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DESIGN OF CLINICAL TRIALS FOR CONTRACEPTIVE STEROIDS. ASSESSMENT OF EFFICACY

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SUMMARY

The clinical investigation of hormonal contraceptives is divided into 3 stages: planning, performance and evaluation. Planning includes a definition of the trial aim(s), determination of the clinical and biometric requirements, and the drawing up of the trial protocol (record form). By performance is understood a "controlled clinical trial", *i.e.* a trial which includes one or more control groups. The various forms of treatment (trial preparation, standard preparation, for certain problems placebo as well) are allocated to the groups strictly by random. In the evaluation and interpretation of the results a distinction is made between method-effectiveness and use-effectiveness. The three stages of the investigation are illustrated by examples and discussed in detail.

INTRODUCTION

As with any other drug, the object of the clinical trial of a hormonal contraceptive is to acquire reproducible information from which a reliable conclusion regarding the effect and/or safety of the preparation can be drawn. Trials of this nature can never be conducted on a given population as a whole, but only on samples of it. However, these samples represent neither the whole population nor the indication to be treated. If only one contraceptive is being investigated in such a sample—that is, if no comparison is being made with an untreated or differently treated control group—the result of this "uncontrolled" trial cannot be interpreted: it remains uncertain and inappropriate for generalization because it is valid only for the whole complex of a treated, systematically distorted section of a population.

The picture changes immediately when two or more different drugs or methods of treatment are allocated to the sample strictly at random (controlled clinical trial). The only difference now between the sub-samples is the different therapy, and irrefutable, relative conclusions can be drawn. This type of trial design is a logical requirement and thus a principle of modern clinical pharmacology and should accordingly also be an underlying principal in trials of hormonal contraceptives.

If the pertinent literature is surveyed from this point of view, it rapidly becomes clear that, since the introduction of hormonal contraception by Pincus in 1958, practically all newly developed preparations have only been subjected to "uncontrolled" trials. An objective comparison of the quality of the various preparations is therefore impossible. Future trials must without fail avoid this error of the past, which means that the efficacy and safety of new hormonal contraceptives should be investigated exclusively in controlled trials in comparison with existing standard preparations. Before any more is said about suitable trial designs, however, the terms effectiveness and safety must be defined.

Table 1

Effectiveness
1. **Method effectiveness** ("Pharmacologic effectiveness; theoretical effectiveness; corrected failure rate") Antifertility action of the procedure under ideal conditions, without omissions or errors in technique
2. **Use effectiveness** ("general or uncorrected failure rate") Level of protection achieved by a population using the method in a given place, at a given time under given circumstances: omissions or errors in technique are included
3. **Demographic effectiveness** Impact of the contraceptive method on population growth. Most important in terms of socio-political aspects

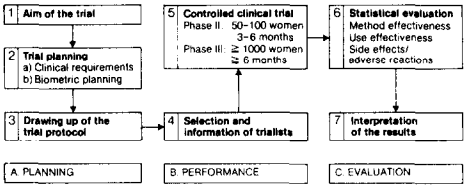
The basis for the assessment of the effectiveness of a contraceptive method is the pregnancy rate which is observed during the use of the respective contraceptive. The term "effectiveness" can be diversely defined. Nowadays a distinction is generally made between method-effectiveness, use-effectiveness and demographic effectiveness (Table 1), but we want to restrict ourselves here to the first two terms. Although method-effectiveness is the most important factor for the individual *per se*, use-effectiveness is more important generally for all aspects of fertility control: it provides an indication of the general usefulness and acceptability of a method, including the ability of an individual to follow a given prescription [19; 29].

By the "safety" of a contraceptive we mean—as with any other drug—the nature and frequency of side effects and adverse reactions. Only when efficacy and safety have been objectively assessed by means

Table 2

Some frequent faults in conducting and evaluating clinical trials with hormonal contraceptives
1. Inadequately defined aims
2. Omission of biometric planning
3. Uncontrolled trials instead of controlled trials
4. Unsuitable statistical calculating procedures
5. Comparison of the results achieved by trialist A with preparation X with those of trialist B with preparation Y
6. Extrapolation of results from one ethnic group (e. g. Caucasian women) to another (e. g. Asian women or mestizas)

Table 3



of a suitable clinical design can a confident judgement of the benefit/risk relationship of a preparation be made.

