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Design considerations in pregnancy outcome studies of occupational populations

by Sherry G Selevan, PhD [1]

SELEVAN SG. Design considerations in pregnancy outcome studies of occupational populations. *Scand j work environ health* 7 (1981): suppl 4, 76—82. Increased attention has been focused on the relationship between adverse pregnancy outcomes and occupational exposures to parents of both sexes. However, the characteristics and dynamics of working populations impose limitations on potential study populations. These limitations result from the combined effects of workforce size, exposure, age distribution, and marital status, which limit the number of pregnancies available for study. The smaller populations available typically result in retrospective studies covering extended time periods. Potential data sources for these studies include interview data, medical records, vital statistics data, and insurance records. All sources may have biased ascertainment of certain pregnancy outcomes such as early fetal loss due to errors in recall in interview data, legal requirements for recording vital statistics data, and differences in medical care patterns.

Key terms: epidemiologic methods, occupational diseases, pregnancy.

In recent years, increased attention has been focused on the effects of occupational exposure on human reproduction. Although many epidemiologic studies have investigated causal relationships between various factors and pregnancy outcome, the study design for occupational exposures has unique aspects which require a different approach from those used in more traditional studies.

Traditional studies are defined in this context as those covering potential causal factors of the parents, such as genetically inherited disorders (7, 27), demographic characteristics (1, 3, 24), medical conditions (9, 27, 28), prescription and nonprescription drug use (21, 23, 25, 28), and personal habits such as alcohol and caffeine consumption (5, 23, 28). Occupational exposures for either parent are those physical, chemical, or biological exposures (9, 10, 26) related to employment within a specific industry or job.

Exposures to potential hazards can affect pregnancy outcome during one or more phases of the reproductive process. Malformations, functional defects, or death can occur through several routes; exposure may damage genetic material preconceptionally through damage to either parent's germ cells, or postconceptionally in the embryo/fetus. Postconceptional exposures may cause cell death or dysfunction in the embryo/fetus, especially during the period of organogenesis when cells are rapidly multiplying and differentiating into organ systems (28). Either type of exposure can result in fetal death or malformations or in a variety of other effects such as behavioral effects or transplacental carcinogenesis.

Study design considerations: Traditional versus occupational studies

Occupational pregnancy outcome studies may differ from traditional pregnancy studies in a variety of ways, including the

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size of the population available for study and the type and degree of exposure. The population size, in turn, limits the outcomes possible for study. Occupational studies examine workplace exposure in limited populations, whereas traditional studies usually cover a broader-based population. The underlying differences between the two study approaches are a result of the frequency of the factor/exposure being studied in the general population which determines the size of the potential study population.

Factors affecting study population size

The number of events (N) for study is determined by the interplay of three factors, the population size (P), the incidence density (I) of the number of pregnancies occurring within the time period of observation, and the length of the observation period (T).

$$P \times I \times T = N$$

If a given number of events (N) is to be maintained for study, a decrease in P, I, or T must be counterbalanced by an increase in the other variables. Rates of pregnancy (I) vary by age of the parents and over calendar time due to social and economic secular trends, etc. Traditional studies, usually with a larger population (P), can achieve the necessary number of events (N) in a shorter time period. These studies may include only current or very recent pregnancies and thus allow better control over data. Pregnancies within an occupationally exposed cohort of families may not fall into a recent time period, since the workers may range from very young to retirement age. Sufficient populations for occupational studies of current pregnancies are rare and would require longer observation periods. For pragmatic reasons of timeliness and cost, these studies have thus far been conducted retrospectively rather than prospectively.

Population size and outcome under study

Potential outcomes for study include early and late fetal loss, neonatal death, reduced birth weight, alteration in sex ratio at birth, proportion of births with either total or specific congenital malformations, infant or childhood death, childhood malignancies, and developmental disabilities (2). Estimates of the population size necessary for study vary with the rate of occurrence of the outcome of interest. The less common the outcome studied, the larger the study population necessary for the evaluation of the effects of exposure. Populations for occupational pregnancy outcome studies are typically defined by exposure and are usually cohort studies. Table 1 illustrates the variation in predicted population size under identical conditions, the risk ratio being 2, alpha

Table 1. Population sizes required for a cohort study of various pregnancy outcomes.[a]

