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The Role of Epidemiology in the Regulation of Oral Contraceptives

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Synopsis

The U.S. Food and Drug Administration (FDA) has relied to a great degree on epidemiologic studies in the regulation of oral contraceptives (OC). These epidemiologic studies range from individual case reports of adverse reactions to case-control studies and cohort studies.

Important findings about adverse reactions to OCs have been communicated through "labeling," which includes information leaflets provided as package inserts for physicians and patients. Also, the FDA communicates its position through publications in medical journals, the FDA Drug Bulletin, public advisory committee meetings, workshops, and symposia. The agency responds to new epidemiologic information; labeling guidelines are under continuing review and revision.

Patterns of oral contraceptive use have been affected by the dissemination of this information. There has been a decline in the use of OCs, a shift to formulations with lesser steroidal content, and a greater emphasis on OC use in optimal groups, such as young, nonsmoking women.

Considered for future epidemiologic studies that may have an impact on regulatory action are a clarification of the role of various progestins in regard to blood lipid alteration and atherogenesis, a delineation of the possible persistence of cardiovascular risk after termination of OC use, and further clarification in regard to neoplasia, particularly breast and cervical carcinoma.

THE FOOD AND DRUG ADMINISTRATION (FDA) has relied extensively on epidemiologic findings in its regulatory approach to oral contraceptives (OC). It is fair to say that no other class of drugs has been subjected to as exhaustive epidemiologic study as have OCs. The circumstances have been favorable from an epidemiologic point of view. A potent physiologic agent had been given to large numbers of healthy women. By 1980, it was

estimated that about 53 million women were using oral contraceptives worldwide. Background levels of disease in these women were low. Individual case reports had indicated that certain serious diseases were being induced. Physiologic bases existed for suspected associations of thrombotic disorders and cardiovascular effects.

Sources of Data

Shortly after individual reports of adverse reactions were published, case-control studies were instituted. As data accumulated from retrospective studies and it seemed probable that OC use was associated with certain adverse reactions, prospective studies were instituted to establish, more firmly, the causal role of oral contraceptives. In the late 1960s several large cohort studies were initiated. Three important types of data bases available to the FDA contributed to the accumulating epidemiologic findings. The first type consisted of individual case reports in the medical literature, reports to the FDA of adverse reactions, and registry data (for example, the Armed Forces Institute of Pathology hepatoma registry). The second type, case-control studies, are represented by the Boston University Collaborative Drug Surveillance Program (*1*), the Drug Epidemiology Unit, Boston University, and the Minnesota-Michigan Medicaid base. The third type of data bases are the prospective cohort studies such as those of the Royal College of Family Physicians (*2*) and the Oxford Family Planning Association (*3*) in the United Kingdom and the Kaiser-Permanente study in Walnut Creek, Calif. (*4*).

This list is not exhaustive. The FDA has relied upon other studies, particularly other case-control studies from the United Kingdom. The Minnesota-Michigan Medicaid base is recent, and it has not yet had an impact in terms of OC regulatory policy.

General Appraisal of the Studies

The general criticisms of the strengths and weaknesses of the various epidemiologic approaches, that is, individual case reports, case-control studies, and prospective cohort studies have been well addressed in the scientific literature. Specifically, in regard to the epidemiology of oral contraceptives, the following observations are important.

1. Adverse reports on individual patients in the medical literature were invaluable in providing early indications of cardiovascular effects, particularly thromboembolic disease. The FDA's own adverse reaction reporting system did not contribute significantly in the early years to the delineation of the problems associated with OC use.

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2. The subsequent case-control studies generally provided an efficient, comparatively inexpensive method of defining relative risks associated with oral contraceptives.

3. Delineation of attributable (absolute) risks in the use of OCs has been a difficult problem. Case-control studies, for the most part, did not provide this information. However, some crude estimates were available in certain case-control studies in which the catchment population was clearly defined, and the total number of serious reactions within that population was recorded.

4. Cohort studies, in general, confirmed the findings of case-control studies and gave better information in regard to attributable risks. These studies, although perspective, were observational rather than interventional in design and thus were not completely free of biases.

