be stated how many get pregnant by months while not using contraceptive.

Dr. Scott stated that Depo-Provera consists of implanted pellets and varies in dosage according to the administration. He was concerned with what happens to the subjects after the treatment is stopped. They may have abnormal spotting and anovulatory cycles. He stated that he is not happy with the agent.

Dr. Segal stated that there is lack of concern for animal toxicity. For example, there is adrenal cortical atrophy identified in dogs who underwent chronic administration of the drug. He stated that more data is needed on the adrenal. He also stated that there is little regard for the endometrium. It should be checked for response to estrogens. He also stated that with regard to efficacy, the total number of patients is small with the figures provided. (288 patients completed 11 months). A life table is necessary for acceptability.

Dr. Tietze stated that the use effectiveness figures are crude. The pregnancy rate and the drop out rate are affected by availability of alternative methods.

Dr. Adamsons remarked that the suppression of adrenals in animal studies was described at 1,000 times the human dose. The normal dose is unlikely to lead to adrenal atrophy in the human. He also stated that this may be the only drug available for some groups, for example, the mentally subnormal.

Dr. Goddard stated that he is upset about the quality of the investigation and the exposure of women to this investigational regimen.

Dr. Tietze stated that a smaller study would have produced inconclusive data. He also stated that post treatment amenorrhea is hard to evaluate.

Pelvic Inflammatory Disease Report:

Dr. Scott presented his concern about three cases of deaths from sepsis following insertions of intrauterine devices without perforation. He stated that these 3 deaths occurred within 3 weeks of insertion. They all had the same picture as infected abortion. Two of the 3 patients had positive culture for streptococcus viridans. He stated that in many instances the sterile technique has been disregarded by the physicians who insert the devices. He then presented his recommendations as follows:

1. Reliable figures for prevalence and incidence of pelvic inflammatory disease in various control population groups should be found or determined.

2. A national survey should be made and reporting should be encouraged in order to learn the magnitude of serious inflammatory processes associated with the insertion of IUDs.
3. Further clinical and laboratory research including control populations should be encouraged to determine the relationship of IUDs and infection.
4. Sterile prepackaging of all devices and inserters which cannot be autoclaved should be mandatory.
5. Standards for aseptic precautions to be used by the physician inserting a device should be established.

Dr. Adamsons stated that the rate of infection may be related to exposure. Dr. Tietze referred to a tabulation of pelvic inflammatory disease in the users of intrauterine devices classified by different categories including years of use, age, parity and intervals between last confinement and insertion. He pointed out that the incidence of pelvic inflammatory disease is markedly decreased with increase in age.

Dr. Adamsons stated that the infection which develops immediately after insertion is probably iatrogenic while that which develops later is probably due to exposure.

Dr. Scott's recommendations were then discussed. It was recognized that obtaining the prevalence and incidence of pelvic and inflammatory disease in various control population groups was useful, but very hard to obtain.

After various suggestions were evaluated the Committee decided that in order to collect this information Dr. Scott should send a form letter to all members of the American College of Obstetricians and Gynecologists requesting data on such side effects of IUD's as: perforations, serious complications, strangulations, and deaths from pelvic inflammatory disease.

These recommendations were accepted with minor modifications.

Dr. Tietze stated that there seems to be a relationship between pelvic inflammatory disease and insertion of the device rather than wearing of the device.

Report Of The Task Force On The Histopathologic Effects:

Dr. Hartz presented the report which states that studies conducted to date have not identified any higher incidence of malignancy of the cervix in users of IUDs than in a comparable population. The incidence of carcinoma of the endometrium has not been studied. Various prostheses of similar material have been used in humans for several years without evidence of carcinogenesis, there is no concern about such reaction developing from the use of IUDs.

Dr. Hellman asked if any possible carcinogens are present in the devices. Dr. Hertz stated that most of them are made of polyethylene. Dr. Hellman stated that during manufacture proper care may keep the device safe.