Outcome	Probability in general population [b]	Population size required for each group: exposed and nonexposed
Fetal loss	15 % of recognized pregnancies	160 pregnancies
Reduced birth weight	7.4 % of live births	376 live births
All major birth defects (recognizable at birth)	2 % of live births	1,525 live births
Most frequent major birth defect (club foot)	0.6 % of life births	5,199 live births
"Objective" minor birth defects	10 % of live births	266 live births
Sex ratio (106 male/female × 100)	51.5 % male live births 48.5 % female live births	4,193 live births

[a] Schlesselman's equation was used (22); two-sided alpha = 0.05, beta = 0.10, and risk ratio = 2, except for the sex ratio, risk ratio = 1.1.

[b] Source of rates: Fetal loss: Bufler (2); reduced birth weight: National Center for Health Statistics (17); all birth defect rates: Hook (8); and sex ratio: Leridon (12).

0.05, and beta 0.10. Fetal loss, the most common outcome, requires the fewest observations. Since the occurrence of a twofold risk ratio in sex ratio is extremely unlikely, a risk ratio of 1.1 is considered and results in a much larger population necessary for study.

It may be possible, in some situations, to examine occupational effects on reproductive outcome in a community-based case-referent study with the population identified through hospital or vital statistics records. The sizes needed for each group of cases and controls can be estimated from published formulas (3). If 1 % of the cases are exposed to the potential hazard under study, each group would need more than 3,200 observations (risk ratio = 2). If the proportion exposed is 5 %, the number of observations needed drops to almost 700 in each group and, at 10 %, to approximately 380. Such a study might occur in a small community where the exposed workforce contributes a relatively substantial proportion of the events studied. A case-referent study would be extremely difficult for a plant in a large city with many industries; only a very general study which combines similar exposures into classes would be possible in this case.

The pregnancy outcome is determined by the hypothesized effect(s) of the exposure under study. Fetal loss, reduced birth weight, and major malformations are relatively easy to study through either interview or recorded-data sources.

Population sizes for occupational studies

The population for occupational pregnancy outcome studies is affected by the actual size of exposed industrial plant population(s), the level of exposure to the factor under study, the frequency of job transfers or changes between jobs of different exposure levels, the age distribution of the study population, and the proportion of married workers. The rate of turnover can also affect the proportion of pregnancies occurring within the period of employment; high rates of turnover combined with lag time between first exposure and its potential effect on pregnancy outcome can reduce the effective time of observation (fig 1). All these factors work together to determine the final number of pregnancies actually qualifying for study. For example, the population may be old enough to have children, but high turnover rates resulting in many workers with few years of seniority would reduce the number of pregnancies for study. In addition, workforces totaling less than 500 exposed and nonexposed workers are common.

The population size and definition are also affected by the sex of the workers

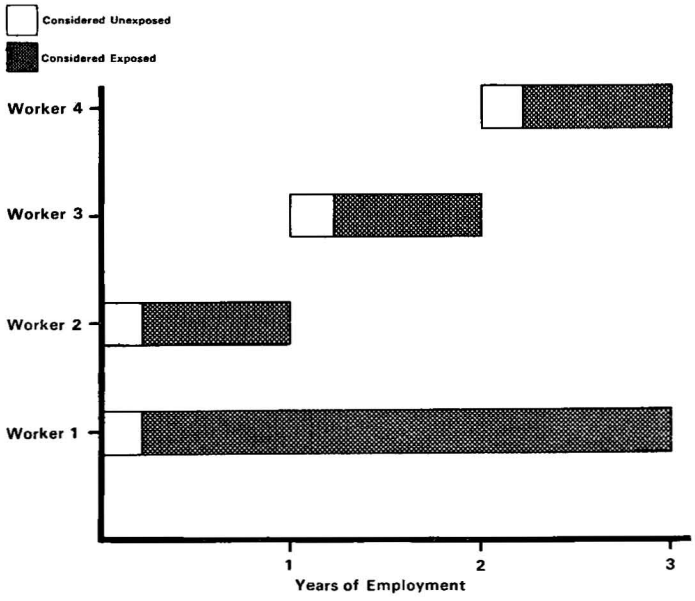

Fig 1. Effects of turnover of male workers on time periods with potential for exposed pregnancies. This figure is based on exposures to male workers. Semen changes would not be observed prior to 11 to 15 weeks after the first exposure (13). Therefore, any conceptions occurring during this time would be considered nonexposed. Although workers 2 through 4 have the same total person-years of employment as worker 1, the total time for potentially exposed conceptions is less.