Some of the most frequent errors committed during the performance and evaluation of clinical trials of drugs—specifically of hormonal contraceptives—are presented in Table 2. Two steps must be taken prior to the start of the trial if these pitfalls are to be avoided: firstly, the aim of the trial must be defined very exactly and secondly, the nature of the trial design and of the statistical evaluation of the results must be carefully planned from a biometrical point of view. Accordingly, a clinical trial must generally be divided into 3 stages: planning, performance and evaluation. This is shown in Table 3 and the following remarks orient themselves on this scheme.

PLANNING

Although it stands to reason that the aim of the trial should first of all be exactly defined, it is amazing how seldom this is actually done: in practice it always seems to be assumed that the demonstration of effectiveness and safety are such obvious trial aims that it is unnecessary to provide a more detailed characterization of these terms in the individual case. As

Table 4

Definition and delineation of possible aims of contraceptive trials
Acquisition of information and evidence regarding efficacy, safety, practicability and acceptability of
1. a new pharmacological principle of fertility control
2. a new principle of administration
3. a modified dosage or dosage relation of the contraceptive steroid (s)
4. New steroidal compounds

Table 5

Trial planning
A. **Clinical requirements**
1. Definition of trial phase (for first-time use of a preparation: abortion available on demand)
2. Definition of mode, frequency and duration of administration
3. Definition of inclusion/exclusion conditions for the women of the trial group(s)
4. Definition of objective and subjective assessment criteria
5. Quantification of the subjective criteria (scoring systems)
6. Definition of selection criteria for clinical investigators
7. Compilation of scientific information material for the trialists
8. Preparation of a co-ordination plan for multicentre trials
9. Preparation of a trial protocol (record form) with due regard to biometric planning
10. Determination of start and duration of trial, estimated cost

the examples in Table 4 show, however, it is indeed possible to define the aim of the trial more exactly. It is, furthermore, necessary, since different trial techniques must be employed to achieve different aims. It is also easier to provide a clear description of the aims if they are based on sound medical reasoning.

The achievement of a given trial aim can, however, be rendered difficult or even impossible by the occurrence of unforeseeable events during the trial. An example of such an event is an unexpectedly high loss-to-follow-up rate in one of the groups being studied. The possibility of such contingencies makes it necessary to determine alternative courses of action when defining the aim of the trial.

The trial planning must take into account clinico-biometrical requirements. The clinical conditions are laid out in Table 5. Some of the points in this list are described in greater detail in the following. If the nature, frequency and duration of the administration of the contraceptive(s) are defined, then it is necessary to determine the conditions for the inclusion or exclusion of women in the trial group(s) [21; 26; 29]. Some important criteria for the selection are shown in Table 6; most of them require no further explanation but the problem of motivation is worthy of closer examination.

The motivation of women for any type of (hormonal) contraception plays a major role not only for the recruitment of the necessary number of cases for a trial, but also—and this will be dealt with later—for the continuation rate and the use-effectiveness. Whereas motivation is naturally dependent on the factors which together comprise the acceptability of the method (*e.g.* simplicity of use, tolerance), the often greatly varying degree of "socio-cultural orientation" within different population groups is also a substantial contributory factor. Differences of this type, which are summarized in Table 7 using examples of rural and urban population groups [17], have considerable

Table 6

Some criteria for the selection of women for contraceptive trials
1. Susceptibility to motivation (in Phase II trials 85% should complete at least 6 months)
2. Ability to keep menstrual diary cards
3. Possibility of continuous supervision (local residents; social workers available for visits; follow-up possible in respect of recovery of fertility and exclusion of congenital defects in subsequent children)
4. Age (e. g. 18–42)
5. No pathological gynecological findings
6. Absence of other serious diseases (liver, kidney, cardiovascular system, endocrine system)
7. Normal menstruation (definition!) during last 12 months or at least 2 normal cycles since last pregnancy or last use of O.C's or I.U.D's
8. Proven fertility or good reasons to expect fertility
9. Coital frequency (e. g. 2–4 times per week)

