

Epidemiologic studies of adverse reproductive outcomes in working populations

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Epidemiologic studies conducted by the National Institute for Occupational Safety and Health (NIOSH) on reproductive health in working populations can be placed into the following three general categories: (i) semen quality studies in populations of exposed men, (ii) pregnancy outcome studies in populations of exposed women or among the wives of exposed men, and (iii) studies of hormone levels in either exposed men or women. Our objective is to describe design issues common to these studies, issues specific to male and female reproductive studies, and new approaches in female reproductive studies.

Of the two basic approaches to disease investigations, NIOSH has emphasized cohort (or cross-sectional) rather than case-referent studies. The cohort approach has been the usual choice for several reasons. First, in the general population of the United States, the frequency of exposure to a specific occupational hazard is generally rarer than the outcome (fetal loss, birth defects). Even for a common exposure such as video display terminals only a small percentage of pregnancies are exposed. The relative rarity of occupational hazards usually renders a cohort study more statistically powerful than the case-referent study. A second reason is that cohort studies allow examination of the effect of occupational exposure on the entire spectrum of reproductive outcomes or conditions. Part of the NIOSH mission is to provide the Occupational Safety and Health Administration (OSHA) with health data on specific hazards, and the cohort approach allows us to do this efficiently. Finally, there are few registries or other sources of pregnancy outcome data in the United States that can provide complete case ascertainment. This is particularly true of fetal loss and studies of male reproductive effects. However, through employer records, large numbers of exposed workers can be identified and interviewed about their reproductive histories. NIOSH has a unique ability to obtain these

detailed employment and exposure data because the OSHA Act of 1970 grants NIOSH legal access to employment records and other pertinent information relevant to research studies. Much of the information obtained through legal right of entry is not available in other records; for example, only 13 states currently collect paternal and maternal occupation information for birth certificates.

Objective definitions of exposure are critical in these studies, since recall bias is often a major concern. Because NIOSH has legal access to company records, recall of exposure data has not been a problem. Where possible, we now attempt to obtain biomarkers of exposure for individual workers, and our new research studies are obtaining biomarkers of outcome as well.

Male reproductive studies

Basic information about reproductive hazards to men in the workplace needs to be generated. These hazards include direct, measurable effects on the male reproductive tract and its products, as well as effects on libido and potency. In a recent State of Massachusetts survey of reproductive hazard restrictions in Massachusetts companies, 58 restrictions from work activities or areas using a known or suspected reproductive toxicant were recorded for women; only one was recorded for male workers whose partners were trying to conceive (1). NIOSH is one of a few centers in the United States committed to male reproductive studies. Since 1980, eight NIOSH epidemiologic male reproductive studies have been done or are in progress. These studies are generally modest in cost, because of their cross-sectional design, and they yield results rapidly and with a relatively small group of participants. Strong union or corporate support or both is critical for a study, however, because each man who participates must give informed consent to one or more sensitive procedures. The willingness of workers to cooperate is independent of the NIOSH legal right to enter the workplace for a study, and it determines participation rate.

Male reproductive epidemiologic studies have the ability to detect modest changes in the male reproductive profile. These changes can indicate the potential dysfunctional impact of a reproductive toxicant, as was the case for our studies in which altered semen quality was found among workers exposed to glycol ethers

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(2) and ethylene dibromide (3). Two methodological aspects of male reproductive studies, however, remain problematic: design and interpretation of outcome measures, and participation.

Design and interpretation of outcome measures. In a NIOSH male reproductive study, over 50 measures of semen quality and hormonal levels are assessed. If a panel of questions to evaluate libido and potency is added to the study, an additional five to ten measures are included. It is likely that some of these measures will be significantly associated with an occupational exposure by chance alone. Bonferroni corrections or multivariate analyses of variance for related variable groups are two approaches we have taken in data analysis to address this problem (4). A second problem occurs when a statistically significant difference is found between exposed and unexposed workers, but both groups' results fall within a range judged to be clinically normal. An evaluation of previous research and clinical norms may be necessary to interpret and communicate these findings adequately. Finally, self-reported reproductive outcomes and conditions are a potentially important portion of the study. In some cases, these data are only considered ancillary information (eg, number and outcome of pregnancies fathered). In other studies, such as the current NIOSH study to reexamine workers studied earlier (5) for health effects from the estrogenic-like chemical stilbene (4,4'-diaminostilbene-2,2'-disulfonic acid), self-reported information on libido and potency is a primary outcome of the study. A pretested, previously validated survey instrument (6) is being used in the current study to help overcome some biases incurred by the obligate use of this self-reported information.

