Epidemiologic Detection of Low Dose Effects on the Developing Fetus

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Evaluations of the health effects of exposures in the workplace and environment have broadened to include effects on reproduction, as well as on the development of cancer. Models to assess risks associated with varying doses of exposure rest almost entirely on data about cancer. In this paper we discuss some distinctive features of reproduction which bear on the interpretation of such models, when applied to reproduction, rather than carcinogenesis. Dose-response curves describe the relationship between two exposures (smoking and alcohol drinking) and two outcomes (spontaneous abortion and birthweight) are used to illustrate some of the questions which arise in attempting to determine a "safe" level of exposure.

We have been studying the associations between environmental exposures and human reproductive events for more than a decade. It is bound to seem dilatory that only in response to the agenda of this conference did we begin seriously to build models that would enable the risks of varying doses of hazardous exposures to be assessed quantitatively. This is not altogether surprising, since most existing epidemiologic models for such assessment rest almost entirely on data about cancer. The models have been developed in response to needs created over the past decade by the Delaney amendment, which mandates government efforts to regulate exposures which have the potential to induce cancer. The broadening of evaluations of the effects of exposures in the workplace and the environment to include reproduction is recent. With this new focus, the need to assess and predict risks at varying doses intrudes upon the domain of reproductive epidemiology.

We begin by considering several advantages and problems in quantitative risk assessment that may be special to the field of reproduction. Next we present models based on our own data of the effects of varying doses of two exposures, smoking

and the drinking of alcohol, on two reproductive events: spontaneous abortion and birthweight. Exposure to these substances is largely a matter of personal choice and thus differs from many of the exposures for which dose-response curves have been fitted. In the last section of this paper, we consider the questions that arise with attempts to specify "safe" levels of exposure to smoking and alcohol during pregnancy.

Special Features in Quantitative Assessment of Risks in Reproductive Epidemiology

We think it important for the scientific development of the field, no less than for regulatory agencies, that contrasts be drawn between the models for quantitative risk assessment in reproduction and in oncogenesis which provided the initial approaches.

First, in a comprehensive approach to adverse reproductive outcomes, the range of events is wide and various (1). Deserving of attention are male and female infertility; abnormalities of the conceptus rarely or never seen at birth, such as abnormalities in chromosome number or structure, or mutant genes; ectopic pregnancy; malformations unassociated with chromosomal anomalies, occur-

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ring in spontaneous abortions, or at birth; spontaneous abortion of conceptions which are not morphologically or chromosomally abnormal; stillbirths; neonatal deaths; premature deliveries (i.e., later than 28 weeks); offspring with central nervous system defects, or with functional disabilities unaccompanied by detectable central nervous system impairment (for instance, mental retardation or hyperactivity); growth retarded offspring born at term; disorders appearing postnatally, such as adenoma of the vagina, congenital syphilis, deafness from cytomegalovirus.

This list makes no attempt to be complete, but it suffices to show that the possible adverse outcomes are many, that they are different in type, and that they involve a range of processes and causes. For some outcomes, (for example, the conception of a triploid zygote and the birth of an infant damaged by intrapartum delay) it is obvious that the underlying causal mechanisms must differ. For other outcomes, it is not always so clear whether the underlying processes are the same or different. An illustrative case to be considered below is the association of smoking with both spontaneous abortion (2) and low birthweight (3-5).

A second distinction between reproductive epidemiology and the study of oncogenesis is the relation of timing and duration of exposure to outcome. The time frame of an exposure in reproduction is crucial to almost any tenable causal model. The differentiation and the rapid growth of the organism during gestation requires, almost by definition, that certain effects (primarily, morphologic malformations) must follow on exposure at a precise and relatively short period of development. In relation to oncogenesis, there are only two examples, the associations of prenatal exposure to estrogens and to irradiation with cancer, where such precision in the timing of exposure is needed to produce an effect. With such environmental teratogens such as rubella and thalidomide, the vulnerable period for exposure is confined to the period of organogenesis. In some circumstances the timing of the insult can be even more precisely limited. We have found an excess of tetraploidy and hypertriploidy among spontaneous abortions where conception occurred in the presence of a spermicide (6). These chromosome anomalies are among the few thought to arise after conception. We infer that they are produced by a physical encounter between zygote and spermicide which takes place within hours (and at most one or two days) of fertilization. In each instance, bounds are set on the timing of the origin of a defect, be it in morphology or in chromosome structure, by the staging of development.