Table 8

Reasoning against childlessness and for multiparity
Children are necessary:
1. to avoid supernatural punishment (children are gifts of god)
2. to keep the marriage intact
3. to be socially accepted; male: evidence of virility [e. g. "machismo"]
female: fulfilment of motherhood
4. as a substitute for material wealth
5. for economic security
a) in young age: to obtain governmental support (family allowance)
b) in old age: lack of social welfare systems
6. for balance in sex ratio: with all girls or all boys in a family child-bearing is not complete
7. to avoid legal punishment for using contraceptive measures
8. to compensate for increased infantile mortality

significance above all for the investigation or introduction of contraceptive methods in developing countries. Here the idea of family planning is often opposed by motives (Table 8) which can only be overcome slowly and with an abundance of patience and understanding.

Let us now take a look at the criteria for the selection of the trialists (Table 9). Just as the women must be motivated to participate in the trial, the trialists must be motivated to conduct the trial according to the plan [4; 29]. This involves principally a realistic assessment of his investigative capacity on the part of every trialist. Experience has also shown that the better the continuous supervision of the treated women is, the more reliably phase II, but mainly phase III trials proceed [21]. In most cases this demands the availability of an adequately trained paramedical team (*e.g.* social workers) [6; 8; 18; 36; 40].

A major point which must be observed is that trialists in various geographical regions be entrusted with the trial of a hormonal contraceptive. The idea of this is to allow for any differences in respect of the efficacy and safety of one and the same preparation in population groups of different races and living habits. The possible significance of ethnic and nutritional factors (*e.g.* undernourishment) has not yet been adequately elucidated [3], although there are indications in the literature that the efficacy and frequency of side effects of the same contraceptive can vary not only from country to country [7; 9; 15], but also from region to region of the same country [32].

Constitutional factors can play a role in this. It is known, for instance, that some steroids [*e.g.* quinestrol, 20; 33] are deposited in fatty tissue after absorption and have a sustained effect because of their slow release. The effects of a constant dosage in slim women can therefore be different to those in adipose women. We ourselves have observed an example of this with a continuous progestational contraceptive ("mini-pill") at the same dosage: the pregnancy rate was high in Caucasian women but low in a group

Table 7

Some differences in "socio-cultural orientation" between rural and urban population groups (LANDA-JOCANO 1972; modified)

	Rural	Urban
Social grouping characterized by	Homogeneity	Heterogeneity
General orientation influenced by	Tradition; less money-oriented	Present trends; more money-oriented
Dominating institutions of control	Religion/family	Secular institutions
Overt conduct in morals	Puritan tendency	Liberal tendency
Personal communications	Interpersonal relations	Impersonality prevailing
General education	Lower grade	Higher grade
Type of decision making	Influenced by community	More individual
Knowledge of sexual mechanisms and birth control	Superficial	Rather profound
Decision taking on sexual activities	Male privilege	Increasing equality of rights

Table 9

Criteria for selection of investigators
1. **Competence and experience**
1.1. In gynecology and/or obstetrics
1.2. In family planning methods
1.3. For performance of adequate clinical trials consistent with professional ethics
2. **Motivation for the research project**
2.1. Adherence to the trial-plan (including supervision)
2.2. Meticulous completion of the individual record forms
3. **Realism**
3.1. Not to enrol more patients than can be supervised and followed up
4. **Facilities**
4.1. Sufficient space, equipment and staff (social workers)
4.2. Adequate technical means of communication (i. e. telephone, traffic facilities etc.)
5. **Worldwide distribution**
5.1. so that particular population groups can be studied
5.2. to avoid bias due to unbalanced ethnic and geographical selection of population groups

