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ASSESSING RARE AND DELAYED SIDE-EFFECTS OF CONTRACEPTIVE STEROIDS

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SUMMARY

Rare side effects pose special problems for detection by virtue of their low incidence or unusual nature. They are often missed in initial clinical trials due to their low frequency of occurrence and are only picked up after widespread usage of the contraceptive agent.

Rare side effects are usually brought to attention by voluntary spontaneous reporting, occasionally by means of intensive monitoring systems. Once suspected, their rarity makes an initial prospective study infeasible but retrospective investigations can be conducted with less expenditure of time and resources. If warranted, prospective studies can later be initiated to further quantitate and verify the findings of the retrospective investigations. The advantages and disadvantages of retrospective and prospective studies are discussed.

In order to determine if contraceptive steroids affect subsequent fertility, a prospective study is most desirable as the temporal relations between pill taking and conception must be obtained in great detail. Some of the problems in the design of such an investigation are elaborated.

1. INTRODUCTION

It is a vexing problem to assess the rare side-effects of any drug or chemical, but it is a task worth undertaking when the drug in question is used, as in the case of the contraceptive steroids, by at least 50 million women.

2. DEFINITIONS OF RARE AND DELAYED SIDE-EFFECTS

A "rare" side-effect may be defined as an unwanted drug effect that occurs at a low frequency amongst users.

A "delayed" side-effect may not necessarily be rare, but it is an unwanted drug effect that occurs either after prolonged use or months or years after the initial exposure, which may have been brief.

A well-known example of a rare side-effect is the aplastic anemia which occurs as a result of Chloramphenicol administration in about one of 60,000 persons exposed to this antibiotic [1].

An example of a "delayed" side-effect is the development of adenocarcinoma of the vagina among girls who were exposed to diethylstilbestrol *in utero* but developed the tumor 14 to 20 years after the initial exposure [2].

Both rare and delayed drug effects pose special problems of detection, quantitation and investigation and their elucidation requires the combined skills and interests of clinicians, pharmacologists, toxicologists, epidemiologists, the drug industry, and drug regulatory agencies.

3. THE PROBLEM OF DRUG MONITORING

Adverse drug reactions are monitored in many of the industrialized countries but in few of the developing nations of the world. Drug monitoring can be of several types, each with its own advantages and limitations.

The collection of voluntarily submitted reports of adverse reactions is an important method of detecting possible new drug side-effects. It suffers greatly from the problem of under-reporting and the critical deficiency that not only is the numerator event (the adverse reaction) uncertain, but the denominator (population exposed to the drug) is usually unknown. Thus, the degree of risk and the strength of the reported association between drug and disease usually requires further investigation. Nonetheless, these systems are often the very first way in which rare side-effects are brought to the attention of the medical profession.

In the case of the contraceptive steroids, the first reports of the association of these agents with thromboembolic disease came from a number of astute clinicians who noticed what they regarded as an increased frequency of this disease among their pill-taking patients. These reports provided the first warning that there might be an association between thromboembolic disease and estrogenic compounds, but were unable to answer this question conclusively as the incidence of this disease in the general population was unknown, and, furthermore, the incidence among oral contraceptive users was also unknown. Subsequent retrospective and prospective studies have contributed to answering this question, but the monitoring system provided the first clues.

In passing, it should be mentioned that intensive monitoring of hospitalized patients for rare drug effects suffers from the small number of individuals that can be monitored under these systems, but has the advantage of capturing unusual and serious diseases that may be drug-related, as aplastic anemia.

Table 1. Fourfold tabular symbolic representation of relative risk

Suspected drug	Cases	Controls
Used drug	a	b
Did not use drug	c	d
Total	a + c	b + d

The relative risk is then derived from the ratio:

$$\frac{\text{Rate in drug users}}{\text{Rate in non-users}} = \frac{a}{a+b} \div \frac{c}{c+d} = \frac{a(c+d)}{c(a+b)}$$

The assumption is then made that the number of persons affected by the disease is small relative to those unaffected (the usual case in studies of rare events) and so d is approximately equal to (c + d) and b is approximately equal to (a + b): the relative risk formula then reduces to ad/bc.

