seemed to derive from a handful of small and uncontrolled studies that used beta-blockers to treat high cardiac output. Unsurprisingly, reduced fetal growth was noted in women who received beta-blocker therapy.  

In late-onset preeclampsia, the authors postulated a high cardiac output state, a normal-to-low SVR, and intravascular volume overload. Interestingly, in both these phenotypes, the crucial missing link is whether all 3 cardiovascular alterations emerge simultaneously or 1 preceded by the other. Intravascular volume overload may not lead to a high cardiac output. In contrast, volume overload may reduce the effective pressure gradient for venous return. An improvement in the cardiac contractility or a rise in the heart rate can elevate the cardiac output in a volume loaded patient. Furthermore, a low to normal SVR may not be consistent with a high diastolic pressure, which is not infrequent in late-onset preeclampsia. An increased cardiac output with a low to normal SVR may produce only isolated systolic hypertension. Based on current understanding, the authors could not have got the evidence to link myocardial contractility with a high cardiac output in late-onset preeclampsia. 

Arguably, the cardiac pathophysiology in both the phenotypes could be different, but the underlying vascular endothelial dysfunction may be similar. Endothelium-derived vasoconstrictions are the predominant component in preeclampsia. Therefore, assuming a low to normal SVR in late-onset preeclampsia seems to suggest a different pathophysiology for both the phenotypes. Concomitant vasodilator therapy or other antihypertensive medications are likely to alter the cardiovascular hemodynamic parameters.

Suggesting a management strategy without a detailed understanding of the sequence of cardiovascular events may be counterproductive.

TO THE EDITORS: I read with great interest the article published by Jacoby et al, which reported risks of early pregnancy loss (EPL) before 20 weeks’ gestation for pregnant women with COVID-19, based on the data collected from the Pregnancy Coronavirus Outcomes Registry (PRIORITY) cohort study. Participants included in the study were enrolled at <14 weeks’ gestation, and the EPL rate was reported as 6% for both the group with COVID-19 and the group without COVID-19. 

I considered that adjustment was required to calculate the EPL rate with COVID-19 to be comparable with the reference EPL rate without COVID-19. When the pregnant women enrolled in the PRIORITY study, they were both pregnant and under the investigation of COVID-19. There was a delay between their pregnancy and the possible infection that lead to their enrollment in the study; the EPL risk during this period of delay was avoided in the reported study. Moreover, the period of early pregnancy consisted of weeks with high EPL risk. Moreover, the necessity to make such an adjustment was supported by the statistics presented in the study; among those, 6 reported EPL events, 5 EPLs occurred at 7 to 12 weeks and 1 EPL at 15 weeks; none of the EPL occurred at weeks 5 and 6, which are normally considered as the weeks with the highest EPL risk. 

Suppose the participants of the study were equally distributed between week 5 (diagnosis of pregnancy) and week 14 (enrollment deadline) at their enrollment, their mean value of gestation will be 9.5 weeks. The remaining risk of EPL by gestational week 9.5 (until week 20) was estimated at around half of the overall risk (from week 5 to week 20). Therefore, the adjusted EPL risk reported in the study should be doubled, which means the adjusted EPL risk should be 12% instead of 6%, which is still an acceptable level. If the authors could include the actual gestation week during enrollment in the study, it would be possible to make a more accurate estimation of the adjusted EPL risk.

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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, where the period between pregnancy and vaccination is unintentionally excluded.

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The author reports no conflict of interest.

The author reports no funding sources.

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Reply: Selection bias in estimates of early pregnancy loss

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 a systematic review from a systematic review of 4 studies dating back to 1970. 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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The authors do not receive any financial support for this work.

REFERENCE

© 2021 Published by Elsevier Inc. https://doi.org/10.1016/j.ajog.2021.07.024