Participation. High participation rates have not been the norm for semen quality studies, and unexposed groups are the least likely to participate in a male reproductive study. Disinformation, lack of appropriate worker education, and requirements for masturbation, blood draw, and a physical examination have all been identified as reasons for refusal. Perceived fertility concern, on the other hand, may be a predictor of participation. A characterization of nonparticipants is necessary so that unavoidable enrollment biases present in male reproductive studies can be identified.

Interview studies of pregnancy outcome

Pregnancy outcome studies of women can contribute to the identification of a toxicant effect on fetal development or survival. Such studies collect pregnancy outcome data by interviewing women exposed at work. When the wives of men exposed to a potential toxicant are studied, as in the NIOSH dioxin study, adverse effects on the children of male workers can also

be evaluated. Because of the absence of registry data, these studies are very labor and time intensive and require a much larger sample size than do traditional male reproductive studies. Six of these studies have been completed at NIOSH (7) and three [dioxin workers' wives, operators of video display terminals (8), and flight attendants] are in progress.

There are several problems inherent in conducting pregnancy outcome studies in the United States. The NIOSH studies on dioxin and video display terminals illustrate the types of difficulties we encounter.

Sample size. Pregnancy outcome studies of women require large study populations to detect low-to-moderate relative risks (below twofold). Several thousand women need to be interviewed, compared with 100 or fewer men in each group of a male reproductive study.

Outcome definition and validation. Objective definition of outcomes, such as spontaneous abortion, has been difficult and has generally been approached by obtaining medical and vital records in addition to interview data. The pragmatic problems of this approach include the following: (i) early fetal losses are often not seen by a physician, so there is no medical record of the event; (ii) records are often destroyed or lost; (iii) vital records contain only minimal information on the child, and many states are reticent about providing this confidential information.

Tracing. Locating the current address and phone number of female study participants is one of the most time-consuming and costly tasks in conducting pregnancy outcome studies. In our study on video display terminals (8), most of the women were still employed. However, initially we were able to obtain a working phone number for only 50% of the population. After extensive efforts, we were able to contact 81% of the population. In our study of wives of men exposed occupationally to dioxin, tracing is a different process. Tracing of current wives is made easier because we have the name of the man. In the United States, telephone numbers and other sources for tracing are generally kept in the man's name, and this procedure is unlikely to change. However, we also need to obtain information from the ex-wives of these men, since it is often the first wife who was married to the study participant during employment.

Cooperation. Our experience has shown that once contacted, women are generally very willing to share accurate information regarding their reproductive histories. We have, however, found that overall, ex-wives are somewhat less cooperative than current wives.

New approaches in female reproductive studies

Emerging laboratory technology has presented a new approach to reproductive research. NIOSH is currently evaluating the feasibility of conducting a reproductive study of flight attendants, who have multiple exposures of interest including ionizing and nonionizing radiation, alterations of circadian rhythm, and numerous airborne contaminants. One component of the study will examine ovulatory dysfunction with respect to a group of flight attendants' urinary steroid metabolites estrone-3-glucuronide and pregnanediol-3-glucuronide and the gonadotrophins follicle stimulating hormone and luteinizing hormone. An evaluation of these biomarkers requires far fewer women (several hundred) than a pregnancy outcome study (several thousand). A second study component will be a pregnancy outcome interview study as has already been described. The third study component will measure urinary human chorionic gonadotrophin as an index of early fetal loss in a subset of the interview population. We anticipate that these biomarkers will yield a more accurate, detailed and valid characterization of ovulatory dysfunction and early spontaneous abortion than any questionnaire currently available.

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