For many adverse reproductive outcomes, however, current knowledge indicates a much longer time period over which the insult may occur and there is less information to go on in conjecturing whether exposures of short or long duration are pertinent. Low birthweight, in the absence of any other defect, or the spontaneous abortion of a chromosomally normal fetus, for instance, belong in this class.

The possibility of a long latent period for chromosomal anomalies in the zygote resembles the ill-defined or open-ended intervals typical of oncogenesis. For almost all such anomalies, if an environmental exposure were to be involved, in theory, exposure would have to occur either prior to conception or at the time of conception. With errors of replication originating in the mother, the period prior to conception when an error may arise is long. The first stage begins in the oocytes of the mother-to-be, while she herself is still an embryo, and does not end until ovulation; the second stage of meiosis is completed only at fertilization. Given this long period during which environmental exposure may occur, multiple-hit or cumulative chronic exposure models are as tenable, or more tenable, than single-hit models. A possible example of a single-hit model, or at most of an exposure to one agent over a short time, is provided by Watanabe (7). In a study of conceptuses from induced abortions, maternal drug-taking in the period immediately preceding fertilization was associated with a raised rate of chromosome anomalies. In contrast, a possible example of multiple-hit or cumulative exposure beginning many years before conception is the association of irradiation exposure with triploidy and trisomy (5); indeed, the effect may be limited to older women. Although these observations serve to illustrate the possibilities, both need confirmation through replication.

Variations in timing, dose and duration of exposure may also explain the diversity of adverse reproductive outcome associated with a single agent. For example, alcohol drinking during pregnancy has been associated with the spontaneous abortion of chromosomally normal conceptions (2), with depressed birthweight (9-11) and with the fetal alcohol syndrome (12-14). Each of these three outcomes seems to be associated with different levels of exposure. The timing and duration of exposure may also influence the effect but the available data are not sufficiently detailed to study this possibility.

A third distinctive feature of reproductive epidemiology is that exposure can impinge on at least two, and as many as three individuals, although the outcome is usually described in only one

individual. Attempts to assess the effects of both maternal and paternal exposure are rare; anesthesia (1) stands alone as an example of an exposure where repeated systematic attempts have been made to separately assess both avenues of exposure. Among spontaneous abortions, a distinction may be made between processes operating through the conceptus to produce defects which are incompatible with intrauterine survival (most chromosomal anomalies) and processes operating through the mother to produce an abortion without causing detectable defects in the conceptus.

There is one aspect of the biology of human reproduction which has no parallel in carcinogenesis and which can be used to great advantage in searching for modest effects. Happily for the population, and unhappily for chronic disease epidemiologists, rarity is the norm in chronic disease. To detect moderate (e.g., doubling) increases in the frequency of a rare event, data are needed on large samples of both exposed and unexposed individuals. The collection of such data is costly and difficult, and sometimes an insufficient number of exposed individuals to yield the sample size needed may prove an insuperable obstacle. From estimates derived from abortion rates combined with cytogenetic studies, we learned that at least 95% of all karyotypically abnormal conceptions are spontaneously aborted. Hence, among spontaneous abortions, chromosomal anomaly ceases to be a rare event; at least 35% of aborted conceptuses are karyotypically abnormal and another 30% show abnormalities in morphologic development. For those anomalies which are lethal in utero, and this is by far the vast majority of anomalies, etiologic factors can only be detected through a study of spontaneous abortions (15). For those anomalies which only occasionally survive to term, the search for etiologic factors among aborted conceptions is considerably more parsimonious in terms of the numbers of pregnancies which need to be studied than a similar search among birth (16).