4. RETROSPECTIVE INVESTIGATIONS OF ADVERSE REACTIONS

The retrospective or case-control method of investigating adverse drug effects has been much maligned, mainly, in my opinion, due to a misunderstanding of the method as used in epidemiology in contradistinction to the manner it has been applied in clinical research or reports of a series of cases by a practitioner. The method as applied by most epidemiologists has a rigor and power quite different from that of a mere collection of case reports from a clinic file or what Dr. Philip Sartwell has chidingly called "a case-series in search of a statistical universe".

A retrospective or case-control investigation is one in which cases of a disease are collected and compared to controls with respect to their exposure to the presumed cause (*e.g.*, a drug). This method was used by Vessey and Doll[3] and Sartwell *et al.*[4] to determine the relative risk of developing idiopathic thromboembolism among oral contraceptive users as compared to non-users. In both studies, the results were remarkably similar.

The methodologic issues of greatest concern in these studies are the criteria for case selection, selection of controls, choice of matching characteristics of controls to cases, avoidance of bias and methods of analysis. The purpose of matching is to eliminate the effects of variables that may confound the analysis of the study variables; the guiding principle is to select the controls in a way that ensures the control group having the same distribution as the cases with respect to certain variables that are believed to be confounding. For example, the age of a woman is related both to her predisposition to use oral contraceptives and to the frequency of thromboembolism and so was selected as a matching variable by both Vessey and Doll and Sartwell in their studies. There is the possibility of overmatching in this type of investigation which, rather than reducing the influence of confounding variables in the analysis, may reduce the statistical efficiency* of the study.

The method of analysis of case-control studies may vary but the ultimate purpose in studies of adverse effects is to achieve an estimate of *relative risk*. In order to do this, a fourfold table is constructed (Table 1).

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Relative risk can also be estimated in matched pair case-control studies by analysis of the ratio of the discordant pairs as illustrated in Table 3 (pairwise analysis).

Table 3. Distribution of 175 case-control pairs according to whether or not oral contraceptives were used within one month of admission for thromboembolic disease [4]

Oral contraceptive used by control?	Oral contraceptive used by patient?		
	Yes	No	Total pairs
Yes	10	13	23
No	57	95	152
Total pairs	67	108	175

The estimate of relative risk is the ratio of discordant pairs: 57/13 = 4·4.

Advantages of retrospective case-control studies in investigations of adverse reactions, such as thromboembolism, include the smaller sample size needed, ease of carrying out the study, reduced cost and the shorter time required (compared to prospective studies). Disadvantages include problems of possible bias, the necessity of knowing in advance both the suspected cause and the effect whose association is being studied and the inherent limitations of a research design which measures only associations between factors.

* Statistical efficiency is defined as the likelihood of revealing a significant difference, if a difference is present.

Table 2. Patients with postoperative thromboembolism and matched control patients classified by use of oral contraceptives during month before admission [9]

	Thromboembolism case	Matched control
Used oral contraceptives	12 (a)	9 (b)
Did not use oral contraceptives	18 (c)	51 (d)

$$\text{Relative risk} = \frac{ad}{bc} = \frac{12 \times 51}{9 \times 18} = 3{\cdot}8.$$

Another serious disadvantage of the retrospective method is that it must often rely on the patients' memory: in the case of estrogens, the women must identify the particular product. The multiplicity of products makes this a confusing and difficult task. Nonetheless, the retrospective studies independently conducted have shown an increased risk of certain thromboembolic conditions associated with use of the oral contraceptives.

5. PROSPECTIVE STUDIES OF RARE SIDE-EFFECTS

Ideally, a prospective study would approximate an experimental design where persons are randomly assigned to treated and non-treated groups and the direct incidence of adverse effects in both groups are compared. The required sample size needed for such studies has been estimated in the case of oral contraceptives and is in the order of 10,000 women [5].