Dr. Adamsons stated that devices currently manufactured do not contain substances known to be carcinogenic to primates. They are straight chain chemicals and no aromatic substances have been used. It may be useful to consider this in drafting regulations for future devices.

Dr. Hellman asked if there are any conclusions or recommendations.

Dr. Tietze stated that the oral contraceptive report has lack of uniformity of format in the several task force reports. He suggested that the report on IUDs should be edited so that the task force reports are similar in format.

On questioning from Dr. Masi, Dr. Tietze stated that one percent of the cases observed in his series of wearers of IUDs had Class three Pap smear which reverted to normal without removing the device or giving therapy.

Report Of The Task Force Of Biologic Effects:

Dr. Corfman read a very comprehensive report which outlined the mechanism of action as well as the effect on different organs of the IUD's in several species of animals. The contraceptive effect in the human is thought to be due to acceleration of transport of ova in the tube. There are conflicting reports as to the effect of IUD in uterine contractility in the human.

Report Of The Task Force On Effectiveness, Utility And Safety:

Dr. Tietze presented his report, in which he discussed effectiveness, incidence of pregnancies, expulsions, and removal of device and by age parity, time of insertion after delivery and time of the device had been worn. The data was obtained from a cooperative study sponsored by the Population Council. He stated that he is using life tables in order to compare one study group with another.

Under side effects and complications he discussed pelvic inflammatory disease, perforation of the uterus and its sequallae, sterility, damage to the fetus if pregnancy occurs with a device in situ and ectopic pregnancy. Although it is not mentioned in his report, Dr. Tietze stated that there is a suggestion that the incidence of ovarian pregnancy may be increased in users of IUD s.

It was also stated that some perforations are associated with a particular MD. Clinic patients are more likely to tolerate the discomforts of IUD's than private patients.

Dr. Hellman had the following comments on Dr. Tietze's report:

1. It would be useful to include tables in the report.
2. The life table method of computation of effectiveness is a good contribution. It needs amplification and further explanation.

3. The report should contain a bibliography.

Dr. Hellman stated that he would like a complete bibliography on IUDs included with the report. A brief discussion followed and it was decided to consult Dr. Ley for the usefulness of a bibliography

Dr. Hellman suggested amplification of statistical data.

Dr. Tietze stated that data on life tables now being prepared for WHO will be available soon.

Report of Task Force On Legislative Recommendations:

Dr. Fuller presented the report of his committee which summarized, first of all, the regulations to which the new drugs are subjected. He stated that at the present time devices are not covered by similar legislation, but that legislation is being drafted at the present time to subject certain devices to preclearance and entitles the FDA to monitor investigation of these devices and also their labeling and promotion. The recommendation number 3 which stated that the proposed legislation should not be specifically related to intrauterine devices and therefore implied that it should cover other devices was the subject of some discussion. It was suggested that the committee would be imposing into other fields, legislation which was useful in the field of devices. Arguments for the recommendation included the idea that this type of legislation should not be limited to the regulation of contraceptive because of its social and moral implications. Also, since the legislation was found useful for the regulation of contraceptive devices, we would like to extend that usefulness to other fields of medicine as well.

The following statement was found to reflect the feeling of the Committee in this matter: "The Committee has reviewed the proposed legislation and finds it to adequately insure the safety of contraceptive devices. However, the Committee is opposed to legislation specifically intended to regulate contraceptive devices.

Dr. Segal presented several distribution figures of intrauterine devices.

Dr. Sartwell and Dr. Masi stated that the retrospective thromboembolic phenomena study started as a pilot study at Johns Hopkins is currently being expanded. Several hospitals in the Philadelphia area have been included and now the program is going into New York area.

I certify that I attended the Sixth meeting of the Food and Drug Administration Obstetrics and Gynecology Advisory Committee on May 18 and 19, 1967 and that these minutes accurately reflect what transpired.

Edwin M. Ortiz, M.D.

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Executive Secretary