

Abstracts

Preconference papers

Fallacies in time to pregnancy studies

PC1 THE TIME TO PREGNANCY DESIGN OPTION

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Time to pregnancy (TTP) as a research measure was probably first used by demographers to describe the biological capacity (fecundity) to reproduce in a population. They studied time from marriage to when the couple had their first child—a measure that is only useful in populations where marriage and sexual activity is closely linked. In populations that practice strict birth control and plan their pregnancies, it is, however, possible to record the time from “unprotected” sex to the time of pregnancy (or birth). Since these time periods are few in countries that have low fertility (the same countries that practice birth control), the amount of information available to be harvested in an epidemiological design is limited.

As it is often the case, the design of choice is a follow up design with prospectively collected data on occupational exposures before and during the time of trying. Such a study is expensive because a large group of couples have to be approached to get a reasonable sample size, unless one would settle for a cohort of pregnancy planners seeking infertility treatment. Such a group is of course not representative of the population of pregnancy planners at large, and the infertility treatment may well influence the exposures they control themselves.

The most frequently used design measure is TTP among pregnant women. This design can be done at low costs because pregnant women are easy to identify in most countries; however, the time to pregnancy measure includes only those who did get pregnant and the design is very sensitive to an equal compliance to the pregnancy attempt in the groups to be compared. One should furthermore recognise that the exposure information at the time of pregnancy planning will not be comparable in time. Those who had the longest waiting time had exposure time slots earlier than those who became pregnant shortly after trying. Survey data have also been used because women are often able to recall TTP back in time, at least over a time period of up to five years, and perhaps longer if the reporting only has to given in broad categories. It may be more difficult to remember occupational exposures with the necessary precision back in time and most of the survey data have focused upon determinants such as age, smoking, place of residence, etc.

Only the follow up design will provide a direct estimate of the fecundability, the probability to conceive within a given cycle. That fecundability is, in most populations, around 15–30%. The aim of our epidemiological research is to identify exposures that decrease (or increase) the fecundability, but the route to making any causal inference is saddled with several sources of biases.

PC2 BIAS IN TIME TO PREGNANCY STUDIES

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Introduction: Biological fertility can be measured using time to pregnancy (TTP). Retrospective designs, although lacking detailed timed information about behaviour and exposure, are useful as they have a well defined target population, often have good response rates, and are simpler and less expensive to conduct than prospective studies. Validity of recall has been shown to be acceptable, but several potential biases have been identified. This presentation describes them, and explores their importance and the ways in which they can be addressed.

Methods: Sensitivity analyses are presented using data from four European retrospective TTP studies: the European Multicentre Study on Infertility and Subfecundity, the ONS Omnibus Survey, the Danish Twin

Study, and the Odense Prenatal Study. Statistical analysis is by discrete-time survival analysis, with censoring at 14 months.

Results: Response bias can be minimised by embedding the fertility questions in a general purpose survey. Planning bias can be checked by carrying out a parallel analysis to the main survival-analysis regression using the same covariates, a logistic regression with the proportion of contraceptive failures as the outcome variable, and by sensitivity analyses. Medical intervention bias can be avoided by censoring and by inclusion of unsuccessful pregnancy attempts. Truncation bias can be a serious problem if unrecognised, especially if studying time trends or an exposure that is trended. It is avoidable with appropriate study design (information on continuing attempts, or subjects who have completed their reproductive history) and/or analysis (exclusion, or modelling). Behaviour change bias can be minimised by assessing covariates at the beginning of unprotected intercourse, rather than at conception (or during pregnancy).

Conclusion: The major methodological problems can be avoided or minimised by appropriate study design, conduct, and analysis. More complete inference is possible if the study design covers the whole population, not only those who achieve a pregnancy. While the identified biases tend to have small impacts, the effects are not systematic across studies, and sensitivity analyses are recommended routinely.

