Commentary

Control Definition in Case-Control Studies of Ectopic Pregnancy

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Abstract: In case-control studies of ectopic pregnancy, the optimal sampling frame for control selection is influenced heavily by the hypothesis being tested. The selection of women completing an intrauterine pregnancy, a common choice for a control group in studies to date, is appropriate only if the hypothesis does not relate to exposures that selectively prevent an intrauterine pregnancy (e.g., use of an intrauterine device (IUD) at the time of conception). Even for other exposures, the selection of such women can yield misleading results if the exposure is related to the likelihood of completion of the intrauterine pregnancy. On the other hand, the selection of nonpregnant women as controls, while permitting a valid evaluation of the risk associated with exposure such as the use of an IUD, can introduce a substantial degree of incomparability between cases and controls with regard to other contraceptive practices and their correlates.

Whichever of the two sampling frames that is chosen, an appreciation of these potential biases can lead to ways of tailoring the selection of individual controls to minimize the magnitude of the bias. (*Am J Public Health* 1985; 75:67–68.)

Introduction

During the past one to two decades, the incidence of ectopic pregnancy has been increasing in many parts of the world.[1–5] Because changes in the prevalence of hypothesized and/or identified risk factors for this disease have been too small to account for the trend,[3] it is likely that research into the causes of ectopic pregnancy will intensify in the near future.

Epidemiologic studies of ectopic pregnancy can be expected primarily to be case-control in nature, given the efficiency of this design in exploring a wide variety of risk factors for a still relatively uncommon condition. Yet, among prior case-control studies of ectopic pregnancy, very different sampling frames for control selection have been used. For example, Levin, *et al,*[6] and Daling, *et al,*[7] selected as controls women who completed an intrauterine pregnancy, while Ory, *et al,*[8] specifically excluded such women and restricted the control group to nonpregnant women. Part of the reason for the difference in approaches relates to the hypothesis being tested in the respective studies. Ory, *et al,* were particularly interested in the relation of the use of an intrauterine device (IUD) at the time of conception to the occurrence of ectopic pregnancy. Had they chosen women with an intrauterine pregnancy as controls, and had they found a smaller proportion of IUD users among them than among cases, they would have been unable to discern the effect (if any) of the IUD in increasing the risk of ectopic pregnancy from its effect of lowering the risk of intrauterine pregnancy.

For a number of other possible risk factors for ectopic pregnancy, the choice between pregnant and nonpregnant control subjects also could have an impact on the results, albeit a more subtle one. Our purpose here is to describe why this occurs and, for the particular choice of control subjects that is made, some ways in which the degree of bias resulting from that choice can be minimized.

Limitations of a Control Group Comprised of Women with a Full-term Intrauterine Pregnancy

In many societies at the present time, the proportion of intrauterine pregnancies that terminate in an induced abortion is high. For example, in a 13-state reporting area of the United States during 1979, there were approximately 390 induced abortions for every 1,000 live births.[9] In contrast, only a small fraction of women with an ectopic pregnancy have its "completion" prevented by an induced abortion because: a) for many women, the symptoms and signs of the ectopic pregnancy are the first indication that she is pregnant at all; and b) evacuation or curettage of the uterus of women with ectopic pregnancy prior to its diagnosis will not terminate the pregnancy.

Among women with an intrauterine pregnancy, prior contraceptive practices and other aspects of reproductive life often differ substantially between those who do and do not attempt to carry it to term. For example, 32.4 per cent of a sample of women undergoing abortion during 1979 in the United States reported having had at least one previous abortion,[9] in contrast to only about 13 per cent of US women of similar age who delivered a child.*

Thus, a comparison of women with an ectopic pregnancy to those with an intrauterine pregnancy who are planning or who have undergone a full-term delivery will be biased for any characteristic or exposure that is associated with an induced abortion. With respect to a previous history of induced abortion, for example, the finding of any excess risk of ectopic pregnancy that arises from such a comparison probably would be falsely large. The magnitude of this bias can be estimated as follows:

Assume that no association exists between prior induced abortion and ectopic pregnancy. The percentage of women with ectopic pregnancy who report having had an

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*We know of no data on a national sample of women giving birth to a child to indicate the percentage that have earlier undergone an induced abortion. The figure of 13 per cent is the average of percentages (12.8 per cent and 13.1 per cent) reported in studies conducted in Boston[6] and Seattle[7] in the late 1970s.

abortion would be identical to that of women who conceived an intrauterine pregnancy. This percentage would be equal to the weighted average of those for women who did and did not attempt to carry the pregnancy to term:

$[(13.0\% \times 1000) + (32.4\% \times 390)] \div 1390 = 18.4\%.$

These cases would be compared to controls who had chosen not to abort their intrauterine pregnancy, of whom about 13 per cent would have had a prior abortion. This would give a relative risk estimated (from the relative odds) to be $18.4/81.6 \div 13.0/87.0 = 1.51$, rather than the correct value of 1.0.