Table 10

Trial planning
B. **Biometric planning**
1. Establishment of trial design (e.g. by block design to prevent system-linked bias)
2. Determination of methods of data collection
2.1 Accounting for different types of drop-outs (LIFE-TABLE method)
2.2 Permissible reasons for subsequent exclusion of patients
3. Establishment of the basic concept for the statistical evaluation
3.1 Hypotheses to be tested, statistical calculating procedures
3.2 Tables and graphs for a data survey (according to trialists, countries and variables)
4. Determination of sample size (including the control group(s)) with due regard to the acceptable risks of error and
4.1 Maximum sample sizes possible per group
4.2 Minimum number of women per trialist

of Latin American women. In relation to height, the average body weight of the Latin American group (mestizas) was considerably greater.

The significance of possible differences in the biliary excretion, enterohepatic circulation and the metabolism of synthetic sex hormones in different ethnic groups has not yet been clarified. The total duration of use has, however, been shown to be important: some steroids have a self-inducing effect on their enzymatic breakdown system, a phenomenon which becomes evident by the decrease in the elimination half-life [16]. The role played by the interaction of hormonal contraceptives with other, simultaneously administered drugs is also becoming increasingly apparent. By means of enzyme induction drugs such as analgesics, sulfonamides, barbiturates, hydantoins, imipramines and rifampicin accelerate the breakdown of the steroids to less active metabolites and lead to a greater incidence of bleeding disturbances in the women [2; 14; 25; 39]. The possible interaction of hormonal contraceptives with other drugs must accordingly be borne in mind when monitoring any trial.

Factors to be considered in the biometrical planning of trials are listed in Table 10. It is assumed that the investigation of a given contraceptive will be conducted as a "controlled clinical trial". This means that one or more control groups (= other contraceptives, with reservations placebo as well) will have to be defined, whereby the allocation of the treatments must take place strictly according to a system of randomization.

The necessity for carrying out a clinical trial in this manner has never been greater than it is today: new preparations are constantly being developed which either contain new steroid hormones or represent modifications to the dose or dose-relationship of known steroids or changes in the administration periods (sequentials). Other than the controlled clinical trial there is no way of objectifying the safety of these preparations or of establishing a possible superiority over standard preparations with regard to efficacy.

Although this type of investigation is also highly feasible with hormonal contraceptives [19], its use has been and still remains extremely rare [24; 28; 38], despite the fact that there are some excellent examples of it [11].

A controlled trial does not necessarily mean a double-blind trial against placebo: one or more standard preparations can, of course, take the place of the placebo. The aim of the trial is the deciding factor: for an objective comparison of the efficacy the trial preparation must be investigated against a standard preparation—a placebo group is only necessary if the aim is to assess the absolute incidence of side effects.

The following objections are usually raised to the employment of controlled trials: firstly, that contraceptives of different origin cannot be investigated in a double-blind trial because the pills of the various manufacturing companies differ for example in colour, size and weight [29]. This problem, however, can be solved quite easily by placing all the pills in identical, non-transparent capsules, the only prerequisite being that the capsules dissolve readily in the gastro-intestinal tract to ensure that the bioavailability of the active ingredients of the pills remains unchanged. Capsules of this type are, incidentally, readily available. The second objection is that use of a placebo is ethically unjustifiable, and if the women were to give their informed consent they would automatically be excluded from the trial because their motivation would be virtually non-existent: it would be a matter of indifference to them whether they become pregnant or not and it would then be impossible to generalize on the basis of the findings raised in this group of women. This is a valid argument. The only solution to this problem is to issue all the women in the trial, both the placebo group and the treated group, with a non-hormonal vaginal contraceptive, for example a spermicidal foam [11].

PERFORMANCE

The possibilities which exist for controlled clinical trials with hormonal contraceptives (including injectable preparations) are summarized in Table 11. It is impossible to compare hormonal contraceptives with I.U.D.s in a double-blind trial because it would necessitate a sham insertion in the control group.

