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EDITORIAL

Studying and preventing stillbirth: what are the methodological issues?

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Though recent work has highlighted the global mortality burden attributable to stillbirth and called for increased research and policy attention,[1-4] there remains much that is unknown about this catastrophic outcome. Many challenges of researching stillbirth owe to the fact that the causal processes leading to intrauterine fetal demise (IUFD) and even the event itself are difficult to accurately detect, measure and study, because they occur in the intrauterine environment.[5] More research at all levels will be necessary to elucidate causal mechanisms, inform clinical practice and decrease the population burden of stillbirth.

Drs Ray and Urquia[6] have contributed to our understanding of stillbirth with their paper in this edition of the *Journal of Perinatology* that includes detailed and thoughtful analysis of the impact of intrauterine growth restriction on stillbirth. By examining extremely preterm stillbirths and employing multiple birthweight cutoffs (including centiles at the extremes of the distribution of birthweight) in a large data set, the authors analyze elements of stillbirth that remain understudied and poorly understood. Among others, the findings on fetal sex and extreme smallness-for-gestational-age (SGA) at very preterm weeks of gestation highlight important questions for future research on placentation, intrauterine growth, IUFD and their associations.

Other methodological and content-related topics fell outside the scope of this article but are nonetheless important to future research on stillbirth. Multiple methods of calculating stillbirth rates have been proposed, and Drs Ray and Urquia graphically presented their results using both. Methodological discussion on this topic dates back to the 1980s,[7,8] but the controversy remains as to which denominator is appropriate for GA-specific stillbirth rates: the number of births in a given week of gestation or the number of pregnancies in the cohort continuing at or beyond that GA (that is, the fetuses-at-risk approach).[9-12] As GA-specific stillbirth rates vary greatly depending on the denominator (Ray and Urquia[6], Figures 1a and b), this subject deserves more attention for stillbirth and other obstetric/perinatal outcomes.

Another methodological challenge to the study of stillbirth is the distinction between antepartum and intrapartum fetal demise. The two conditions differ in terms of risk factors, etiology and clinical management,[13,14] but are often not delineated in large databases. In this case, more fine-grained data collection/reporting would aid in analysis. The authors mention another persistent challenge to the study of stillbirth, which is the accurate dating of IUFD.[15] The time elapsed between IUFD and birth is likely to be on average greater at earlier gestations when women are seeing their providers less frequently, meaning that the bias in weight-for-GA measurement might be more pronounced at very preterm weeks. This would be another area where more detailed data collection would be ideal but may be unfeasible; observational research might still help assess the extent of the bias. A final issue that is not addressed in the current paper is the use of ultrasound-derived electronic fetal weight standards versus birthweight standards to classify SGA and LGA.[16,17] This study employed birthweight standards, though there is no consensus as to which choice is appropriate for which outcomes. Differences between ultrasound and birthweight standards are likely to be greatest at early GA, when the infants born are less representative of the fetuses remaining *in utero*.[17,18]

Most of these challenges originate from the complexity of stillbirth, the fact that it is obscured by pregnancy, and the resulting data limitations. This paper has clearly laid out several of these issues for readers, and addressed them where possible. Future research on stillbirth will require analyses that focus on both the population-level causes and trends in stillbirth and the fine-grained details of its associated causal and clinical processes. In addition to research that gets at causality, we also need improved methods to identify pregnancies-at-risk and prevent stillbirth. Our current clinical standards of antenatal testing and induction of labor, although crudely effective, can be greatly improved. More importantly, once we have identified that someone is at increased risk of stillbirth, when should intervention occur?

In the setting of such high-risk pregnancies as pregestational diabetes or chronic hypertension, antenatal testing begins at 32 weeks' gestation and this is thought to decrease the risk of stillbirth if abnormal testing is acted upon. However, when should we deliver such patients? If the goal is to reduce mortality, then simply denoting risk of stillbirth is inadequate; there is a need to compare the risk of mortality from intervention at a particular GA to the risk of mortality from expectant management. For example, at 32 weeks' gestation, the risk of neonatal mortality is still high enough to strongly discourage intervention except in cases of very high risk of stillbirth, such as reversed end-diastolic flow on uterine artery Doppler.[19]

In a recent study, investigators compared the risk of intervening (that is, neonatal mortality at the index GA) with that of expectant management (stillbirth risk plus risk of neonatal mortality at the next week of gestation).[20] In this study, it was demonstrated that while at 37 weeks, perinatal mortality is decreased by expectant management, at 39 weeks of gestation, perinatal mortality may actually be decreased by delivery. This observational study does not include neonatal morbidity, but the results are intriguing.

This study points out that while identifying risks for stillbirth and quantifying these risks are important, such risks are only one aspect of perinatal risk that includes neonatal mortality and also morbidity. Such risks of stillbirth must be framed in a broader perspective that incorporates these other risks. In the end, although the challenges posed by studying stillbirth are many, the gravity of the problem demands our thoughtfulness, rigor and analytical creativity. It is only through such work that we can hope to reduce the risks.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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