CORRESPONDENCE

Exogenous sex hormones and birth defects: Continuing the dialogue

To the Editors:

Practicing physicians are placed in an extremely difficult position (that is certainly not of their making) when trying to wade through the hazardous currents of conflicting data that flow from epidemiologic studies in general and from teratologic studies in particular. What are they to believe? And how are they to act on contradictory data? All physicians are in the enterprise of reducing and eliminating disease and disability whenever possible. Certainly no one wishes to contribute to damaging babies. Nor does anyone wish to see safe and efficacious drugs withheld from clinical use.

The fault does not appear to be in a lack of sincerity on the part of the epidemiologic investigators. Rather it is through their failing to recognize that the methods that must be applied to detecting low-level teratogens, which may cause birth defects in 1% or 2% of pregnancies exposed at a vulnerable period of embryogenesis, are more rigorous than those that are needed to unmask high-level teratogens, which cause defects in 50% to 80% of pregnancies exposed at a vulnerable period. It should be emphasized that in the case of almost all human teratogens, except for thalidomide and rubella, for every paper purporting to show a causal association with birth defects, there is another paper to refute this claim. The physician is left standing in the middle. Even with thalidomide (50% to 80% malformation rate), it took four years from the time the drug came on the market until a sufficiently compelling data base was produced to encourage its withdrawal. How much greater is the challenge to discover low-level teratogens!

A question immediately comes to mind: If a drug causes malformations in only 1% to 2% of those exposed, does it really matter all that much? It matters most tragically to those who must live with the burden of disability and death, particularly if the use of the drug was not absolutely essential. From the point of view of society it also matters. If a drug is very commonly used in pregnancy, then the potential exposure rate is high, and even if the malformation rate following exposure is only 1% to 2% this could mean thousands of babies born every year in the United States alone with birth defects that could have been prevented. Thus, to the individual burden must be added an unnecessary and unacceptable burden to society. A few years ago we made the estimate that given only a 1% increased risk of cardiac malformation following hormone exposure, about 3,000 babies with congenital heart disease were being born in the United States each year under circumstances in which hormones could be implicated. If we assume that this is correct, hormones could be considered a more common cause of congenital heart disease than any other single identified etiologic factor, all on the basis of only a 1% increase in risk of cardiac malformations.

There are many points in the article by Wilson and Brent[1] that require challenge, but in the space of a letter we must severely limit our response to only three areas. The first has to do with animal data. The second has to do with fundamental errors in epidemiologic design that are of such magnitude as to invalidate *any* possible conclusions of "no effect" of hormones in the production of birth defects. The third has to do with the erroneous perspective that sex hormones act only on so-called target tissues.

Wilson and Brent appear not to be totally familiar with the animal data on sex hormones and birth defects. In going through out reprint files we found 12 studies that challenge the statements they made about the lack of animal data.[2–5] Whatever the human applicability and merits of individual studies may be, there is no serious deficiency in data suggesting a causal association between sex hormones and malformations in animal models.

Second, a critical error that flaws every epidemiologic study that has not found a significant association between hormone exposure and birth defects is the failure to associate the time of exposure to the hormone with the vulnerable period of embryogenesis for the defect in question. This requirement must include cases with malformations to establish that the putative causal exposure occurred at the vulnerable period for production of the defect and conversely *must also exclude* cases not resulting in malformations if the hormone exposure occurred outside the vulnerable period. To illustrate this point, many of the studies looked at transposition of the great arteries. Truncoconal septation is completed by day 34. Any teratogenic influence of this structural development must take place before day 34. Therefore, a hormone given after day 34 cannot be considered responsible for transposition of the great arteries, nor can a case where hormone exposure after day 34 that failed to produce transposition be tallied as showing no effect. In our own studies we emphasized the absolute necessity of correlation of

the time of exposure with the stage of vulnerability.