PC3 PARADOXICAL FINDINGS IN TIME TO PREGNANCY STUDIES: NATURE AND MECHANISMS

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Older age is the strongest risk factor for reduced fertility in women. However, fertility has appeared to increase with age in some retrospective studies on time to pregnancy (TTP). The proposed reasons for the spurious findings are, for example, exclusion of sterile women, and the age related differences in infertility treatment effectiveness and in persistence of trying. However, while fecundability decreases with age, sterility does not necessarily increase. Moreover, the apparent increase in fertility was seen already from the age 22 onwards. It does not seem plausible that the persistence of trying would start decreasing or effectiveness of treatments would start decreasing at that age. Whatever the biases may be (and they still are not clear), they have apparently overwhelmed the true effect of age. Could similar biases also mask other true associations?

A few occupational examples can be claimed as paradoxical or contrasting: male exposure to lead has been found to reduce or improve fertility or show no effect in studies using blood lead for exposure assessment. The exclusion of childless couples, truncation bias, and the differences in susceptibility to the toxic substances may have influenced these findings. Also, infertility may lead to apparent association between occupational exposures and fertility through the “infertile worker” effect. In particular, farm couples may redistribute works tasks when family situations change.

Indirect selection may confuse the association of fertility with potential risk factors. For example, previous caesarean section was associated with reduced fecundability in one study. However, caesarean section in the first pregnancy was more likely among women with prolonged TTP than among those who conceived immediately. Thus, the association of caesarean section with subsequent subfertility may simply be caused by selection.

The use of different study designs or study decisions—for example, regarding inclusion of unplanned pregnancies—may also cause contrasting findings. For example, studies on TTP (this design typically excludes unplanned pregnancies) have shown increasing fertility over time, but a decrease in fertility was observed in a study using primary infertility approach (this design includes unplanned pregnancies as fertile). In summary, the mechanisms behind the paradoxical or biased findings in TTP studies may be due to heterogeneity in intrinsic reproductive capability; heterogeneity in reproductive and social behaviour; varieties of selection; and variations in study design or study decisions, for example, regarding the inclusion of unplanned pregnancies or childless couples.

PC4 REVIEW OF OCCUPATIONAL TIME TO PREGNANCY STUDIES: METHODOLOGICAL ISSUES

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Introduction: In occupational studies on reproductive disorders, time to pregnancy (TTP) is frequently used as a measure of fertility and fertility problems. Despite many positive reports about the validity of TTP studies, the interpretation of the results seems to be hampered by several methodological issues.

Methods: A literature study was done on occupational TTP studies performed since 1990. Published results and remarks on methodological issues were supplemented with expertise on TTP studies from the research group Reproductive Epidemiology of the Radboud University Nijmegen Medical Centre in the Netherlands.

Results: Occupational TTP studies have mainly been focussed on male and/or female exposure to lead, organic solvents, pesticides, persistent organochlorines (PCBs, DDT, dioxins), and shift work. For all of these exposures, associations were found with prolonged time to pregnancy in a substantial number of studies. However, some studies showed only weak associations, whereas no effects on TTP were found in others. In only a few studies, prolonged TTP was reported for exposure to

formaldehyde, styrene, and welding fumes, as well as for hairdressers. Inconsistencies in results between different studies may be due to the people exposed (men, women, or both), the specific substances they were exposed to, duration of exposure, whether or not the use of personal protective equipment was taken into account, the presence or absence of adequate exposure assessment in the relevant time window, retrospective or prospective collection of TTP data, the pregnancy studied (for example, first or last), correction for coitus frequency and other strong confounders, and the design and analysis of the study. The latter especially may have large consequences for the amount of bias (for example, time trend bias, planning bias, pregnancy recognition bias, behaviour modification bias, and the infertile worker effect) that was introduced and/or adjusted for in a specific study.

Conclusions: The results of a number of occupational TTP studies will be discussed in the light of the above mentioned methodological issues.