In Table 1 we illustrate this increase in efficiency. We have calculated the sample sizes of exposed and unexposed populations which would be needed to detect, with 80% statistical power ($\alpha = 0.05$, two-tailed test), that an exposure has led to a doubling in the rate of trisomy 21 at conception. Approximately 30% of trisomy 21 conceptions survive to be born (Down's syndrome). In a study of the prevalence of trisomy 21 among livebirths, 15,217 births would need to be studied. In contrast, to detect this same increase in risk in a study of abortions, where trisomy 21 is 13 times more common, 1,117 abortions would need to be karyotyped. Trisomy 21 is, however, only one of the many trisomies found among spontaneous abortions. If it were to be true that exposure to a factor which doubles the risk of trisomy 21, also doubles the risk of all other trisomies, then only 102 spontaneously aborted conceptions would need to be karyotyped. In the final column of Table 1 we calculated the number of exposed conceptions which would be needed to yield the samples of births and abortions assuming that 15% of recognized pregnancies end in abortion. Quite obviously, a study of chromosomal anomalies among abortions rather than among births affords substantial gains in statistical power. With many environmental hazards, the size of the exposed population is small as well limited; a search for the effects of such exposures on the frequency of chromosomal anomalies would be conducted with advantage among spontaneous abortions.

Changes in the overall frequency of spontaneous abortions, without reference to karyotypes can also be used as an indirect index of an increase of anomalies at conception. A doubling in the incidence of trisomy at conception will produce a 17% increase in the frequency of spontaneous abortion, from an expected 15% to 17.5%. In order to detect this rise, 3,480 conceptions would need to be studied in both the exposed and unexposed populations (again, for 80% power, $\alpha = 0.05$, two-tailed).

In spontaneous abortion rates are to be used in this way, then it must be borne in mind that neither mutagenesis (the production of point mutations in genes) nor teratogenesis (the genesis of dysmorphs) are terms which encompass all the mechanisms that can increase the rates. For instance,

Table 1. Sample size estimates for exposed and unexposed populations which are needed to detect, with 80% statistical power, a doubling in the rate of trisomy 21 at conception, depending on the outcome where prevalence is measured.[a]

Event	Prevalence in unexposed sample	Sample size of exposed and unexposed	Number of conceptions in each group
Trisomy 21 among births	0.0015	15,217 births	17.903
Trisomy 21 among abortions	0.0199	1,117 abortions	7,447
All trisomies among abortions	0.1750	102 abortions	680

[a]All calculations assume a two-tailed test at $\alpha = 0.05$.

smoking is associated with the spontaneous abortion of chromosomally and morphologically normal fetuses (2, 17).

Dose-Response Relations

Smoking and Alcohol Drinking, Spontaneous Abortion and Low Birthweight

We turn now to consider the dose-response relations of two exposures, smoking and alcohol drinking and two reproductive outcomes, spontaneous abortion and birthweight. With both types of exposure, the time frame is restricted to experiences of the mother between conception and parturition. We shall illustrate the dose-response relations of each type of exposure separately, controlling for effects of the other exposure, and for other potentially confounding factors.

The data draw on an ongoing epidemiologic study which is being carried out in three New York City hospitals. Over the past six years, we have identified all women admitted with spontaneous abortions to either the private or public facilities of the hospitals (cases). Over this period, 2802 women have been interviewed and in about 30% of these cases we have completed a cytogenetic examination of the aborted conceptus.* A comparison group, matched for maternal age and payment status (private or public patient), has also been selected and interviewed. This group comprises women seeking prenatal care at the same three facilities whose pregnancies continued longer than 28 weeks gestation (controls). We have included 1343 interviewed controls in the comparisons with women experiencing spontaneous abortions; data on 972 singleton livebirths to these women have been processed and are available for the birthweight analyses. The study design and sample is described fully elsewhere (2, 18).