The magnitude of the problem of using the first 3 months as the vulnerable period rather than the first month (a 67% mismodeling bias) may not be readily apparent until one performs the appropriate calculations.[6] If one builds into a study a 67% error through mismodeling (as compared with a tolerable 5% error), the number of cases needed to show no association of hormones with birth defects at a fourfold increase in risk balloons from only 140 cases to 2,299 cases needed in a retrospective study or to 12,122 cases (rather than 1,663) in a prospective study. To put it another way, 16 times as many retrospective cases are needed to show "no effect" if the first trimester rather than the first month is used as the true vulnerable period. But how many cases are in the various "negative" studies? Not 2,299 or more retrospective cases or 12,122 prospective cases. The range of numbers is from 29 to 227 cases. This exercise is based on showing "no effect" at a fourfold increase in risk. What if the increase in risk is only twofold (as in increasing congenital heart defects from 1% to 2% in exposed groups)? Then 60,231 cases would be required to show "no effect" in a prospective study.

Clearly, no study can tolerate a 67% mismodeling bias. The solution for future studies seems to be self-evident. Precision in design greatly reduces the number of cases needed to reach confident conclusions. One may either have tens of thousands of cases imprecisely studied or a few hundred cases that are studied with precision. Financial resources will no longer permit the profligacy of enormous but imprecise studies. Small, elegant, well-designed studies will achieve the answers with greater economy and accuracy. But what can be done about the critically flawed studies already completed? This answer also seems to be self-evident. They should be rejected as not having the power to answer the questions posed. Favorably comparing one set of flawed data with another set of flawed data to buttress one's own position is not a viable solution for any of us.

Wilson and Brent stressed the undeniable role of hormone receptors in the mediation of hormone effects. If their perspective were correct, i.e., that sex hormones act almost exclusively on the limited number of target organs related to primary and secondary sexual characteristics, then it would be hard to visualize how hormones could indeed malform nonprimary target organs. However, sex hormones probably interact with receptors in other organs, including the liver and hypothalamus, which leads to the potential for widely disseminated effects. The liver definitely receives and metabolizes hormones. There also apparently are sex hormone receptors in the hypothalamus, and the potential for a widespread effect of sex hormone influence to be derived through this axis is, of course, obvious. Certain synthetic progestogens inhibit biosynthesis of estrogens. There is also the phenomenon of nonphysiologic effects of hormones that appear not to be receptor mediated. And what do sex hormones do to the placenta? A point of view that may be expressed with regard to hormone receptors is that they are present in greater or smaller amounts in almost all tissues. When present in certain tissues in great amounts, they may be easily identified. Their presence in small amounts in other tissues may be difficult to identify and may be small for some valid physiologic reason. Perhaps the organ or tissue in question cannot tolerate high levels of hormone and is designed to respond to very low levels. An example of a tissue that does not yet have "demonstrated" hormone receptors, but is still exquisitely sensitive to sex hormones, is bone. Surely no one would argue against the effect of sex hormones on bone growth and epiphyseal closure.

What also needs to be emphasized is that many adverse effects of many drugs may be derived not from the drugs themselves but from their metabolites. Reactive intermediates are known to be teratogenic, carcinogenic, and mutagenic.[7] In fact, after two decades of investigation, a mechanism for teratogenicity of thalidomide has finally been proposed as being attributable to a reactive intermediate arene oxide. There is a lot more to the story of hormone receptors and damage to the developing embryo than has been discussed by Wilson and Brent. The fact that every link in causality from hormone receptor to specific malformation has not yet been defined does not mean that hormone effect does not take place.

For years, the tobacco industry has put forward their epidemiologic studies refuting a causal relationship between tobacco, cancer, heart disease, and other problems. Even in 1982, in response to the latest Surgeon General's report that tobacco causes 340,000 deaths per year, the Tobacco Institute continues to contest the issue. This year the thrust of their message is that a causal link has not yet been established. Although it may appear to be reaching rather far for parallels, it is possible to see similarities between the arguments against causality in tobacco-related disease and hormone-related birth defects.

