Lecture Notes in Medical Informatics

Edited by D. A. B. Lindberg and P. L. Reichertz

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Long-Term Studies on Side-Effects of Contraception – State and Planning

Symposium, Munich 1977

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Symposium of the Study Group 'Side-Effects of Oral Contraceptives – Pilot Phase'

Munich, September 27–29, 1977

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PREFACE

Conference reports of scientific meetings do not automatically justify publication. Our decision to publish the Proceedings of this Symposium was based on a number of reasons.

The subject of more or less grave adverse side-effects of oral contraception is of major importance for all women. If the research institutions of Gynecology make fundamental mistakes in this subject, then the trust in them will diminish substantially. National institutions will have to shoulder a part of that burden, too, if they do not succeed in timely prevention of grave and widespread health risks and damages.

Adverse side-effects of oral contraception become only apparent in later life and probably only after a latent interval of at least 10 years. The German female population will be fully exposed to that situation during the next decade. Up to now about 40 % of the women aged 35 years or older have no experience with the pill. Ten years later nearly all of them shall have used the pill for a short period at least. If serious long-term side-effects exist, we have to build up our research strategy now to detect these health hazards in time.

Large-scale studies cannot be generated just out of nothing, the development and review of ideas in a pilot phase is necessary. The pilot phase of a German long-term study began three years ago. We shall report our experiences of that pilot phase, because this might be of value for other projects of this kind.

This integration of international experiences is part of the strategy in the pilot phase of epidemiologic large-scale studies. In this Symposium we wanted to learn from research groups working in this field. Furthermore we wanted to use the experience from currently conducted studies for the planning of a German research program.

Medical Statistics and Informatics as well as Epidemiology are the major tools in this research. The publication in a methodological series seemed therefore obvious.

The Study Group 'Side-Effects of Oral Contraceptives - Pilot Phase' is grateful to the 'Bundesministerium für Forschung und Technologie' (i.e. Federal Ministry for Research and Technology) for the promotion and funding of the project (under MT 0281/3).

We wanted to keep shades of interpretation, which might become lost in translating contributions. Therefore the Proceedings of this Symposium have been published in German, too. The German version appeared under the title 'Langzeitstudien über Nebenwirkungen der Kontrazeption - Stand und Planung' (Hrsg. Ursula Kellhammer) in the series 'Medizinische Informatik und Statistik' (Bd. 7) of the Springer-Verlag.

Munich, May 1978 Karl Überla

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1. Experience with Studies in Several Countries

CHAIRMAN: KARL ÜBERLA

INTRODUCTION TO THE GERMAN PROJECT AND AIMS OF THE SYMPOSIUM

Karl Überla

The aims of this Symposium are to get an outside opinion and constructive criticism on the work we have done up to now as well as first ideas on a model for a German long-term study on the side-effects of contraception.

We are very much obliged to the Federal Ministry of Research and Technology, who provided the means for this gathering. We appreciate the Ministry's support in making this international exchange of ideas possible and we welcome our guests to the Symposium on Long-Term Studies of Side-Effects of Contraception.

Let me introduce you briefly into our present series of pilot studies and into the German situation in general. Our project title is:

"Side-Effects of Oral Contraceptives - Planning Stage"

You might as well take this title as a short description of our German situation, because the state of our knowledge on side-effects of oral contraception has not changed much during the last few years. Let me quote an editorial from Lancet in 1976:

> "The long-term consequences on the health of the user are unknown and may become apparent in later life. For this reason alone, it is to be hoped that ... studies ... continue."
> (Lancet, 2:942-943, 1976)

The available studies are not sufficient to state with confidence that we will have no serious side-effects in the years to come. The German female population has only been exposed for a few years, the long-term effects, if they exist, are to be expected to appear within the next five to ten years.

About ten years ago in Germany the first proposals for a long-term study were made. The difficulties in rising funds shifted the start of the planning stage to 1974.

The goals of this planning stage are

- to clarify methodological problems in data collection and evaluation
- to determine the feasibility of a long-term-study in our environment by empirical field studies
- to generate empirical evidence, as to how such a study should be organized
- to develop questionnaires for patients and documentation forms for physicians
- to develop the data processing facilities for such a study

The planning stage does not have the goal of making statements about specific side-effects, rather it is our goal to develop the instruments for making such statements. We are very much indebted to the Federal Ministry of Research and Technology and to the expect panel of this ministry for their support of this planning stage (Contract No.: MT 0268). We think an extensive preparation is necessary if a long-term study is to be successful, since the methodological and practical problems are immense. This Symposium is part of our strategy of careful preparation.