under study. It is common for female workers to leave employment during pregnancy or after having a live birth. If those with adverse outcomes remain at or return to work more quickly, and those with live births never return to the company under study, the estimate of the risk of exposure will be inflated if only current employees are examined. Past employees should be included in the study population, since the probability of leaving employment is associated to different degrees with several of the pregnancy outcomes frequently under study (fetal loss, live births, and infant deaths). Studying female workers may also result in fewer exposed pregnancies per worker since subsequent pregnancies in terminated female workers may not occur during employment in the industry. Unfortunately, obtaining data on past female employees may prove to be more difficult due to residence and/or name changes. They may also be less willing to cooperate since they are no longer associated with the industry or exposure under study.

Studies of male workers are considerably less complicated since it is unlikely that their employment status is affected by their wives' pregnancy outcomes. Therefore, it is probably not necessary to include terminated employees to prevent bias.

Exposures under study

Environmental exposures can be studied in either of two contexts, as a general environmental exposure or as an occupational exposure. Studies of general environmental exposures, such as air and water pollution or communities around certain types of plants [as in the studies of Edmonds et al (4) and Nordström et al (9)], have advantages associated with more traditional studies of pregnancy outcome. The larger population allows more flexibility in study design, the ability to study rarer events, and reduction of the time period of the study. However, the lower exposures observed in the general environment probably reduce the magnitude or frequency of any adverse effects and tend to offset these advantages. Studies of effects through general environmental exposure to *only* the father or *only* the mother would be more difficult since, by definition, both are exposed. There may be additional difficulty in locating a comparable area without the exposure under study, especially when the exposure is related to the degree of urbanization of the community. The effects of other concomitant exposures are also more difficult to separate.

As mentioned before, occupational populations would generally be smaller in size [as in the studies of Infante et al (11) and Nordstrom et al (20)], with the attendant disadvantage of requiring longer periods of observation. However, study of an exposure through the occupational setting also carries several distinct advantages. More control can be exercised over the combinations of potentially adverse exposures by proper selection of the workforce. This fact, coupled with a higher level of exposure, may increase the likelihood of identifying any adverse pregnancy outcomes. It is possible, however, that different levels of exposure could result in a different spectrum of outcomes — higher levels might result in an increased proportion of early fetal loss, but lower exposure levels might result in an increased proportion of live births with reduced birth weight or congenital anomalies. The limitation of exposure to one spouse in occupational studies results in more information concerning possible routes of effect. However, with some occupational exposures (eg, lead), a "carry-home" exposure can occur when a potentially hazardous substance is brought into the home on the worker's hair or clothes. The spouse may be exposed, and the result is a potential for multiple routes of exposure to the offspring, preconceptionally through either parent and postconceptionally (in utero exposure) through the mother.

Occupational pregnancy outcome studies are usually cohort studies since the method of population definition is by exposure. However, after all pregnancy outcomes for the study population are identified, relatively common outcomes of interest could be examined in a nested case-referent study within the workforce for information on different levels of exposure, job titles of interest, and other difficult-to-gather variables. The small population sizes in occupational studies mean that rare out-

comes usually cannot be examined in any systematic way unless an overwhelming risk exists.

Comparison population selection

The selection of a suitable comparison population can also present difficulties. Some difficult-to-measure health and socioeconomic factors may be related to the workers' type of employment or employability and the outcome under study. Therefore, the comparison population should be as similar as possible to the exposed population in frequency, duration, and type of employment — usually blue-collar. The population(s) should also come from the same geographic area so that differences in environmental exposures, health care availability, etc, are minimized.

Data sources

Both traditional and occupational pregnancy outcome studies can use the same data sources, either those recorded at the time of the event or interview data, but the ease of collection differs. Ease of collection is related to both the accessibility of data and the ability to identify the event under study within the data set.