5. Certain important questions have not been clearly answered by any of these studies, for example, the possible association of use of oral contraceptives and cervical neoplasia.

6. Registry data have been valuable in at least one instance—the delineation of the association of hepatomas and OCs.

7. The results of early epidemiologic studies may no longer be entirely applicable to current OCs that have lower steroidal contents.

8. Current and future epidemiologic study of OCs will be strongly affected by patterns of use that have resulted from the recommendations arising from the findings of earlier studies.

FDA's Response

FDA responded to the accumulating data in a number of ways. In August of 1966, the Food and Drug Administration convened an advisory panel (*5*) to address the adverse effects of OCs. At that time, the panel, the Advisory Committee on Obstetrics and Gynecology, expressed its opinion as follows:

There will always be a sensitive individual who may react adversely to any drug, and the OCs cannot be made free of such adverse potentials, which must be recognized and kept under continual surveillance. The potential dangers must also be care-

fully balanced against the health and social benefits that effective contraceptives provide for the individual woman and society.

Anticipating quite correctly, the panel continued:

"The OCs currently in use are probably not those that will be employed 10 or even 5 years hence. Drugs utilizable in smaller dosage will undoubtedly be developed.

The committee, in its recommendations, encouraged further case-control and prospective studies.

Continuation and strengthening of the surveillance system of the FDA were emphasized. Some means toward this end were review of the mechanism of storage, retrieval, and analysis of surveillance data and the recommendation to hold a conference of representatives of the FDA and the respective drug firms to consider uniformity in prescribing information and increased efficiency in reporting of adverse reactions.

The Advisory Committee on Obstetrics and Gynecology also advised that the labeling of contraceptive drugs follow guidelines to be formulated by the FDA. Two types of labeling were made mandatory. One would be directed to physicians and would contain detailed epidemiologic information and comprehensive discussions of adverse reactions. The other would be directed to the patient and would contain similar information in nontechnical language. The agency moved to implement these recommendations.

A primary example was FDA's action in regard to uniform OC labeling and patient package information. In the Federal Register of June 11, 1970 (*6*), in a novel regulatory initiative, FDA required manufacturers and dispensers of OCs to make information about the use of these products available to patients. The agency required that dispensers give OC users a brief information leaflet about the products' benefits and risks. The leaflet summarized in simple language the results of the epidemiologic findings on OCs during the preceding decade.

In 1978, in response to new information on the benefits and risks of OC use, the FDA revised substantially its patient package insert requirements (*7*). As revised, the regulation significantly expanded the amount of information required to be provided to patients when the drug product was dispensed.

Although "labeling" (which includes package inserts) is the most important method of communication, and it has established regulatory authority, the FDA uses other methods to inform the practicing physician and consumer about the agency's position. They include publication in the medical literature. A recent publication (*8*) concerning epidemiologic findings and OCs is a good example of FDA's use of this method of communication.

In addition to the general medical literature, the FDA has its own publications. The best example is the widely read bimonthly Drug Bulletin. Directed to practicing physicians, it communicates FDA's concerns in many areas. On several occasions FDA has presented positions on OCs (*9,10*) in that publication.

Another public forum that is useful for disseminating information is the meetings of the advisory committees of the FDA. Although the primary function of these meetings is to provide consultation to the agency, the meetings are open to the public, and they offer an opportunity for the exchange of ideas. Frequently consumer groups have spoken at these meetings.

For example, the relabeling of OCs has been discussed in several recent FDA advisory committee meetings. How the various epidemiologic findings would be reflected in the new labeling was discussed by the Fertility and Maternal Health Advisory Committee. Its members included obstetricians, gynecologists, a teratologist, a biostatistician, and a representative of consumer interest groups. Also present as *ad hoc* consultants were an epidemiologist from the Centers for Disease Control and several scientists from the National Institute of Child Health and Human Development. The meetings were open to the public, and there was active participation of consumer groups. The guidelines for the new OC labeling will be published in the Federal Register and, again, they will be subject to comment from all interested parties and may undergo revision.