The Pilot Studies we use for reaching the above mentioned goals are overlapping each other in time, as may be seen in Figure 1.

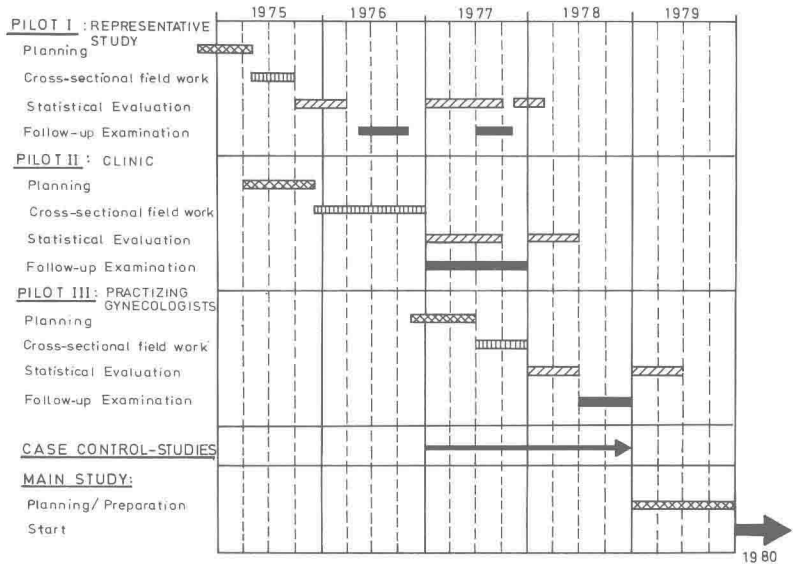

FIG.1 : OVERALL PROJECT PLAN (October 1, 1977)

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We have three Pilot Studies. Every pilot starts with a planning phase of 6 months in general. This is followed by a field survey of about 6 months and a statistical evaluation period of six months. One year after the first data collection we execute a follow-up survey and carry out the final evaluation. So every pilot runs at least two and a half years. In Pilot-I - the 'representative' study - we have extended the plan for another field survey and evaluation period. In Pilot-II - the clinical study - we have a longer fieldwork period, because the recruitment of women in the outpatient-department of a university hospital takes longer. But the basic structure is the same in all three pilots. The three pilot studies started at different points in time, so the experience of every study can be applied to the following ones. Pilot-III - the practising gynecologists' study - is actually two separate pilots. Furthermore we have had a few case control studies going on since the beginning of this year. We plan to start the main study in the beginning of 1980.

The Pilot-I interview started in 1975. Pilot-I had the following goals:

- to get a representative sample of the female population, aged 12 - 45 years, for comparative purposes and to describe the situation in the population
- to obtain a detailed description of pill-takers and non-takers especially regarding social variables to find matching criteria
- to test our fieldwork techniques, the cooperation with physicians and with the clinic of a university hospital of Obstetrics and Gynecology
- to develop data processing and evaluation procedures

The three main practical questions in this study were:

- how many women - collected in a random sample - can be motivated to go to the gynecologist?
- if three options for an examination are offered, what proportion of women will choose their own gynecologist, what proportion decides for another practising gynecologist, and how many prefer the university clinic?
- how many women can be kept under observation for one year?

We took a household-representative sample of 639 women in two age strata: 133 were girls aged 12 - 19 years and 506 were adults aged 20 - 45 years. Additionally the sample was stratified for Munich-city

(429 cases) and the country side (210 cases). The study started with an interview of about 45 minutes duration. There were only female interviewers. The questionnaire contained 132 questions regarding health-consciousness, anamnestic problems, personal attitude towards physicians, pill-taking and contraceptive history, two short psychological tests (FPI-K and Gießen Test), social level and other sociodemographic variables. 64.5% of this representative sample underwent a gynecological examination. 70.8% of the women aged 20 years and older visited a gynecologist, whereas it were only 44% of the girls under 15 years of age. Takers were more frequently examined by the gynecologist than never-takers (71.4% vs. 47.1%). We think that these percentages indicate success, especially when comparing these with participation rates in our national cancer screening program, which are 30 - 40% for women aged 30 years or older. It appears to be possible to start a long-term study like the Pilot-I study: a household-representative interview followed by a gynecological examination, which imposes a certain selection on the sample.

