

Ethics and the Use of Drugs During Pregnancy

The use of drugs in pregnancy, as in other situations, ideally is based on knowledge of the possible risks and the possible benefits to the woman and the fetus. A casual reading of package inserts tabulated in *Physicians' Desk Reference* for the last two decades indicates that the most recently introduced drugs are not approved for use during pregnancy. This poses a problem for the physician who cares for pregnant patients: either he does not use the recently developed drugs, or he gives them to patients without knowing the possible consequences to the patient and the fetus. Thus, the physician has either to practice medicine as though there had been no advances in drug development in the last 30 years or so, or to possibly risk the well-being of the patient and fetus. The further risk—legal action for administering a drug not specifically approved for use in pregnancy—also exists.

Intelligent drug prescription for a population requires a careful study of the particular agent in that population: in that way, knowledge about optimum use can be acquired for each situation. Those who oppose research in humans because of possible risk must realize that information gained in other species may not apply to humans. Similarly, studies in nonpregnant patients may not apply directly to pregnant women.

The five questions we considered arose from our attempt to evaluate two antibiotics (erythromycin and clindamycin) frequently used during pregnancy. Those questions were:

- 1) Should a study of antibiotic pharmacology be performed in pregnant women?
- 2) If a study is to be performed in pregnant women, in what ways can it be conducted to minimize risk to both mother and child?
- 3) Should detailed pharmacological studies in pregnant women be coupled with information about the drug in the fetus?
- 4) What kind of permission is required to examine fetal tissues?
- 5) If legal action results from conducting a valid scientific investigation, what steps should be taken to preserve the legitimacy of that research?

Origin of the project. A personal experience of one of us (A.P.) prompted the study. During a pregnancy she developed bronchitis, which was treated with the antibiotic ampicillin. However, the therapeutic response was delayed and suboptimal. It occurred to her that even though the usual dose of ampicillin was

being taken, inadequate amounts of drug might be reaching the bloodstream and the site of infection. Perhaps during pregnancy the body absorbed, distributed, or excreted the drug in an altered way, causing the poor clinical response. She measured the ampicillin in her blood after a usual dose and found that it was considerably below the "normal" level that had been found in routine pharmacological studies in young, healthy men. After the pregnancy she took an identical dose of ampicillin, measured her blood levels, and found that they were normal.

These facts opened wider questions. Were most pregnant women being given drugs in doses based on observations made in nonpregnant individuals? Were some or possibly many of these doses not ideal for pregnant women?

Ethical question of pharmacological studies during pregnancy. On arriving in the United States, she found two physicians (L.D.S. and D.C.) who were receptive to her suggestion that they investigate drug metabolism during pregnancy (one, D.C., had already done some studies on the pharmacology of antibiotics in pregnancy). The selection of drugs was based on the criterion that they should be substances that were frequently used in pregnancy and for which the information obtained might eventually be of use in treating pregnant women. One important consideration was that certain infections in the pregnant woman can be passed on to the fetus and can cause fetal death or severe congenital anomalies. One of the best-known examples of such a disease is syphilis. The major drug in the treatment of syphilis is benzylpenicillin (penicillin G). It has been estimated that 3 to 10 percent of the U.S. population is allergic to penicillin, and there has been a report (1) that erythromycin is ineffective in treating congenital syphilis. Because it is difficult to grow the organism that causes syphilis, *Treponema pallidum*, in vitro, the treatment failure reported could have several possible explanations: (i) the organism is resistant to erythromycin, (ii) the drug is not absorbed, (iii) the drug is absorbed but very rapidly excreted, (iv) the drug is adequately absorbed and normally excreted but fails to pass the placenta, or (v) the drug passes the placenta but is inactivated in fetal tissues. Because erythromycin and clindamycin have been used for patients who are allergic to penicillin, these drugs were chosen for the study. Another reason for selecting these antibiotics was the belief that they are relatively safe. Thus, our tests with

pregnant women would involve drugs that were not likely to harm the patient and for which no fetal damage had ever been recorded.

Since a drug to be used in a population should be tested in that population, the results of experiments on humans should have utility for those in the group being tested, and there is an urgent need for the results of this sort of experiment, the decision to study the pharmacology of erythromycin and clindamycin in pregnant women seemed to solve adequately the first ethical question.

Second ethical question: How to minimize possible damage. Although the two antibiotics chosen for study were known for their safety and neither had ever been reported to cause fetal damage, we considered the possibility that such damage might occur, a side effect that would be difficult to accept. To completely avoid this possibility, we chose to administer the test antibiotic only to pregnant women who, for independent reasons, were anticipating elective abortion and consented to participate in the study. Since no viable child would be born, there was no possibility of congenital damage. Furthermore, if adverse drug effects to the mother were accentuated by pregnancy, the termination of pregnancy would eliminate the accentuating factor.

Third ethical question: Should antibiotics be measured in the fetus? One of our objectives was to learn whether the drugs being studied actually entered the fetus, as determined by drug levels in the umbilical cord. We also sought information on whether some fetal tissues received more or less antibiotic than others. Surgical specimens are routinely sent to the pathology department for examination and material not removed by the pathologist is destroyed. Since most fetal material removed at each abortion was handled in this manner, we reasoned that we could assay antibiotics in various fetal tissues before they were destroyed. Such tissue samples would be obtained without inconvenience to the patient on whom the operation was performed and could provide information on the optimal use of antibiotics in treating or preventing intrauterine infection.