Another recent example of the usefulness of the advisory committee was the meeting in regard to the inappropriate promotional use of the findings from the Walnut Creek study (*4*) by the drug companies. The agency maintained that the study's scope did not allow certain claims of safety and that certain "reassuring findings" were based on too few patients. Subsequently, the Walnut Creek data were used by drug companies in a more balanced manner.

In addition to the advisory committees, the FDA conducts workshops and symposia, and frequently their proceedings are published. For example, in April 1983, in conjunction with the National Institutes of Health, the FDA conducted a workshop addressing animal models for testing steroid contraceptives. In addition to issues of preclinical testing, the workshop participants addressed the implications of current epidemiologic findings and the possible effect that these findings might have on the agency's position concerning new approaches to animal models.

The FDA is also involved directly in epidemiologic studies. The FDA supports financially studies performed by the Boston Collaborative Drug Surveillance Program and the Drug Epidemiology Unit in Boston and participates in protocol reviews.

The agency's Division of Drug Experience has progressively improved its capabilities in data entry and retrieval. The data being collected constitute an increas-

ingly important resource in the evaluation of adverse drug reactions.

Drug labeling has been the most important means of communicating information about OCs; the labeling of these drugs for health professionals provides a good summary of the epidemiology of oral contraceptives. The contraindications section of the labeling describes the most serious and best defined risks. The warning section is comprehensive and contains specific epidemiologic data given in tabular form. The boxed warning notice concerning the deleterious relationship between cigarette smoking and oral contraception appears prominently. (Boxed warnings usually concern life-threatening reactions.) The warnings for OCs, as well as those for other drugs, requires a standard of evidence less stringent, for example, than that required for granting an efficacy indication. Individual case reports and results of uncontrolled studies may contribute to the warning sections. New warnings are frequently included on the initiative of drug companies. The Code of Federal Regulations, paragraph 21CFR 314.8d, permits addition of important safety information to the labeling without prior approval. The agency may subsequently request deletion of these additions if it judges that the documentation is inadequate, even by the lesser standards required for warnings.

In the interests of maintaining the labeling as a lucid, accurate, and practical document, the FDA, as a matter of policy, encourages reasonable restraint in labeling. In addition to providing important information to the physician, the professional labeling provides the basis for the patient package information and the advertising material that is permitted in the promotion of drugs.

Effects of Epidemiologic Findings

There is no question that epidemiologic findings and their subsequent effect on FDA policy have had an important impact on OC use. Three major trends have occurred: (*a*) use of the oral contraceptives has generally decreased, (*b*) there has been a shift to formulations of OCs with lesser steroidal content, and (*c*) there is a greater emphasis on use in optimal groups where the risk of adverse reactions are lowest, such as young, nonsmoking women without cardiovascular risk factors.

The table shows the content of estrogen in OCs marketed in the United States. The market shares of the formulations by estrogen levels are compared for 1973

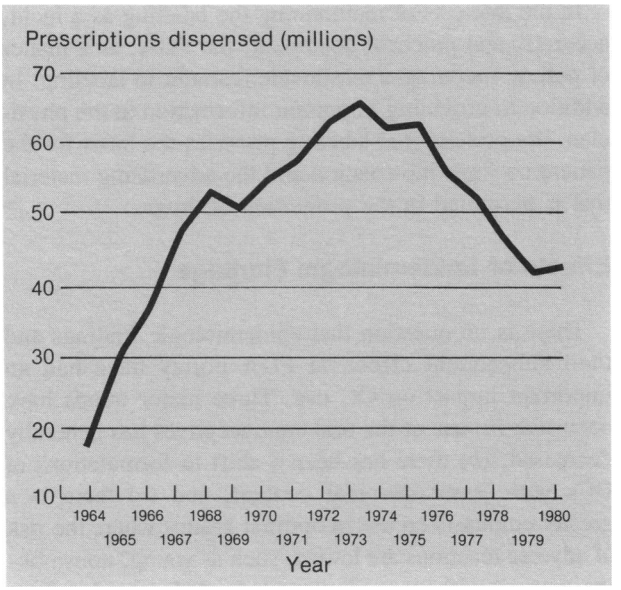
Dispensed oral contraceptives, by progestin and estrogen content, 1973–1980