Table 11

Possibilities for controlled clinical trials with hormonal contraceptives

	Combinations*	Mini-Pill	Postcoital Pill	Depot Injections	Placebo
Combinations*	+	+	−	+	(+)
"Mini-Pill"		+	−	+	(+)
Postcoital Pill			+	+	(+)
Depot Injection				+	(+)

*Fixed combinations and Sequentials (+) Additional vaginal contraceptive required for all groups; conclusions about efficacy limited

The use of the so-called "cross-over trial" is also problematical. For the most part it must be expected that residual effects of the initial treatment will be present in subsequent phases. For this to occur it is not absolutely necessary for substance from the initial treatment to linger on in the tissue, learning effects can also induce bias.

According to Grizzle[13], a cross-over design is advantageous only if the residual effect of therapy A on therapy B is equal to the residual effect of therapy B on therapy A and if positive correlations exist between the measurements made at consecutive points in time in the same patient. However, since the correlations are never known in advance, cross-over trials usually cause more uncertainty and disadvantages than advantages. Apparent advantages are frequently only the result of false evaluation and misinterpretation of the trials. It is therefore advisable to use a system of non-individual controls.

A brief account of how the so-called side effects are established is now called for. Most of the "side effects" commonly associated with oral contraceptives are not reactions to the medication but represent a composite of the symptoms normally present in the population together with the complaints elicited as a placebo response [1; 5; 10; 11; 23]. The clinical trialist should not, therefore, inquire specifically about particular symptoms, but should merely pose casual questions to the women of all groups involved in the trial. If this procedure is not followed, for example because the investigational protocol (record form) requires him to ask about particular symptoms, the rate of "side effects" thus arrived at will usually be excessively high.

As regards the number of women in whom a new contraceptive should be investigated, the literature seems largely to agree with the opinion of Mishell[21] that "results with an oral contraceptive involving 1000 women for 6 months with a total of 6000 woman-months experience will usually be sufficient to judge efficacy and clinical side effects". However, this general pronouncement can only be valid for uncontrolled trials, the disadvantages of which have already been pointed out. With a controlled trial, on the other hand, the number of women per group, that is, the sample size, is determined on the basis of two previously established hypotheses. The first hypothesis, for example, states that, in a comparative trial of two contraceptives, no differences exist in respect of their efficacy and/or frequency of side effects. The second hypothesis is based on the assumption that there is a certain relevant difference between the two contraceptives; this difference must be recognizable with a probability of 90%. The biometrician than calculates the number of women per group required to prove this.

The problem is, however, complicated by the virtually unpredictable discontinuation rate: for the most diverse reasons a number of women always discontinue the treatment at various stages of the trial. These reasons will be shown in detail later, but two of them are the acceptability and the practicability of the contraceptive method. In our experience and that of other research workers [12; 19; 27; 29], this discontinuation rate can be quite substantial for orally administered hormonal contraceptives, amounting to 10–25% in the 6th month of treatment, 30–60% in the 12th month, and up to 90% at the end of the 2nd year of treatment. It is therefore essential before the start of the trial to determine the percentage of the discontinuation rate which appears to be tolerable in the light of the respective circumstances. The biometrically determined number of women must then be increased by this percentage.

In our own investigations we set a limit to this value of 15% for a trial lasting 6 months.

The following example of a controlled trial should help to explain the procedure which we follow. To be compared are: a continuous progestational contraceptive ("mini-pill"), a standard fixed combination and a placebo. The three types of treatment are allocated to the women strictly according to a system of randomization. All the women receiving the placebo plus a randomly determined percentage of the two contraceptive groups are instructed to employ a spermicidal vaginal foam in addition. The trial design is such that 20% of the total number of women in the three groups use the vaginal contraceptive. The object of the trial is to determine the efficacy of the two hormonal contraceptives and the incidence of common side effects in comparison to the placebo group.

The hypothesis to be tested in respect of the efficacy is that the two contraceptives are equally effective. If, in actual fact, the pregnancy rate after 6 months of the trial amounts to 0·75% for the mini-pill compared to 0·05% for the fixed combination, this difference must be recognizable with a probability of 90%. If the assumed discontinuation rate in these 6 months is 15%, then 1460 women are required for each contraceptive group.