Recorded data sources

Recorded sources include fetal death certificates, birth certificates and death certificates, hospital or physician records, and insurance records. These data are recorded at the time of the event, and the medical conditions and treatments are usually described by a clinician. Use of these types of data results in a decreased chance for inaccuracies due to recall bias. Unfortunately, there is no quality control in recording these data, and they may be transcribed incorrectly or incompletely (18). Adverse events occurring early in pregnancy may frequently not be documented, and pregnancies identified by these sources are selectively incomplete due to differences in the length of gestation, prevailing medical care patterns, and socioeconomic status and demographic characteristics of the parents. Also, these records usually contain little or no specific information on work history.

Vital records such as fetal death certificates, birth certificates, and infant death certificates contain medical and demographic data. They have two major advantages in that this source constitutes a relatively centralized data system and that there are legal requirements for complete population coverage (6). These records have been found to be complete with respect to basic demographic data but not for such items as congenital malformations and medical conditions of the mother or infant (14). Changes in the reporting forms over time can result in data that are not strictly comparable. Requirements for reporting fetal loss varies by geographic area, usually by state in the United States. Typically, fetal losses occurring prior to 20 or 28 weeks of gestation are not reported. Therefore, early fetal loss usually cannot be studied through this source.

Medical records may contain data that are not available from other recorded sources. Physicians' records may contain data on some prenatal drug prescriptions, maternal weight gain, and complications of early pregnancy, and hospital records may contain data on events occurring during labor and delivery. Unfortunately, the information recorded and methods of recordkeeping vary among physicians and hospitals, and the comparability of these data is therefore reduced. Also, medical records for specific individuals are likely to be scattered in many hospitals or physicians' offices and thus are more difficult to identify and obtain. Interviews would probably be necessary to direct the searches, and medical record release forms are needed to obtain access to these records. Early fetal losses may or may not be recorded, the recording depending upon medical care availability, cost, and attitudes concerning medical care of the worker and spouse. Also, as the events of interest may have occurred over many years, the medical records may have been lost, destroyed, or discarded. This situation is especially true of physicians' records, for which relocation or death of the physician compounds the problems already cited.

In many studies comparing possible data sources, hospital records have been used as the standard against which the

others are compared. Consequently, the overall accuracy and completeness of these records are difficult to assess. However, one study has shown hospital records to be less complete than vital statistics records with respect to demographic variables, but more complete for medical conditions of the mother or infant and for congenital malformations (14).

Insurance records may be a useful source from which to identify pregnancies, especially for a working population covered by the same carrier. Malformations of the offspring identified later in life may be found through this source. The data available in these records would usually be limited to those events requiring hospitalization and would usually contain little specific medical data. Since there are limited or no medical data included in these records, another data source is necessary. Unfortunately, the retention time may be less for insurance records than for other data sources.

Interview data

Interview data may be the single most useful source. Interviews provide information that cannot be obtained elsewhere, such as information on personal habits and lifetime work histories. Data on all reproductive events for a couple can be obtained from one interview. The success of interview studies depends on the cooperation of the subjects. The level of cooperation (ie, the response rate) reflects the subject's feelings toward the study, and the response time and potential inconvenience associated with participation. Recall may be affected by time, the number of events to recall, the emotional nature of the outcome of the event, knowledge of a prior adverse reproductive outcome or exposure, or the subject's education (15, 16).

Comparison of data sources

Traditional pregnancy outcome studies frequently identify their populations through medical or vital statistics records. This method of identification makes the execution of the study fairly straightforward since the study population is identified through the source of the study data. Some studies have carried the data-gathering process even further and have interviewed the subjects for information not available from the records.

Specific occupational populations usually cannot be identified in the way described. First the study populations are usually identified from company or union records. The subjects must then be interviewed for reproductive events that fit the criteria for inclusion in the study. Finally, recorded data such as vital statistics and medical records used to validate interview responses may be obtained, the interview data being used to guide the search.

Occupational pregnancy outcome studies also have another problem not found in traditional pregnancy outcome studies. Though workers are the most easily accessible for an interview study, male workers would be proxy reporters of their wives' reproductive and work histories, and the wives would be proxy reporters for their husbands' total occupational history. Such a situation increases the chances for inaccurate data. Take-home or mailed questionnaires or telephone interviews of the spouses could be used to avoid this problem.

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