27% of the women chose the university clinic for the gynecologic examination. 31% of the women chose their own gynecologist and 41% chose a gynecologist unknown to them from a list which was provided by the gynecologists' association. This shows that a population-representative study is not feasible with clinics alone, it has to take the practising gynecologist into account.

The clinic in this Pilot was the outpatient-department of the II. Universitäts-Frauenklinik (i.e. II. University Hospital for Obstetrics and Gynecology), Director: Prof. Dr. Kurt Richter. Dr. Ingolf Schmid-Tannwald performed all the examinations. The clinic had more extensive examination program than the practising gynecologists (colposcopy, skinfold measuring and the usual serum tests) and the cooperation was excellent.

Pilltaking in age groups in Pilot-I is distributed, as Figure 2 shows:

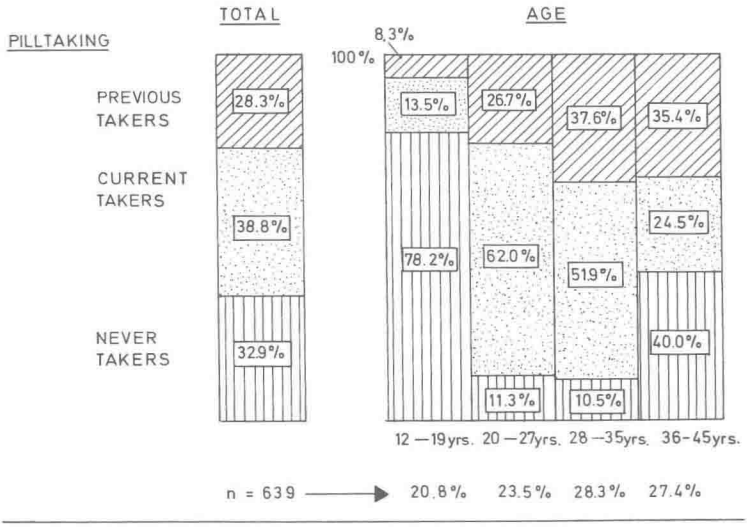

FIG. 2 : PILLTAKING AND AGE

About 90% of the women between 20 and 35 years have had experience with the pill. About 30% of all women stopped taking the pill. A large proportion of women over 35 years of age (40%) have had no experience with the pill. The main side-effects occur in this age group. When the exposed female population reaches this age group and as the exposure time is extended serious side-effects could develop. If there are grave side-effects, we shall see them in 5 to 10 years from now in Germany.

The cross-sectional evaluation of Pilot-I is available at the Study Group. The questionnaire-variables are tabulated in 11 subgroups: 4 age-groups, 3 categories of pill-taking, 2 location-classes (city/ rural area) and gynecological examination (yes/no). The variables of the medical examination are tabulated for age, pill-taking and for clinic-patients versus patients of practising gynecologists. χ^2 and 2 I - statistics were calculated and a standardisation by age was applied. The material is also available as a data base in our interactive evaluation system SAVOD.

Pilot-II started at the end of 1975. Women were obtained for the study from the outpatient department of a university hospital. Our aim was to explore this method of recruitment, its problems and advantages, and to compare the results with Pilot I.

In this Pilot we cooperated with the I. Universitäts-Frauenklinik (i.e. I. University Hospital of Obstetrics and Gynecology), Director: Prof. Dr. Josef Zander. Dr. Christina Sattler performed all the examinations and the cooperation was excellent. The women first underwent a gynecological examination, then a self-administered questionnaire was handed out to them to be completed at home. This questionnaire contains roughly the same questions as the Pilot-I questionnaire, but it was slightly modified to facilitate self-administration. The medical examination included liver tests and some endocrinological and coagulation tests.
330 women entered this Pilot Study during 1976. The recruitment-phase took longer than in Pilot-I, since only 2 - 4 women per working day could be examined. An additional group of 138 women was obtained from the obstetrics department in order to explore the approachability of women regarding contraceptive problems during puerperium. The reexamination after the one-year-interval is presently being performed and will be finished at the end of 1977. Therefore we are not yet able to give you the final number of patients who could be kept in this study for one year, but as far as can be already estimated, the results shall be of the same order as in Pilot-I.