Such prospective studies are clearly difficult in studying the oral contraceptives because of the large sample size required, the high drop-out rates and the long time required for completion as well as tremendous cost. Because of these problems, few prospective studies of the thrombogenic effects of the oral contraceptives (as a primary objective of the investigation) have been reported, although at least three are now in progress. However, a recent large scale prospective study has been carried out under the aegis of the National Institutes of Health to determine the most efficacious therapies for coronary artery disease (postinfarction) and this study produced unexpected evidence concerning the relationship of estrogens to the occurrence of pulmonary embolism. The Coronary Drug Project committee decided to break the protocol and discontinue the group receiving 5 mg conjugated estrogens because of the high incidence of pulmonary embolism in this group as compared to the placebo group (Table 4).

The prospective design of this study produces a direct incidence rate and hence a direct method of estimating risk; it substantiates the indirect method of estimating relative risk of the Sartwell study (relative risk = 4·4).

In a prospective controlled clinical trial of diethylstilbestrol (DES) in the treatment of prostatic carcinoma, it was noted that those patients receiving the highest dose of estrogen had a higher rate of fatal coronary thrombosis and other thrombotic complications than the control group [6]. Thus there are two prospective studies showing increased thrombotic disease rates associated with exogenous estrogen administration; however, both studies were done with men only, and neither administered oral contraceptives to the study group, but rather high doses of other estrogens.

The Royal College of General Practitioners has just reported the results of a long-term prospective study of the side-effects of the oral contraceptives and they found the risk of idiopathic venous thrombosis was between five and six fold greater among pill-users than those women using other methods of contraception [7]. Thus, the retrospective studies of Vessey and Doll and Sartwell and his colleagues have also been confirmed by the prospective method.

6. THE SPECIAL PROBLEM OF THE EFFECT OF STEROID CONTRACEPTIVES UPON SUBSEQUENT FERTILITY

The occurrence of amenorrhea in women who had recently stopped oral contraceptives was first reported in 1966; other reports have followed. These reports have naturally led to speculation that oral contraceptive use might lead to a reduction in subsequent fertility. There are both retrospective and prospective studies of this question.

In the United States, Westoff *et al.* interviewed women after they had had at least one pregnancy, and asked how long it had taken them to conceive after stopping contraception [8]. They reported that pill takers reported no difference in the time it took them to conceive as compared to users of other contraceptive methods.

The Royal College of General Practitioners' prospective study also examined this question and concluded that a slight delay in conception does occur among women who have used oral contraceptives, even excluding from the analysis those women known to have amenorrhea. However, at the end of two years after stopping the pill, at least 85% of the nulliparous and 93% of the parous women had conceived [7].

It is probable that only prospective studies will help further delineate the problem of possible reduction of subsequent fertility following pill use since temporal relationships, duration of pill use and months required to conceive are not the kinds of information that lend themselves to successful collection *via* the retrospective method.

Table 4. Coronary drug project: incidence of definite pulmonary embolism [6]

Treatment	No. of patients	Pulmonary embolism cases	
		Number	Percent
5 mg estrogen	1119	17	1·52
Placebo	2788	10	0·36

Note: 1·52 ÷ 0·36 = relative risk of 4·2.

REFERENCES

1. Toxicity of chloramphenicol: *Brit. med. J.* **1** (1967) 649–650.
2. Herbst A. L., Ulfelder H. and Poskanzer D. C.: *New Engl. J. Med.* **284** (1971) 878–881.
3. Vessey M. P. and Doll R.: *Brit. med. J.* **2** (1969) 651–657.
4. Sartwell P. E., Masi A. T., Arthes F. G., Greene G. R. and Smith H. E.: *Am. J. Epidemiol.* **90** (1969) 365–380.
5. Seigel D. and Corfman P.: *J. Am. med. Assoc.* **203** (1968) 950–954.
6. The Coronary Drug Project Research Group.: *J. Am. med. Assoc.* **214** (1970) 1303–1313.
7. The Royal College of General Practitioners, *Oral Contraceptives & Health.* Pitman Publishing Corporation, New York (1974).
8. Westoff C. F., Bumpass L. and Ryder N. B.: *Social Biol.* **16** (1969) 1–10.
9. Vessey M. P., Doll R., Fairbairn A. S. and Glober G.: *Brit. med. J.* **3** (1970) 123–126.