Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

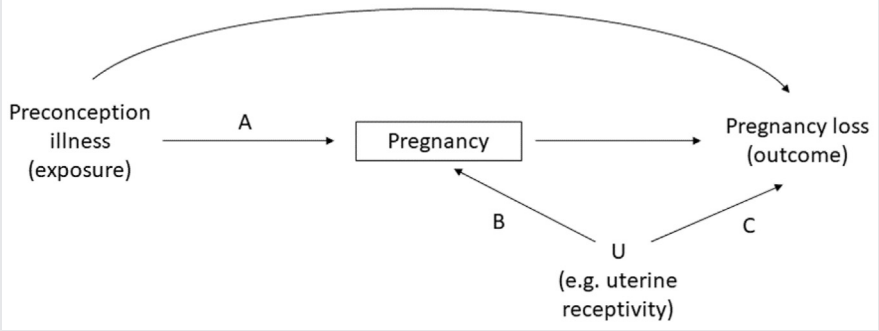
Preconception exposures and postconception outcomes: selection bias in action

As the COVID-19 pandemic continues to wreak havoc across the globe, many unanswered questions remain about the virus's specific health effects. Chief among these are its unknown impacts on infertility, pregnancy, birth, and infant health. Because of this, the recent work by Kasman et al. (1) published in *Fertility and Sterility* on severe systemic infections before conception and pregnancy outcomes is timely and valuable research. Using a large insurance claims database, the authors examined associations between preconception indicators of parental systemic infection and outcomes such as pregnancy loss and preterm birth. Although the data were collected before the COVID-19 pandemic, the research has important implications for the reproductive effects of a virus with severe infectious consequences. The authors observed that several indicators of both maternal and paternal severe infection before conception were related to pregnancy loss and preterm birth. However, as the authors mention, these results are only generalizable to couples who were able to successfully conceive after systemic infection. Given what we know about SARS-CoV-2 and similar viruses, it seems likely that there may also be potential effects on gametes and the ability to conceive (2). If exposure to a virus influences a couple's ability to conceive in the near future, then any cohort of pregnant women is a select group that may be different in many ways from those who were not able to conceive, and examining the effects of preconception exposures on pregnancy outcomes in this group can lead to selection bias. The analysis by Kasman et al. (1) highlights some important methodological concerns that are relatively common in work examining the effects of preconception exposures on postconception outcomes.

To understand these concerns, it is helpful to understand that inherently there are several selection steps that occur during the process of reproduction. Among those trying to conceive, only a portion will achieve pregnancy, and even fewer will go on to have a live birth. While the selection steps of conception and birth are the most obvious, this process can be thought of in more detail: any step where attrition occurs (e.g., fertilization, implantation, each week of gestation) is a step at which the population of ongoing pregnancies is subject to selection. Doing research on pregnancy outcomes requires the investigator to carefully consider these selection processes. This is most crucial when the research concerns an exposure and outcome that are separated by one or more selection steps, such as when examining the effect of a preconception exposure like systemic illness and postconception outcome like pregnancy loss. In such scenarios, it is necessary to consider the potential for selection bias and to take steps to address this bias.

The source of potential selection bias is due to the fact that a preconception exposure can have an effect not only on pregnancy outcomes but also importantly on the chance of becoming pregnant in the first place (i.e., selection into the pregnancy population). To illustrate, we can easily imagine a scenario in which preconception maternal illness influences a woman's chance of conceiving (shown by arrow A in Fig. 1). We can also think of additional factors that may be related to both becoming pregnant and having a pregnancy loss (represented by arrows B and C in Fig. 1), such as age, lifestyle, and uterine receptivity. If we only evaluate women who successfully conceived and we are not able to account for all of the factors that may be associated with becoming pregnant and pregnancy loss (which is likely given that we are rarely able to account for uterine receptivity and other genetic factors), then selection bias is in action. Intuitively, if we assume that illness reduces the chance of conception, then women who experience a preconception illness but still manage to

FIGURE 1



Causal diagram showing the relationships among preconception illness, pregnancy, and pregnancy loss. Arrows represent causal relationships (an arrow pointing from one variable shows that this variable causes the one it points to). Here we assume that preconception illness influences a woman's chance of conceiving (arrow A) and that there are also other factors, such as age, lifestyle, and uterine receptivity that may be related to both becoming pregnant (arrow B) and having a pregnancy loss (arrow C). The box around pregnancy indicates that selection into the population is conditional on pregnancy. If we only evaluate a perception exposure among women who successfully conceived and are not able to account for all factors identified by U (e.g. uterine receptivity), then selection bias is in action.