Pilot-III started in the middle of 1977. The main objective in this Pilot is to explore the recruitment of women via practising gynecologists. To be exact there are two separate studies in this Pilot-III:
- A randomized trial comparing pill and IUD and a field survey, in which practising gynecologists contribute pairs of patients, a pair consisting of a pill-taker and a non-taker.

In the randomized trial we want find out what the limits for statistical experiments in contraceptive research are in our country. We are maybe trespassing these limits slightly in randomising pill and IUD for women with no contraindications to either, but we think that is the only way of finding out the limits to observe in the main study. We are cooperating in this trial with a small group of practising gynecologists in Munich.

The field survey with patient pairs out of gynecological practices also started only recently. We drew a stratified random sample out of all panel gynecologists in Bavaria. The selected physicians have been invited to participate in the study. The design of this field survey and the present state of gynecologists' responses shall be reported upon.

Our Pilots cover a number of recruitment schemes for a longitudinal study: we have a sample, in which we tried to be population-representative, we have a sample from the outpatient department of a university hospital, we have a sample from practising gynecologists. The questionnaire is in its content basically the same for all studies, only it was modified with growing experience and, where necessary, adapted to the data collection technique. The medical examination form also underwent a certain amount of change, especially in the anamnestic part (drug consumption, surgical operations).

I would like to mention some of the methodological problems we encountered during our work and how we thought it best to deal with these.

The reliability of the questions must be known before the beginning of a large-scale study. For this purpose we drew a random sample of adult women and interviewed them twice with the questionnaire of Pilot-I. We got two interviews from about 200 women. In one half of the sample we used the same interviewer for both interviews, in the other half the interviewer was changed.

Another problem was the generalizability of the findings. There was considerable concern about restricting the Pilot Studies to Bavaria, since other States in the Federal Republic might provide a different environment. Bavarians are generally regarded in our country as something like Texans in the US. So we undertook a study in other metropolitan areas, using the questionnaire of Pilot-I. The regional differences are not as big as one might have expected.

Drop-outs are a major problem in every long-term study. During the pilot stage one should try to determine what factors influence the drop-out rate. We did a series of experiments - for instance offering money for completing the questionnaire. We shall go into details later on. It seems to me that we have learned a lot from these expermiments and our results are not too bad.

Since case-control studies are cheaper than field studies and take less time, we have to try this type of study, too. We run two case-control studies investigating the association between myocardial infarction and pill-taking. Both started this year and consequently we do not yet have any results. One of the studies is conducted in cooperation with Prof. Dr. Egbert Nüssel, Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik Heidelberg, the other one with Prof. Dr. Dr. Uwe Stocksmeier, Institut für sozialmedizinische Präventions- und Rehabilitationsforschung e.V., Höhenried. Both started with verified myocardial infarction in women up to the age of 55 years. The problem is that the pill is still not available for such a long time, that it was a common contraceptive during the reproductive age of women, who had a myocardial infarction during the last five years. We hope to get about 70 - 100 women with verified myocardial infarction in each of these two studies, plus the corresponding controls. A special medical examination and our questionnaire (at least in its salient parts) are being applied to these subjects.

Standardisation of statistical methodology is one of the main goals in a planning stage. For the cross-sectional evaluation we have designed a standard methodology, consisting of

- the case-wise detection and elimination of errors by controlling plausibilities
- the tabulation of all variables according to a few basic ones with a standard output (including question-text and variable names)
- special statistical analyses which follow after the baseline cross-sectional evaluation.

Our standard procedure for qualitative variables is a contingency table analysis with a χ^2-test or a 2I - statistic, followed by a standardisation procedure. The quantitative variables are treated with descriptive statistics and the comparisons are done by analysis of variance or t-test. Several other statistical methods are applied as necessary, like faktor analysis, non-parametric tests and so on. We have a wide variety of statistical procedures implemented and available.

The analysis of longitudinal results with two or more observations is not as easy as one might think at a first glance. Some examples of our procedures will be given for Pilot-I.

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