Spontaneous Abortion, Smoking and Alcohol Drinking

In Figure 1, we set out the estimated dose-response curve relating the number of cigarettes smoked per day to the odds of spontaneous abortion for seven levels of alcohol consumption; maternal age and education are controlled. The odds of
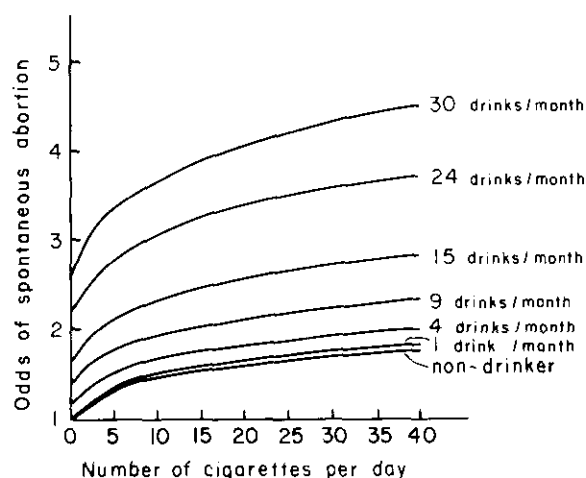

FIGURE 1. Increases in the odds of spontaneous abortion with increases in the number of cigarettes smoked each day for women defined in seven alcohol consumption categories.

abortion increase with each additional cigarette smoked at every level of alcohol consumption. These curves were fitted by using maximum likelihood logistic regression (19-21). The shape of the best fitting curve (p = 0.46 in comparison with the observed data) is a linear function of the logarithm of one plus the number of cigarettes smoked each day. There is no interaction between alcohol drinking and smoking in their effects on the odds of a spontaneous abortion. For each level of drinking, the odds of spontaneous abortion are increased by 46% for the first 10 cigarettes smoked and by 61% for the first 20 cigarettes smoked.

In Figure 2, we set out the estimated dose-response curves relating alcohol drinking to spontaneous abortion for three levels of cigarette smoking; maternal age and education are again controlled.
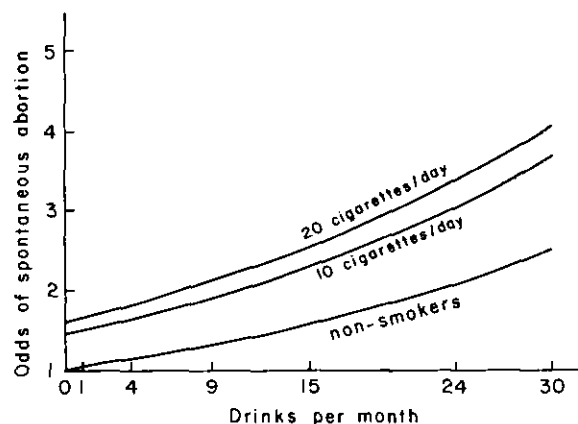

FIGURE 2. The odds of spontaneous abortion with increases in the number of days each month on which alcohol was consumed for women defined in three smoking categories.

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* We enumerate here only those women aged 15-40 years at their last menstrual period since only these women are included in the analyses presented here.

Alcohol drinking has been defined each month on which alcohol was consumed; the seven categories of the variable range from abstinence to daily drinking. The best fitting curve relates the log odds on spontaneous abortion to a linear function of alcohol drinking; the odds of abortion increase 3% with each additional day on which alcohol was consumed. The odds of spontaneous abortion for a nonsmoker who drinks every day are 2.53 times that of an abstinent, nondrinking woman; a woman who smokes one pack of cigarettes each day and who drinks daily has increased her odds of abortion to 4.08.

Since nearly all chromosomal anomalies arise either prior to or at conception and we limited this analysis to exposures which occurred during gestation, we hypothesized that the increased risk with both alcohol drinking and smoking would be confined to chromosomally normal abortuses. We should expect too, that the associations of such exposure with chromosomally normal abortions would be greater than with all abortions, which include conceptions with chromosomal anomalies as well. The odds associated with smoking for the 546 spontaneous abortions which were chromosomally normal (about 65% of the total) are, as expected, slightly greater than the odds of aborting when all abortions, irrespective of karyotype, are considered together (Fig. 3). In contrast, the odds of aborting a chromosomally normal conceptus with increasing frequency of drinking although increased significantly above 1.0, are unexpectedly lower, again not significantly so, than the odds of aborting when all abortions are considered altogether (Fig. 4).