The two hypotheses to be tested in respect of the incidence of common side effects are that the contraceptives differ neither from the placebo nor from one another. These comparisons are tested in the third month of treatment. Differences in the side-effects rate of 5% are defined as medically relevant and, if they exist, should be recognizable with a probability of 90% ($\alpha = 5\%$). In this case the placebo group must consist of 610 women.

Thus, a total of 3530 women is required for the whole trial, randomization being performed in such a way that 610 of them receive the placebo.

EVALUATION

The problems involved in the evaluation of contraceptive trials are no different to those of any other long-term trial:

(a) varying periods of observation of the individual women for organizational reasons (cut off date)

(b) discontinuation not only because of pregnancy, but also because of numerous concurring risks (side effects, change of address, loss of partner, desire for children and other, sometimes inexplicable losses to follow-up).

The method- and use-effectiveness of a contraceptive is still expressed as its Pearl Index. Since, however, this index is calculated from the number of cycles, from which neither the actual duration of treatment nor the number of treated women is really evident, the Pearl Index can lead to misinterpretations.

If the expression of the effectiveness is to be meaningful, then the women themselves must be used as the basic unit of any calculations. This is the case in the modified Life-Table methods [19;35;37], which therefore deserve preference in the evaluation and should accordingly be taken into account during the planning. The Life-Table method has already been adequately discussed at this Symposium, so further comment would be superfluous. However, in compliance with a request from the Organizing Committee of this Symposium, we shall finish with a brief discussion of the question of whether the continuation and discontinuation rates and the use-effectiveness observed during the clinical trial of contraceptives can be transferred to the post-marketing phase.

The answer to this is no for the following reasons:

(1) The samples studied in the clinical trial are not random samples from the whole population, but are biased by the selection of particularly qualified doctors and suitable women.

(2) Following commercial release of a contraceptive, the close supervision and motivation of the women previously provided by the trialists are no longer present.

Table 12

Factors influencing both probable use-effectiveness and continuation rates after commercial release of the contraceptive product

1. Acceptability of technique (mode and frequency of administration, simplicity +)
2. Actual strength of the desire to prevent pregnancy (+)
3. Reason for use: "timing" (−) or "terminating" (+) fertility
4. Age (< 30 −; > 30 +)
5. Marital status (married −; single or divorced +)
6. Parity (low −; high +)
7. Sexual frequency (low −; high +)
8. Ethnic group (Caucasian +)
9. Intellectual level (lower −; higher +)
10. Religion/family (faith, dependency)
11. Lack of medical and/or social services (−)
12. Personal financial situation (product available for cash only −)
13. Lack of distribution (general availability of product) (−)
14. Length of time method used (maximum discontinuation rate during early months of use)
15. Type and frequency of side effects

+/− = positive or negative influences

(3) The preparation must assert itself against competitive preparations.

The use-effectiveness and continuation rate are then influenced by a number of factors, the most important of which according to both our experience and the literature [18;22;27;30;30;31;40] are listed in Table 12. The assessment of a contraceptive in the post-marketing phase is, therefore, only possible on the basis of specific epidemiological studies.

