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EXPERT OPINION

Epidemiological Studies on Fetal Loss – Better Data and Research Methods are Needed

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Abstract: In perinatal epidemiology, fetal deaths occur over the first timeline, from conception to birth or fetal death. Majority of other epidemiological research on human diseases focus on the second timeline, from birth to death. The transition from the first to the second timeline is not a fixed duration of time and it depends on when birth occurs. We discussed the complications when switching from the first to the second timeline in epidemiological studies of early life exposures, pregnancy events, and future health outcomes. Population-based studies often lack accurate data on the date of conception for most pregnancies and the complete count of fetal death, leading to chances for selection and misclassification biases. To address these problems, better research data and methodological advancement in study designs and biases evaluations are needed.

Keywords: fetal loss, miscarriage, bias, birth cohort, epidemiology

Introduction

About (or at least) 30% of all conception end with a spontaneous abortion after the implantation and before gestational week (GW) 22.[1–3] A much smaller part might be lost after that time, often labelled as stillbirth.[4] These fetal deaths occur over our first timeline of interest – from conception to birth or fetal death. Most research in epidemiology on morbidity and mortality addresses the second timeline, from birth to death, and we often leave the third timeline – from death and beyond - to the faculty of theology. Research that addresses preconception and pregnancy exposures on short- and long-term health consequences in the offspring face with challenges of how to define the proper observation time in the first to the second timelines. The transition from the two timelines is not a fixed duration and it depends on when birth occurs. Complications with these changes of time scales have been well known in literature concerning adverse pregnancy and birth outcomes[3,5–7] and more recently also raised for research of long-term disease risk associated with fetal exposures.[8–10] We sought to provide thoughts on these important issues and call for theoretical and practical research that aims to tackle these unsolved problems.

Merging the Two Study Timelines

One could argue a solution to address the ambiguity of observation time is to merge the two timelines and work with the conceptional age. The exposed or unexposed person time will be assigned accordingly starting at the date of conception guided by the principles of cohort analyses including considerations of induction and

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latency periods.[11] However, the main challenge for this approach is we often do not know when the conception occurred, with the exception for some couples who conceived with fertility treatments. Thus, for most pregnancies, the date of conception has to be extrapolated using ultrasound (US) measures of early growth or calculated from the reported date of last menstrual period (LMP). These estimates are vulnerable to misclassification bias. A fetus at risk for mortality might grow at a slower speed than a healthy fetus[12] thus the US-based estimates could underestimate the gestational age (GA). For exposure factors with fetal growth acceleration or suppression effect, studying the association between these factors on preterm delivery classified based on US-based GA estimates is prone to differential outcome misclassification bias.[13] For that reasons, we should in some cases consider going back to LMP data. LMP estimates are imprecise but they may be less susceptible to systematic bias for exposures that can influence fetal growth.

Abolishing the First Timeline

Another argument that could be made was that we should only be concerned about those born alive. After all, we drop the third timeline and why not also drop the first timeline as well? Epidemiology is a discipline to study people who are alive, or at least have been alive, one could argue and it would make all research simpler. Whether this approach is valid depends on when the exposure of interest occurs. Imagine a randomized study of a new treatment for infants born prematurely. Dropping the first timeline with observation starts at the time of treatment (post-birth) is an appropriate design while generalizability of findings might be limited by the inclusion criteria. However, if the treatment group experienced a higher rate of infant mortality during the follow-up period compared with the non-treatment group, the treatment effect on health outcomes ascertained at the end of follow up would subject to selection bias by excluding the deceased.[14] Similar concepts apply when studying pregnancy exposures on adverse health outcomes in the mothers and the child. When an exposure or treatment occurs at the beginning of pregnancy, even if randomized, potential bias due to exposure-related pregnancy loss will still need to be considered when only the survived and selective subsets are included in the final exposure-outcome analyses.[9,10,15,16] By excluding the first timeline altogether would not be a solution for these studies with an interest to study an exposure effect occurs during the first timeline.

There have been extensive discussions of bias due to forces of baseline and follow-up selections in cohort studies.[11,17,18] A well-known example is the "healthy worker effect" eg, those who were physically fit might be selected (by themselves or others) to conduct labor-intensive jobs, and they might for that reason displayed lower mortality rates during the course of employment. The correlation between the jobs and mortality however is not due to occupation-related exposure but was explained by other underlying health factors of the workers.[19] Moreover, for workers deceased (moving from timeline 2 to timeline 3) during follow-up, the long-term risk for specific diseases such as cancers are no longer observable.[20] These concepts for selection based on health status at baseline and follow-up should be similar and applicable to early life exposures and mortality scenarios.

It is sometimes less recognized that the early life selection bias could also impact genetic studies.[21] If a genetic study enrolled pregnant woman after the time of conception, the genetic exposure may already have caused early fetal death leading to a selected group enrolled for later follow-up which can bias the associations between the genes and the pregnancy or child health events.[22]

Pregnancy Planners

In lack of accurate data on the time to conception, we therefore need to establish cohorts of pregnancy planners where early abortions can be measured by repeated pregnancy tests or estimated based on a prolonged time to pregnancy (TTP) or subfecundity.[1] Unfortunately, establishing these cohorts is often a complicated and expensive task and for that reasons we do not have many large cohorts of pregnancy planners. Furthermore, these cohorts are often quite selected, in this case, on fecundity. The most fecund will seldom become pregnancy planners since many become pregnant without planning it. Pregnancy planning is not necessarily a lifelong activity. Couples might give up after having tried for a while to become pregnant, and older couples often give up sooner than younger, especially if they already have a child.[23] A pregnancy planning cohort is likely to oversample the less fecund or older couples without children and this may bias prevalence measures in the cohort such as fetal mortality rates, probably by inflating these rates. If these forces of selection are unrelated to the exposures of interests, comparing the exposed and unexposed groups might still provide an unbiased comparison and ensure the study internal validity. However, the generalizability

of findings to all pregnancies including those unplanned pregnancies and the more fecund couples might be unknown.