Further analyses of our data suggest that alcohol drinking may also be associated with aneuploidy in the conceptus (2). Since about 60% of cases who reported drinking frequently prior to pregnancy
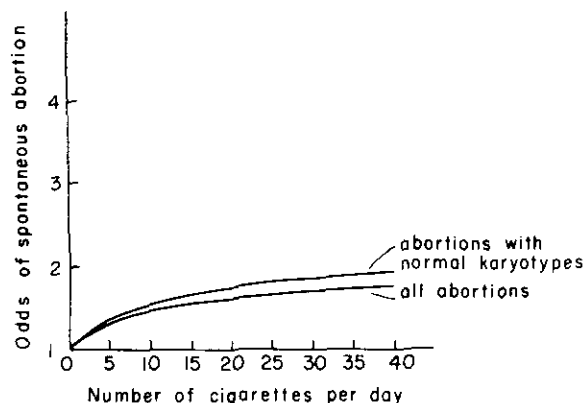

FIGURE 3. Increases in the odds of spontaneous abortion and of chromosomally normal spontaneous abortions with increases in the number of cigarettes smoked each day: nondrinkers only.
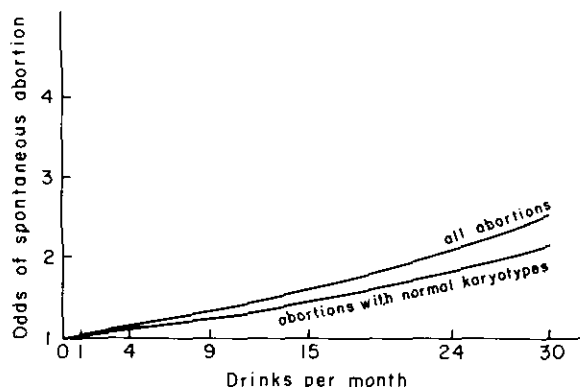

FIGURE 4. The odds of spontaneous abortion and of chromosomally normal spontaneous abortions with increases in the frequency of drinking alcohol: nonsmokers only.

reported similar habits during pregnancy, this finding could, in fact, reflect an effect of preconception drinking habits on the structure of chromosomes. On the other hand, the finding is so different from our expectation that every possible source of confounding must be searched out, something we are still in the midst of doing.

Birthweight, Smoking and Alcohol Drinking

We turn now to examine the relationships of both smoking and alcohol drinking to birthweight. The data refer to the 972 singletons born alive to the controls in our study. Least-squares linear regression was used to fit these dose-response curves. Maternal prepregnant weight, race, and age were controlled in the analysis.

In Figure 5 we set out the fitted dose-response curves of mean birthweight by number of cigarettes smoked per day. Separate curves are shown for white, black and hispanic women, since race and birthweight are strongly associated. Each of these three curves is a logarithmic function of one plus the number of cigarettes smoked each day. For women smoking 10 cigarettes each day, the predicted mean birthweight is decreased by 205 g compared to nonsmokers; the infants of women smoking 20 cigarettes each day will experience, on average, a 260 g decrease in birthweight. A similar analysis of 1837 singleton births to women entering the Columbia Chapter of the Collaborative Perinatal Project showed essentially identical results. In that series, smoking 10 cigarettes per day is associated with a 194 g decrease in predicted mean birthweight; smoking 20 cigarettes per day is associated with a 246 g decrease in mean birthweight.
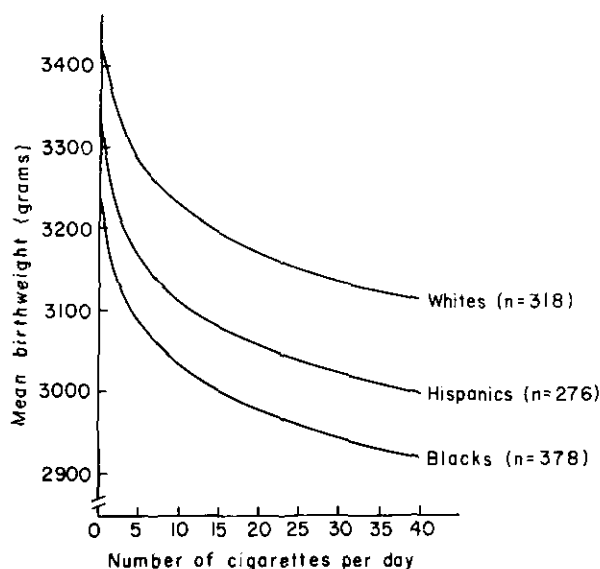
FIGURE 5. Decrease in the predicted mean birthweights of 972 singleton liveborns with increases in the number of cigarettes smoked each day: whites, hispanics, and blacks.