Fourth ethical question: Patient consent for fetal studies. Boston City Hospital, the institution at which we were working, required patient consent for any human study in which drugs would be given or blood or tissue would be removed; they further required that the protocol be approved by the hospital's human studies committee. Our study was so planned and approved. The question of what consent was needed for ex-

amination of the fetal tissues was raised. It was obviously impossible to get permission from the fetus. Furthermore, the samples were to be obtained from a department of pathology, to which they had been delivered as surgical specimens. (For hospital accreditation all surgical specimens must be sent to the pathology department for examination.) Because the operation permission form specifically asks patients for permission to dispose of any tissue removed in whatever fashion deemed appropriate by the staff, it was felt that appropriate permission had been granted. Since patient consent is not sought for other types of examination on surgical specimens—that is, what fixatives, kinds of microtomes, or types of stains are to be used—we saw no reason to ask specific questions about the details of our examination of the surgical specimens.

Fifth ethical question: Response to legal intervention. In contrast to the first four questions, the fifth did not arise from the experiment itself, but from a public accusation of unethical conduct in performing research (2). An investigation had been stimulated by the first of two articles (3, 4) in which we reported the results of the drug study. We and the pathologist who supplied the tissues were charged under an 1814 Massachusetts law entitled Violation of Sepulture (5), which was designed to prevent the robbing of graves to obtain cadavers for use in anatomy. After almost 4 years, the charge was eventually dismissed.

The ethical problems that arose from this legal action were serious: to what extent we should communicate with the press, who would provide financial support for the legal costs, how we should deal with the legislatures that were responding to pressures to limit fetal research.

The major question involved the investment of time and effort to try to prevent the near elimination of fetal research in the United States. What obligations do investigators have to speak out against such restrictive measures? We have not solved this ethical problem. One of us (A.P.) continued her investigations of antibiotic pharmacology during pregnancy, but in Sweden. The others elected to continue most of their scientific and medical work as it had been done before the case. But the question of how the scientific community should respond to investigations of this sort still remains. When we attempted to gain support for our case, the president of one of the largest clinical research organizations in the United States replied that people in medical research should not

speak out too often lest they lose their credibility. Although a number of serious, accomplished senior investigators in science came forth to express their interest and to offer and lend their support, many of them either were friends or were very much involved in virology or problems directly related to the fetus and the newborn. Many other investigators, some of international reputation, were eager not to become involved. The apparent fear expressed by some who were approached was reminiscent of that during the McCarthy era.

It was postulated that the forces promoting the "investigation of possible crime related to fetal research" were related to the antiabortion movement. Although fetal research has little to do with the abortion issue, they became (in our case) intertwined. Investigations of the use of drugs in pregnancy and the implications of such research for fetal welfare are vital. Studies utilizing the pluripotentiality of fetal tissue can add much to medical knowledge and capabilities.

But such investigations cannot be performed without certain assurances. We consider that there are four major requirements for successful medical research: (i) the idea, or formulation of the research project; (ii) the technical expertise, effort, and persistence to follow through the details of the experiment; (iii) the administrative ability to gather the resources (for example, money, laboratory space, workers, and equipment); and (iv) the ability to present the results (sell or package the findings) (6). Under our current laws, item (iii) can be limited by restrictive legislation or utilization of legal and institutional pressures to prevent an unwanted line of investigation.

Summary and conclusion. To ethically use drugs during pregnancy, knowledge of their efficacy in that setting is required. A casual observation by A.P. led to the project in which these ethical problems were encountered. She was eventually able to study the problem of ampicillin pharmacology in 26 pregnant women and found that their peak serum levels were significantly lowered

($P < .001$) during pregnancy (7). Five specific components of this larger ethical problem have been discussed. Relatively easy, practical, rational solutions were found for the first four. A fifth ethical consideration arose—to what extent investigators "are their brothers' keepers." There is some obligation for scientists to communicate with the non-professional component of society; how it is to be done remains a problem. Part of the solution was perhaps summed up by the 18th-century German philosopher Immanuel Kant, who stated, in *The Fundamental Principle of the Metaphysics of Ethics*, that man should not be used as a means to an end but rather as an end in himself. Thus, in each of these ethical considerations it is clearly essential to consider that the subjects of such investigations, as well as the rest of society, must be considered as the end. To protect that end more knowledge is needed; it will never be gained by preventing its acquisition.

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References and Notes

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4. ———, *Clin. Pharmacol. Ther.* **19**, 68 (1976).
5. The law stated: "Whoever, not being lawfully authorized by the proper authorities, willfully digs up, disinters, removes or conveys away a human body, or the remains thereof, or knowingly aids in such disinterment, removal or carrying away, and whoever is accessory thereto either before or after the fact, shall be punished by imprisonment in the state prison for not more than three years or in jail for not more than two and one-half years or by a fine of not more than two thousand dollars."
6. The concept of item (iv) was suggested by M. Laverdiere in 1977.
7. A. Philipson, *J. Infect. Dis.* **136**, 370 (1977).

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Cementum Annuli in Mammal Teeth from Archeological Sites

Bourque *et al.* describe a method for examining mammal teeth from archeological sites to determine seasonality (1). This method elaborates upon techniques used by wildlife biologists, in which teeth are sectioned and their cementum is examined for incremental layers. Bourque *et al.* claim that "recently

Spiess reported a new technique for determining the season of death from archeological faunal remains" (1), and they describe the study of cementum annuli in archeological sites as "Spiess's method." As the method was in use by archeologists some years prior to Spiess's paper (2), this is clearly an er-