Flannagan. Reflections. Fertil Steril 2020.

conceive are likely to also have other characteristics that increase their chance of conception (e.g., younger age, greater uterine receptivity, healthier lifestyle, etc.), given that they have become pregnant despite the detrimental influence of preconception illness. We could imagine that some of these characteristics also decrease their risk of pregnancy loss. Therefore, in a group of women who have all conceived, those who had a preconception illness are more likely to have, for example, high uterine receptivity and are thus less likely to experience a loss. This selection on pregnancy may thus induce an association between preconception illness and lower risk of pregnancy loss through a mechanism that has nothing to do with the actual causal effect of illness on loss. Importantly, although in this example we have assumed knowledge of the direction of the various effects involved, this will typically not be the case, and thus the extent of the selection bias typically remains unmeasured and unexplored.

To address this selection bias, the first steps are to carefully determine the causal question of interest and to determine whether such a question can be answered with the available data. Identifying the question requires consideration of how the research is intended to be used (e.g., clinical decision-making, policy development, etc.) and what pieces of information are required by relevant stakeholders (e.g., what would a physician need to know to counsel a patient who recently contracted COVID-19 and wanted to conceive?). Several types of causal questions in the context of reproduction have been proposed (3), which may be useful in different scenarios. For example, for counseling patients attending an infertility clinic, often the question being asked is, What is the influence of a preconception exposure on the chances of having a live birth? This question is perhaps most fully addressed by considering the full population of couples trying to conceive and answering the question in a real-world setting where some women will not conceive or maintain a pregnancy to live birth. In this way we can estimate the total effect of a preconception exposure through all of the selection processes at play on the outcome of live birth. In some situations, it may be more important to counsel patients about the role of a preconception exposure on pregnancy loss, and in that case the question of interest may be, What is the association between an exposure while trying to conceive and pregnancy loss among women who successfully achieved pregnancy, while removing any potential effect of the preconception exposure on the ability to conceive? Where possible, using data sets that include women enrolled before conception can be a powerful tool for doing this type of research, because they include information on a population of women before selection by pregnancy occurs. This allows us to use techniques such as inverse probability weighting to account for the factors associated with selection and remove the influence of the exposure's effect on conception. However, in many cases, data are not available on the full population of couples planning a pregnancy because of the difficulty of conducting such a study. When this is the case, it is impossible to know the extent or direction of selection bias (4), and thus it may be better to identify other causal questions that can be answered by the available data, such as the effect of exposures during pregnancy on pregnancy loss. In that case the exposure would not be able to affect selection into a pregnancy population.

Preconception exposures are an influential class of pregnancy health determinants, and exposures during this critical window also influence long-term health. The work by Kasman et al. (1) addresses an important gap in our knowledge of systemic infection and pregnancy outcomes, especially in light of the current pandemic. Given the likelihood for infection and other preconception exposures to influence infertility, it is critical to consider the selection bias at work when evaluating preconception exposures and postconception outcomes. Carefully defining the causal questions of interest, and addressing the role of selection bias, will ensure that we are validly estimating unbiased associations to directly answer the most relevant public health concerns.: Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

Kerry S.J. Flannagan, Ph.D.
Sunni L. Mumford, Ph.D.
Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

https://doi.org/10.1016/j.fertnstert.2020.10.057

REFERENCES

1. Kasman AM, Bhambhvani HP, Li S, Zhang CA, Stevenson DK, Shaw GM, et al. Reproductive sequelae of parental severe illness before the pandemic: implications for the COVID-19 pandemic. Fertil Steril 2020;114:1240–7.
2. Segars J, Katler Q, McQueen DB, Kotlyar A, Glenn T, Knight Z, et al. Prior and novel coronaviruses, coronavirus disease 2019 (COVID-19), and human reproduction: what is known? Fertil Steril 2020;113:1140–9.
3. Chiu YH, Stensrud MJ, Dahabreh IJ, Rinaudo P, Diamond MP, Hsu J, et al. The effect of prenatal treatments on offspring events in the presence of competing events: an application to a randomized trial of fertility therapies. Epidemiology 2020;31:636–43.
4. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. Epidemiology 2003;14:300–6.