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Design options and sources of bias in time-to-pregnancy studies

by Jørn Olsen, MD[1]

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Studies of fecundity are few, and there is a need to know how fecundity develops over time and to identify its determinants. Since fecundity is best measured by studying time to pregnancy, valid and well-recognized instruments are needed for data collection. A standardized questionnaire on fecundity not only has to obtain information on waiting time, but also information on the importance of evaluation results. The use of contraceptive methods, the understanding of family planning, and behavioral changes driven by past reproductive experience are issues of importance for designing and interpreting results, as are other sources of bias also.

Key terms epidemiology, fecundity.

Design options

While biomarkers (eg, measures of hormonal levels or sperm quality) can be used independently of pregnancy planning, they are only proxy measures of fecundity. The only direct measure of couple fecundity is the (waiting) time to pregnancy, or the number of menstrual cycles to pregnancy (CTP), for couples who have intercourse regularly without using contraceptive methods. Since such data are not registered routinely, studies must obtain data by questioning samples (asking questions of the population, usually women). Basically the following 3 approaches have been used: (i) reconstruction of reproductive history (including time to pregnancy) for samples of women from the entire population or women selected according to specific exposures, (ii) questioning (early, late or shortly after birth) of pregnant women about time to pregnancy or CTP, or (iii) recording of time to pregnancy and CTP prospectively for couples who start their time to pregnancy at the start of follow-up. The first method must rely on recall, often over long periods of time, the second method requires access to all pregnant women from a given study base, and the third is only available for the small subset of the population that plans pregnancy within the study period. Several hundreds of time-to-pregnancy or CTP values are required for reasonable statistical power, and the source population generally needs to be much larger (1, 2).

Time to pregnancy (or CTP) is considered to estimate fecundity, which is the probability of producing a conception, a clinical recognized pregnancy, or a live birth, depending upon study conditions. It is a composite measure that includes libido, ovulation, sperm quality, conception, and survival of the fertilized egg for a shorter or longer period depending upon study conditions. If data are available on sexual activity, cycle length, or even sperm quality, some of the elements in the definition may be isolated and controlled for. The timing of data collection in a pregnancy sample (model 2) determines which probability the study addresses (ability to produce a recognizable pregnancy or the ability to produce a liveborn).

Since the core information is related to a set of key questions on waiting time, great care must be taken to develop standardized questions (3). More work needs to be done in this field since no experience is available from large studies and rehabilitation studies. It is time to agree upon a "best version" to ensure comparability between studies. We know that the phrasing of the key questions plays an important role (4). We also know that other aspects play a role in the interpretation of data and should therefore be included in a questionnaire.

Sources of bias

Some of the more statistical sources of bias have been discussed in some detail (5), leaving perhaps more important issues practically undebated. The concept of pregnancy planning, the planning culture, and the planning methods available play a major role. A debate on planning bias (ie, oversampling of subfecundity by

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restricting the analyses to couples who planned the pregnancy to obtain valid data) is in many ways misleading. It is probably true that fecund couples are more likely to become pregnant by accident than subfecund couples. Less fecund couples thus reach the planning stage, but the methodological problems are much more related to planning opportunities and the use of planning methods, and unbiased results are not obtained by including unplanned pregnancies in the analysis. We need to have data on the use of contraceptive methods for the setting in which the conception took place. The conception could have been planned or unplanned (and there may have been several levels of planning), and the conception could have taken place during a period in which safe or less safe contraceptive methods were used. Or the conception could have taken place during a period of unknown susceptibility (eg, while breast feeding).

It is also important to know something about reproduction in the past for other reasons. We are concerned about behavior modifications during the period when couples try to conceive and now take care in recording behavioral exposures at the starting time of pregnancy planning (which must be defined in the questionnaire). We should also be aware of behavioral modification driven by past reproductive experience (6). We know that subfecundity has a tendency to repeat itself (7), and we also expect that many reproductive failures are correlated. A past reproductive failure is perhaps the strongest incentive for reducing risk behavior when a new pregnancy is planned, and this "confounding by past experience" is grossly neglected even by experienced researchers in the field. Unfortunately, there are no simple solutions to these problems. The best solution could in many cases be to restrict sampling to couples who plan their first pregnancy, if possible.

Subfecundity is a couple concept, but the consequences of that fact are not well understood. If studies focus upon exposures of relevance for either men or women, we need data on the partner or spouse before we can explore, and, if needed, adjust for factors both associated with the exposure under study and causally linked to the fecundity of the spouse. In light of our limited understanding of sex-specific causes of subfecundity, our scope for confounder control is likewise limited (which is not unusual in epidemiology). We do not even expect that access to biomarkers (eg, sperm measures) entirely eliminates confounding related to, in this case, the male partner. All known sperm parameters are only weakly associated with fecundity, and we need additional information on other determinants for the partner, but we still do not know which ones. This information is perhaps the most important in studies on life-style factors, since these factors are often closely correlated among the partners.

In studies based upon the sampling from pregnant women, all unsuccessful pregnancy attempts are by definition eliminated. This elimination is of course a major limiting factor if studying exposures that lead to an all-or-none effect (infections may be of this type). Fortunately, most exposures change the time-to-pregnancy distribution rather than merely causing sterility. It is of much greater concern that studies have the underlying assumption that there is persistency in trying to become pregnant and that this persistency is unrelated to the exposures under study (ie, the desire for having the child). This assumption certainly cannot be made for "exposures" like age and parity, but it may not be true for social factors or other conditions either.

The analysis of time-to-pregnancy or CTP data has been discussed at some length, and several options exist. The most promising model for analyzing prospective data is to treat each cycle as a separate experiment for a given couple (8), which will allow analyses of cycle-specific exposures and therefore to some extent solve the problems of changing exposures during the period when a couple tries to conceive. This method makes use of all cycles and will capture exposures that are more detectable at the beginning of the waiting time.

It is a problem that the time period of observation without treatment seems to be shorter now than it used to be (9). Treatment may well start before 12 months of waiting time to pregnancy, especially if the couple has had a previous experience with subfecundity. The usual routine of censuring observations after 12 months of waiting may need to be revised and censuring at 9 months should perhaps be considered.

Studies of couple fecundity have made an important contribution to reproductive epidemiology, and we know much more about the methodological pitfalls as a result. Now we have to improve the quality of the data we collect and make sure we obtain data that are as comparable as possible. For that purpose we need a standardized questionnaire which will include data on pregnancy planning, use of contraceptive methods and conditions that influence couple fecundity.

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