Choosing Controls

Women with an Intrauterine Pregnancy

Based on the foregoing, we conclude that a case-control study of ectopic pregnancy that does select as controls women with an intrauterine pregnancy ideally will include women who choose to terminate their intrauterine pregnancy in proportion to their frequency in the population in which the study is conducted. However, this ideal may be more easily stipulated than fulfilled. While it clearly is possible to identify and obtain information from women who have chosen to have their pregnancy aborted (Hren, *et al,*[10] did this in their study in Yugoslavia by adding such women to other controls who had carried their pregnancy to term), this undertaking may pose practical problems for many investigators. Women who have undergone abortion usually would have to be identified from sources (e.g., abortion clinics) separate from that of the other potential controls, and the negative way in which abortion is viewed in many societies could serve to make providers of abortion services reluctant to disclose the identity of their patients for studies of this sort.

The failure to include women who underwent abortion among controls having an intrauterine pregnancy will not detract from the validity of associations with exposures that are unrelated to whether or not the pregnancy is aborted. If the two groups (aborted, completed) have the same proportion of women with the exposure in question, the comparison of cases to either or both will produce the same result. Unfortunately, it is rarely possible to predict, in advance of gathering the data from both groups, which exposures these might be. Therefore, in a study that is obliged to restrict its controls to women with an intrauterine pregnancy who have or are planning to complete the pregnancy, every effort should be made to exclude from both cases and controls women with characteristics associated with a high probability of receiving an abortion. One such characteristic is attempted contraception at the time of conception, for it seems likely that a higher proportion of women who become pregnant while trying not to would seek an induced abortion than would other pregnant women. Another characteristic is not being married at the time of conception. Among single women surveyed in a five-state US sample in 1979, somewhat more than one out of every two pregnancies was terminated by an induced abortion, whereas among married women that proportion was but one out of 13.[9] Thus, restricting the study subjects to married, noncontracepting women would greatly reduce the incomparability of cases and controls, and to a corresponding degree reduce the magnitude of bias present when examining variables associated with induced abortion.

Nonpregnant Women

A control group consisting of women not pregnant at the time the ectopic pregnancy was conceived has the advantage that the question of selective removal of potential controls through induced abortion simply does not arise. This choice more closely simulates the approach that would be used in a cohort (follow-up) study of risk factors for ectopic pregnancy, i.e., the enumeration of cases in exposed and nonexposed person-time while the subjects are not pregnant.

Nonetheless, for the evaluation of some potential risk factors, the use of nonpregnant controls has its own drawbacks. These arise because cases and controls will differ to a large degree with regard to fertility and to birth control practices at the time of the case's conception. A far higher proportion of controls than cases will have been contracepting (most forms of contraception do prevent pregnancy, ectopic or otherwise) or will have been involuntarily unable to conceive. If a risk factor of interest is also related to the practice of one or more forms of birth control or to infertility, it would be necessary to control for the latter's potentially confounding effect. If, for example, certain feminine hygiene practices were associated with the use of contraceptive methods that prevent fertilization, a spurious negative association with these hygiene practices could be found if contracepting status were not taken into account. Unfortunately, in most studies this "taking into account" will have to be accomplished by adjustment in the analysis, and the very different control/case ratio in the two strata (contracepting and noncontracepting, with women from infertile couples excluded) will reduce the study's power. Thus, in this circumstance, it would be particularly important to achieve a high ratio of controls to cases overall to help offset the loss of power. (In the unusual situation in which contracepting status of potential controls could be determined inexpensively in a first stage of data gathering, it would be possible to match controls to cases on this variable before other risk factors were to be ascertained.)

If it is not possible to achieve this high control:case ratio, it may be prudent to accept some bias from the use of controls with an intrauterine pregnancy rather than the substantial imprecision that would result after analytic adjustment for the case-nonpregnant control imbalance in confounding variables. However, when examining the influence of exposures that selectively prevent intrauterine pregnancy (e.g., IUD use at conception), the selection of nonpregnant controls is the only valid approach.

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