REFERENCES

1. Aznar-Ramos R., Giner-Velazques I., Lara-Ricalde R. and Martinez-Manautou I.: *Am. J. Obstet. Gynec.* **105** (1969) 1144–1149.
2. Carter D. E., Goldman I. M., Bressler R., Huxtable R. I., Christian C. D. and Heine M. W.: *Clin. Pharmac. Ther.* **15** (1974) 22–31.
3. Chen L. C.: *Lancet* **i** (1973) 47–48.
4. *Developments in Fertility Control. WHO Technical Report Series* 424, Geneva (1969).
5. Drill V. A.: In *Pharmacological Models in Contraceptive Development. Proceedings of the WHO-Meeting, Geneva* 1973. *WHO Research and Training Centre on Human Reproduction*, Stockholm (1974) pp. 169–202.
6. Education and Training for Family Planning in Health Services. WHO Techn. Rep. Ser. 508, Geneva (1972).
7. Eisalo A., Jarvinen P. A. and Luukkainen T.: *Brit. med. J.* **2** (1964) 426–427.
8. Family Planning in Health Services. WHO Techn. Rep. Ser. 476, Geneva (1971).
9. Goldzieher J. W. and Rice-Wray E.: *Oral Contraception: Mechanism and Management.* Thomas, Springfield, Ill. (1966).
10. Goldzieher J. W.: *Am. J. Obstet. Gynecol.* **102** (1968) 91–94.
11. Goldzieher J. W., Moses L. E., Averkin E., Scheel C. and Taber B. Z.: *Fertil. Steril.* **22** (1971) 609–623.
12. Greaney M. O., Taber B. Z. and Bessler S. A.: *Fertil. Steril.* **19** (1968) 339–343.
13. Grizzle I. E.: *Biometrics* **21** (1965) 467–498.
14. Hempel E., Böhm W., Carol W. and Klinger G.: *Zbl. Gynäk.* **00** (1973) 1451–1457.
15. Howard G., Elstein M., Blair M. and Morris N. F.: *Lancet* **ii** (1969) 24–26.
16. Klinger W.: *Z. ärztl. Forth.* **65** (1971) 1269–1272.
17. Landa-Iocano F.: *IPPF-SEAOR Monograph No. 2*, Kuala Lumpur, Malaysia (1972).
18. Lehfeldt H. and Guze H.: *Fertil. Steril.* **17** (1966) 110–115.
19. Methods of Fertility Regulation. WHO Techn. Rep. Ser. 473, Geneva (1971).
20. Mishell D. R. and Freid N. D.: *Contraception* **8** (1973) 37–42.
21. Mishell D. R. and Nash H. A.: *Loc. cit.* **5**, pp. 266–278.
22. Moos R. H.: *Psychosom. Med.* **29** (1967) 548–549.
23. Morris N. M. and Udry I. R.: *Am. J. obstet. Gynec.* **113** (1972) 763–765.
24. Nilsson L. and Solvell L.: *Acta obstet. Gynec. Scand.* **46** (Suppl. 8) (1967).
25. Nocke-Finck L., Breuer H. and Reimers D.: *Dtsch. med. Wschr.* **98** (1973) 1521–1523.
26. Podell L.: *Fertility, Illegitimacy, and Birth Control.* The Center for Social Research, City University of New York, Prel. Rep. No. 6, New York (1968).
27. Ratner H.: *Science* **155** (1967) 951.
28. Richter R. H. H.: In *Proceedings of the 5th Conference of Europe and Near East and Africa Region*, IPPF, Copenhagen, July 1969. Stephen Austin, Hertford, England (1966), p. 121.

29. Rudel H. W., Kincl F. A. and Henzl M. R.: *Birth Control, Contraception and Abortion.* The Macmillan Co., New York (1973).
30. Ryder N. B. and Westoff C. F.: *Science* **153** (1966) 1199–1205.
31. Ryder N. B. and Westoff C. F.: *Reproduction in the United States* 1965. Princeton University Press, New Jersey (1971).
32. Sartwell P. E., Masi A. T., Arthes F. G., Greene G. R. and Smith H. W.: *Am. J. Epidem.* **90** (1969) 365–380.
33. Smith R. L.: *Loc. cit.* **5**, pp. 149–168.
34. Taber B. Z., Greaney M. O. and Bessler S. A.: *Pacific. Med. Surg.* **74** (1966) 145–149.
35. Tietze C.: *Studies in Family Planning*, Suppl. 18. The Population Council, New York (1967) 1–6.
36. Tietze C.: *Israel J. med. Sci.* **4** (1968) 503–508.
37. Tietze C.: *Clin. obstet. Gynec.* **11** (1968) 698–705.
38. Udry I. R. and Morris N. M.: *Nature* **227** (1970) 502–503.
39. Wenzel M. and Stahl H. J.: *Hoppe-Seyler's Z. physiol. Chem.* **351** (1970) 761.
40. Ziegler F. J., Rodgers D. A., Kriegsman S. A. and Martin P. L.: *JAMA* **204** (1968) 849–853.