Content (in mg)	Tablets dispensed as percent of market							
	1973	1974	1975	1976	1977	1978	1979	1980
Progestin:								
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
10.0	.3	.3	.3	.3	.2	.2	.1	.1
5.0	.9	.8	.5	.4	.4	.4	.5	.3
2.5	5.7	5.7	4.3	4.5	3.8	3.4	2.7	1.9
2.0	5.9	4.9	4.2	3.7	2.7	2.1	1.5	1.3
1.5	.0	.5	2.0	2.6	2.5	2.6	2.9	2.9
1.0	56.1	57.3	58.1	59.0	59.1	56.0	54.5	55.0
0.5	23.1	24.1	23.8	24.7	22.4	23.2	23.5	23.2
0.4	.0	.0	.0	.1	.3	.8	1.1	1.3
0.35	.5	.4	.2	.4	.3	.4	.2	.5
0.3	.0	.0	1.2	4.3	8.3	10.8	13.1	13.4
0.075	.0	.0	.0	.0	.0	.0	.0	.0
Sequentials	6.9	6.0	5.4	.0	.0	.0	.0	.0
Estrogen:								
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
>0.100	.2	.2	.2	.1	.1	.1	.1	.1
0.100	23.0	21.1	18.1	17.0	14.3	11.6	9.8	7.8
0.080	13.9	14.1	14.3	14.0	13.3	11.7	10.2	8.9
0.075	.9	.8	.5	.4	.4	.4	.5	.3
0.060	.1	.1	.1	.1	.1	.1	.0	.0
0.050	54.3	55.5	55.4	58.6	57.5	56.9	55.3	54.3
0.035	.0	.0	.8	1.3	2.5	4.9	7.6	11.3
0.030	.0	.5	3.2	6.9	10.7	13.3	16.0	16.3
0.020	.2	1.4	1.7	1.2	.7	.5	.4	.4
0[1]	.5	.4	.3	.4	.3	.4	.2	.5
Sequentials	6.9	6.0	5.4	.0	.0	.0	.0	.0

[1] Progestin only, minipill

SOURCES: Drug Use and Analysis Branch, Division of Drug Experience, Food and Drug Administration, from IMS, America's National Prescription Audit, and the National Disease and Therapeutic Index.

Dispensed prescriptions for all types of oral contraceptives, 1964 - 80



SOURCE: Drug Use and Analysis Branch, Division of Drug Experience, Food and Drug Administration, from IMS, America's National Prescription Audit, and the National Disease and Therapeutic Index.

through 1980. OCs containing more than 50 micrograms of estrogens declined from 38.1 percent of the market share to 17.1 percent by 1980. Formulations containing 35 micrograms or less of estrogen increased from 0.7 percent to 28.5 percent. Similar, less remarkable trends were seen in regard to the progestin content.

Trends in overall use of OCs are reflected in the chart, which shows the prescriptions dispensed for all types of OCs from 1964 through 1980.

Clarification of the role of various progestins in adverse effects in regard to metabolic and lipid alterations, hypertension, and atherogenesis is an important consideration for future study. Attention must be paid to both qualitative and quantitative factors in regard to the contribution of the progestin compound to the adverse effects of OCs. Also needed is further investigation of the possibility that OC users may have a persistently adverse cardiovascular experience even after stopping use. Correlation with progestin type and quantity should be a primary consideration in such studies.

Finally, health policy decisions in the OC field are not influenced solely by the findings in regard to oral contraceptives. Data that define the risk-benefit ratio for alternative forms of contraception, such as the intrauterine devices and vaginal barrier devices, must also be considered. Recommendations for the use of various contraceptives will increasingly recognize the optimal subgroups for usage and the noncontraceptive benefits of the various contraceptive modalities.

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