We also examined the relation of the frequency of alcohol drinking to birthweight. Unlike the data on spontaneous abortions, alcohol drinking is not related to birthweight in our series. Previous studies have given conflicting results. In those studies in which alcohol drinking does relate to decreased birthweight, the effect is only apparent among women who drink about two ounces of absolute alcohol each day (10, 11). In our series, only 2% reported drinking every day. Given this small proportion, failure to detect an effect may be a consequence of low statistical power.

Interpretations and Implications

The data, as they have been presented thus far, appear fairly straightforward. There is a dose-response relationship between the number of cigarettes smoked each day and both spontaneous abortion and lowered birthweight. In both instances, among the several curves tested (i.e., linear, quadratic), a logarithmic curve best described the data. There is also a dose-response relationship between alcohol drinking and spontaneous abortion: the odds of abortion increase linearly with increases in the number of days each month on which alcohol is consumed. There appears to be no interaction between smoking and alcohol drinking in their effects on spontaneous abortion.

To shed light on the biological processes involved, many more questions must be put to the data. We discuss three types of questions below. Each is relevant to interpreting observed associations, per-

haps especially when modest effects, such as those seen for alcohol and smoking, have been observed.

The first question that must be asked is whether any of the observed associations can be explained by other factors, such as parental characteristics and environmental exposures, which relate both to smoking and drinking and to the reproductive outcomes studied. So far, we have been unable to uncover any other characteristic or exposure which explains the associations. Among the variables which we have examined in addition to maternal age and education, are previous reproductive history, length of gestation (at interview for controls and at abortion for cases), presence of nausea and/or vomiting, coffee drinking, marijuana use, maternal race and prepregnant weight.

The second question to be asked is: Do the observed associations vary with maternal characteristics or exposures to other factors? Here the intent is to explore whether other characteristics or exposures modify the observed associations, rather than to test for confounding which might explain them away.

Our data suggest that the associations of both smoking and alcohol drinking with spontaneous abortion may vary with the education achieved by the woman. We have defined highest level of education achieved in three categories: education beyond high school, high school education and less than high school education. In Figure 6, the associations between smoking and abortion are shown for women grouped by education; for the sake of simplicity, only women who do not drink alcohol are included. In all three education groups there is a significant association between smoking and spontaneous abortion. The data suggest, however, that this association is strongest among women who have attended school beyond high school. The relative odds of abortion for each cigarette smoked are 12.8% greater for women who attended school beyond high school compared to women with a high school education or less. The 95% confidence interval for this increment in odds ranges from -1.4% to 29.1% and thus includes zero. In Figure 7, the associations between alcohol drinking and spontaneous abortion are shown for the same three education groups. Here, only nonsmokers are included. There is a statistically significant association of alcohol drinking with spontaneous abortion at each level of education. In contrast to the smoking association, however, these data indicate that the odds of abortion associated with drinking are less for women attending school beyond high school than for those who did not. The relative odds of abortion for each day on which alcohol is consumed are 2.0% lower for women attending school beyond high school compared with
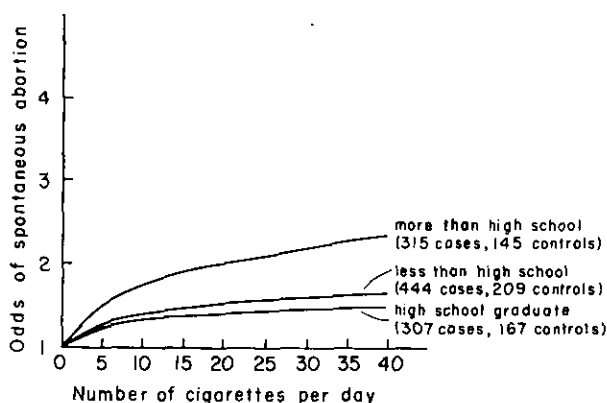
FIGURE 6. Increases in the odds of spontaneous abortion with number of cigarettes smoked for three categories of maternal education: Only those women who do not drink alcohol included.
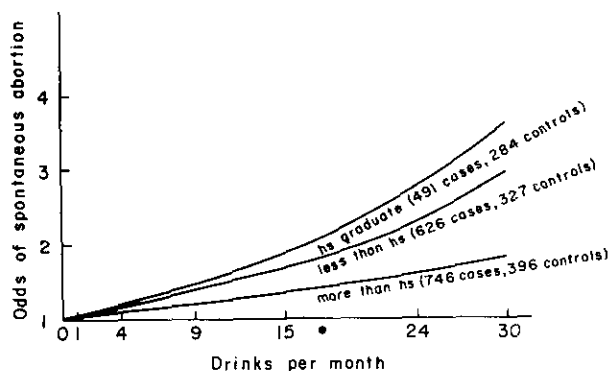