Other Methodological Issues in Studies of Pregnancy Loss

Causes of death is important to consider when concerning exposure-related pregnancy loss. For early fetal death, not all mortality will be documented and for those recorded their specific cause was mostly not determined. Cause of death might be registered for some pregnancies ended in late miscarriage or still birth. Studies of birth defects could benefit from including these deceased cases in research. Sensitivity analyses comparing results using cases among live birth children only can be carried out to estimate whether an exposure-related pregnancy loss selection bias has occurred.[24]

There is a time lag from death to expulsion of the fetus, which could make reverse causation a challenging problem.[25] For example, coffee intake is often lower during pregnancy, perhaps induced by oestrogen-introduced nausea. Fetal death may eliminate this nausea and in turn makes maternal coffee drinking habits return. If so, it will look as if coffee caused the spontaneous abortion when in fact fetal death induced a return to old coffee drinking habits before the fetus is aborted. Time-varying exposure data and time-lag exposure analyses would be needed to avoid misspecification of the causal direction.

Early fetal death may go unrecognized and the fetal tissue may be absorbed. We know that this is quite common in twin confinements and it has been discussed and studied whether this poses a risk to the surviving fetus even early in pregnancy.[26–28] In any case, the "vanishing fetus" produces missing data on fetal death and often we are not aware of this type of fetal death.[29] As discussed above, if these missing data of outcome are related to the exposure groups then bias can occur.

Induced abortions are another type of selection forces that often not well considered. The first study timeline is sometimes terminated for social, medical and personal reasons by inducing an abortion. Taking induced abortions in consideration is important if reasons for inducing the abortion is related to the exposure under study. Unlike early miscarriage that are often undocumented, legal-induced abortions are more likely to be registered together with the reasons for the procedures.[30] Time-to-event analyses should treat these events as censored observations. Adjustment for indications of induced abortions might be needed if these indications are associated with the exposure and outcome of interest.[17,18] Inverse-probably weight can be used when the exposure under-studied directly affects the decision for abortion.[31]

Biases can also arise during the analytical phase of research. It is known that omitting confounding variables in observational study would bias the target causal effect estimate.[11] Potential confounders should be carefully thought-out during the design phase of research. Risk of miscarriage is the highest in early pregnancy and will decline with increasing gestational age.[32,33] If couples were not enrolled prior to conception, such as in pregnancy planner studies, adjustment on the time of study entry during pregnancy is recommended when the endpoint is pregnancy loss.[34] However, we should not blindly adjust for any strong predictors of the outcome in analyses. "Birth weight paradox" is a well-known example of "collider bias" due to an inappropriate adjustment of an intermediate variable (low birth weight) in the analyses of maternal smoking and infant mortality.[35,36] Some predictors for fetal death could simultaneously lie within a confounding path and an intermediate causal pathway.[37] Advanced statistical methods such as marginal structure model or g-computation will be needed in such scenarios to address confounding while avoiding for collider bias.[31]

Summary

In this article, we raised some methodological issues in studies of fetal loss stemming from challenges in defining the proper observation time during the early life time periods. When studying putative causes of fetal loss in the first timeline, we have to accept that we usually do not know exactly when this timeline starts or ends. This issue complicates the accuracy of gestational age measure and render ambiguity of the timing of exposure and outcome classifications. Even when the fetal loss outcome is recorded, data on cause of death are often not available precluding the evaluation of exposure effect on cause-specific mortality. Principles of tracking lost to follow-up due to deaths in epidemiological research should also be applied for studies concerning early life exposures and events. Potential bias due to excluding all spontaneous and induced abortions in the observations needs to be considered.

Our knowledge of the determinants of fetal loss are still lacking and more studies are needed. We need to continue the search for preventable risk factors for miscarriage and stillbirth. Studies should aim to recruit cohort members early in pregnancy as being done in some pre-existing

large population-based cohorts.[38] Very early pregnancy loss, however, might be inevitably missed in pregnancy cohorts enrolled women after the time of conception at the hospitals or clinics. Gestational age of entry into these cohorts needs to be carefully considered in analyses for fetal loss. To get close to the time of conception, pregnancy planners can be used but whether the results can be generalizable to all pregnancies need to be considered.[39]

Moving forward requires better data and research method for studies on fetal loss. Utilizing novel technologies that aid better monitoring of fetal life events could advance the field.[40,41] An improvement of the accuracy of gestational age measure would reduce biases related to misclassifications of the observation time. A more complete registration of miscarriage events in population would reduce missing data and also allow quantitative assessments of potential bias stemming from exposure-related pregnancy loss.[24]

Key Message

Selection and misclassification biases may arise from a transition of research timelines from the first starting from conception to birth (or fetal death) to the second from birth to death. An improvement in the accuracy of the gestational age measures and the completeness of fetal death registrations could help to address some of these issues. Advancing study designs and analytical methods to appropriately track and address lost to follow-up due to fetal death will be needed.

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