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Finally, I consider that such an adjustment to EPL risk calculation is not limited to the calculation of the risk for pregnant women with COVID-19. In addition, it should be applied when calculating the EPL to evaluate the impact of COVID-19 vaccination,[4] where the period between pregnancy and vaccination is unintentionally excluded. ■

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Reply: Selection bias in estimates of early pregnancy loss

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We appreciate the comments from Dr Sun regarding the challenges of calculating the risk of early pregnancy loss (EPL) in the Pregnancy Coronavirus Outcomes Registry (PRIORITY) study. PRIORITY participants were eligible to enroll at any gestational age with known or suspected COVID-19. We presented the final pregnancy outcomes for 109 PRIORITY participants who enrolled before 14 weeks' gestation. In the 94 participants with COVID-19, 6 had EPL (6.4%; 95% confidence interval [CI], 2.4−13.4).

We agree with Dr Sun that the risk of EPL is the greatest in the earliest weeks of gestation. Therefore, the best estimate of EPL would begin longitudinal follow-up at the time of conception. In a community-based sample, such as PRIORITY, this was not possible; the mean gestational age at enrollment was approximately 9 weeks. Therefore, our estimate for EPL may have been affected because only 34 PRIORITY participants (31%) enrolled at <8 weeks' gestation when the risk of EPL is the greatest.

We considered several approaches to address this form of selection bias, also known as survival bias, left truncation, or delayed entry. We considered the use of logistic or Poisson regression models. However, the simplest of these models rely on the assumption that the risk of EPL is time invariant, which is inappropriate. Another approach is to use Kaplan-Meier estimation, accounting for the left truncation as this allows for a time-varying EPL rate. However, with only 6 events and a high degree of truncation, the curve was not precisely estimated. Therefore, we chose to report the actual number of events for the enrolled population with a 95% CI as a descriptive statistic rather than incur errors using more sophisticated analytical methods. In addition, we conducted a separate analysis of the 34 participants enrolled at <8 weeks' gestation where selection bias was diminished and found a similar proportion had EPL (5.9%).

Dr Sun provided a point estimate for EPL based on life-table analysis from a systematic review of 4 studies dating back to 1970.[1] The estimate was based on multiple clinical and analytical assumptions that were not likely to hold in our population. In addition, the estimate he provided of 12% was within the 95% CI of our point estimate that used the actual number of EPL events in PRIORITY. We agree with Dr Sun that selection bias is a critical issue that warrants attention; we believe that our approach of describing the proportion of pregnancies that end in EPL and presenting subgroup analysis in a high-risk group was appropriate and valid. ■

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