FIGURE 7. The odds of spontaneous abortion with frequency of alcohol consumption each month for three categories of maternal education: Only nonsmokers included.

women with a high school education or less. The 95% confidence interval for this increment ranges from -4.2% to 0%.

The exploratory analyses which we have just described raise the possibility that the effects of smoking and alcohol drinking during pregnancy may be modified by maternal characteristics which are related to educational achievement. Quite obviously, further analyses are needed to determine whether these interactions are spurious or are a clue to the biologic processes underlying the associations of smoking and drinking with abortion. A powerful first step would be the replication of this finding in a new data set.

The possibility that some characteristic associated with maternal education modifies the effects of smoking and drinking during pregnancy is relevant to our third and final question. What advice,

if any, is to be given to women who contemplate altering their habits during pregnancy? We do not propose to answer this question here, but to point to several issues which bear on its solution. First, we deal with issues common to most attempts to assess risk in terms of dose with an eye to regulation, regardless of the health problem under study. Then we deal with issues special to the field of reproduction.

In the presence of a continuous dose-response relationship, a safe amount of smoking or drinking during pregnancy depends on the level of risk of a spontaneous abortion which is considered unacceptable. The implication of a continuous dose-response curve is that no level of exposure is without risk. In our data it is not possible, however, to distinguish between several possible models of dose-response relationships at low levels of exposure. For example, the possibility that the odds of abortion were equal among women who smoked one to four cigarettes each day and nonsmokers controlling for the effects of age, education, and alcohol drinking (using the Mantel-Haenszel statistic) could not be rejected. The statistical power to detect the observed odds ratio of 1.18, which is nearly identical to the 1.20 odds predicted by the logarithmic model, was only 20%. Thus we can not exclude with confidence the possibility that light smoking is associated with spontaneous abortion.

When different levels of exposure are associated with more than one reproductive outcome, then the issue of setting a safe level of exposure becomes more complex. Drinking serves as an example. Moderate consumption of alcohol is associated with spontaneous abortion; daily consumption may be associated with decreased birthweight (9-11); and alcohol abuse may be associated with the fetal alcohol syndrome (12-14). Is advice to be given in relation to the outcome with the most severe consequences for the family and child (the fetal alcohol syndrome), or to the outcome which is sensitive to the lowest level of exposure (spontaneous abortion)? This dilemma in decision-making is rarely encountered in oncology, where there is agreement on the severity of the outcome no matter what the specific malignancy.

It is apparent that the conceptus is sensitive to environmental exposures. As the study of adverse reproductive outcomes turns to exposures which are not a matter of personal choice, such as occupational exposures, this sensitivity will be the subject of regulatory policy. This sensitivity may, however, be manifest in associations with any one of the many adverse reproductive outcomes. We end this paper with yet one more question which is relevant particularly to regulatory decisions: How

many outcomes should be examined before we are convinced that an exposure to either parent is without hazard in reproduction?

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