Many studies of hormones that are tallied with the "negative" group do, in fact, show an increase in risk. Indeed, almost every study shows either a small or a substantial increase in risk. This is *exactly what one would expect* of a low-level teratogen. But we must not be misled by the idea that because the individual risk is low, it is inconsequential. The relative risk of tobacco and coronary heart disease is about 1.5 to 1.7. This is the same level of relative risk found in several "negative" studies that has led some to reject the relationship of hormones to birth defects. It is not the 1.5 relative risk that is important here; it is the very wide-spread use of tobacco and hormones. Many thousands of deaths and disabilities can result from a small increase in relative risk. The concerns raised by studies, including ours, that have shown a strong positive correlation between hormone use and birth defects place appropriate emphasis on the judicious use of indicated hormonal ther-

apy. That precaution still holds. The patient should be an informed participant in the use of any drug during pregnancy.

If, as we believe, Wilson and Brent are basing reassurances regarding the lack of significant risk of hormones in pregnancy on critically flawed epidemiologic studies and erroneous assumptions of mechanisms of action of hormones, they are doing a disservice to practicing obstetricians, who may be encouraged into less conscientious use of hormones. Also, if they are wrong, as we believe they are, the ultimate disservice is in the potentially disastrous consequences to those yet to be born. It may be hoped that through dialogues of this type, we will continue to identify errors in design and execution of teratologic studies, profit from these errors, and demand better studies in the future. On the basis of the studies presently in the world literature, and until future adequately designed studies prove otherwise, we submit that the wisest course for obstetricians is still continued prudence.

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Cervical dilatation with pessaries containing a new prostaglandin E_1 analogue in patients undergoing induced abortion

To the Editors:

It was with great interest that I read the article, "Low-dose vaginal 15 methyl prostaglandin $F_{2\alpha}$ for cervical dilatation prior to vacuum curettage abortion," by Drs. Niloff and Stubblefield (AM. J. OBSTET. GYNECOL. 142:596, 1982).

Surgical abortion through the vagina is performed by dilating the cervix with Hegar graduated dilators and mechanically removing the products of conception by curettage or by the technique of vacuum aspiration, or both. Cervical incompetence, spontaneous abortion, premature labor, and other complications have been reported by some workers among patients who have undergone surgical abortion. There is a need to minimize the risk of damage to the cervix during mechanical dilatation.

Recently, several investigators have reported the use of prostaglandin E_2 or $F_{2\alpha}$ to soften the cervix before suction curettage. Moreover, some prostaglandin analogues have already proved superior in terms of safety, greater oxytocic effect, longer duration of action, and lesser side effects. In their article, Drs. Niloff and Stubblefield stated that 15-methyl-prostaglandin $F_{2\alpha}$ used for a 3-hour interval produced adequate cervical dilatation with few side effects in induced abortion.

In our clinic, a new prostaglandin E_1 analogue, 16,16-dimethyl-*trans*-Δ^2-PGE_1 methyl ester (16-me-E_1) was used for preoperative cervical dilatation in 23 pregnant women who had abortion induced for socioeconomic reasons in the first trimester of pregnancy. A single vaginal pessary containing 1 mg of 16-me-E_1 was inserted into the posterior fornix at 3-hour intervals. Thirteen (56.5%) of the 23 patients had complete abortions and two patients (8.7%) had incomplete abortions. In six patients (26.1%) the cervix was dilated to at least 10 mm. The remaining two patients (8.7%) required mechanical dilatation at the time of vacuum evacuation. Apart from mild gastrointestinal symptoms, no serious side effects were noted. It is concluded that the new prostaglandin E_1 analogue, 16-me-E_1, could be used safely and effectively for preoperative dilatation of the cervix before surgical abortion in early pregnancy.[1]

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Iatrogenic prematurity with elective repeat cesarean section

To the Editors:

Dr. Bowers and associates are to be congratulated on their highlighting of the widespread problem of iatrogenic prematurity with elective repeat cesarean sections. It is now clear that gestational age is difficult to document with certainty by any parameter. Ultrasonic