Invited Commentary

Invited Commentary: Isolating Preterm Birth to Assess Its Impact

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Separating the causal impact of early delivery on neonatal health outcomes from the antecedents of early delivery is challenging given the range of pathologies that are typically involved. Isolating preterm births resulting from trauma offers an opportunity to assess the impact of preterm birth independent of the usual causes, and it appears that such births are at substantially increased risk of adverse health outcomes (Am J Epidemiol. 2015;182(9):750–758). Trauma-related preterm births may offer insight into what happens when presumably normally developing fetuses are delivered early. Whereas pathology-related preterm births are preceded by a stressful uterine environment, including multiple contributing factors, and allow for interventions to prepare the newborn for extrauterine life, none of these applies to trauma-related preterm births. However, the trauma itself presumably causes acute problems that lead to the decision to deliver. Generalizing from the findings for trauma-related preterm births suggests that the pathology typically causing preterm birth does not have a strong independent effect and that a longer period leading up to the preterm birth is beneficial whether due to maturation or the opportunity for intervention.

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The phenomenon of preterm birth is complex with respect to both its etiology and its consequences. Like elevated blood pressure or advanced age, it is a powerful marker of risk of important health outcomes but is not inherently harmful so long as the newborn is able to adapt postnatally. As a risk marker, preterm birth is strongly associated with a range of clinically consequential outcomes, including neonatal mortality, respiratory distress syndrome, neurodevelopmental deficits, and chronic diseases over the life course (1, 2). The strength of its predictive impact is highly dependent on severity, with very early preterm birth (before 28 weeks’ gestation) associated with manyfold increases in severe outcomes, diminishing toward 37 weeks (the conventional dividing point between preterm and term) and risk continuing to decline up to 39 weeks. In fact, there is no discontinuity in predictive impact on adverse health outcomes at 37 weeks, as now recognized by the efforts to minimize “early term” births (3, 4). The statistical relationship of preterm birth to health is absolutely clear, just as it is for elevated blood pressure and advanced age, but the important questions for clinical or public health applications are the following: 1) Is preterm birth causally related to the adverse outcomes with which it is associated? 2) Would postponing the timing of delivery directly improve health outcomes?

The question of whether timing of delivery per se is a critical determinant of health outcomes or whether it simply reflects the underlying pathology that causes preterm birth and independently predicts those adverse outcomes is difficult to determine. Preterm birth occurs for a reason, sometimes a clear, specific one such as preeclampsia or placental abruption, and is often due to ill-defined reasons that presumably may include infection and inflammation, uterine irritability, cerebral incompetence, fetal stimulation of the hypothalamic-pituitary-adrenal axis, or other extensively studied pathways (1). Because many known and suspected pathways to preterm delivery involve the intrauterine environment rather than the fetus, the reasonable presumption is that the fetus is often an innocent bystander subjected to whatever fate the maternal environment has in store.

When the potential cause of an endogenous event or state is studied, it is useful to imagine the randomized trial that would be conducted if it were feasible and ethical to assess its causal impact. With behaviors or environmental exposures, it is straightforward to imagine the random allocation
Preterm birth occurs for ill-defined reasons that are intertwined with one another, whereas the initiating event of trauma-related preterm birth has a well-defined single cause. Other investigators have attempted to assign preterm birth to specific causal pathways (6–9), but in practice it is difficult to isolate one causal pathway from another. It is possible that our inability to do so is not just reflecting insufficient knowledge but may accurately reflect the multiple contributors that operate collectively. The abrupt, unanticipated pathway involving trauma is distinctively unifactorial. However, the trauma that induces the preterm birth may well have other direct health impacts on the fetus. Maternal trauma resulting in near-immediate preterm birth is often indicative of significant fetal compromise that precipitates the delivery. Obstetricians seek to optimize maternal status in a trauma to maintain the fetus in utero, so delivery following a trauma is sometimes a reflection of the inability to maintain fetal health through other means. Thus, it is very likely that the fetuses delivered preterm due to trauma were not in the same health state as other normally developing fetuses at that stage of gestation because they were delivered early due to the trauma itself or management of the effect of the trauma. To account for this trauma-related threat to the fetus, we would need data on indication for delivery (i.e., fetal distress), Apgar scores, or cord blood gases. Although the trauma-related deliveries were presumably normal prior to the trauma, the trauma itself resulted in changes that may themselves have consequences for postnatal health.

Preterm birth is typically anticipated some days before it occurs, allowing time for clinical intervention, but this window of anticipation is not available for trauma-related preterm birth. Women who are thought likely to deliver prematurely receive antenatal steroids in the interval before delivery, which are known to reduce the risk of a broad range of neonatal morbidities (10). Prior to 32 weeks’ gestation, women may also receive magnesium sulfate infusions, which is thought to reduce the risk of neonatal neurological morbidity (11). Furthermore, physicians have the opportunity to optize the maternal status to mitigate other neonatal risks (i.e., giving antibiotics to women with group-B streptococcus to prevent neonatal sepsis or giving insulin to women with diabetes to decrease the risk of neonatal hypoglycemia). As Liu et al. (5) point out, trauma-associated preterm births probably did not benefit from these interventions, and this difference likely accounts for some, if not all, of the differential predictiveness for health outcomes that they observed.

The investigators deserve much credit for identifying an unusual and informative subpopulation that generated what appears to be a solid finding of greater risk following trauma-related preterm birth than following typical preterm births. The meaning of that observation is subject to speculation, as offered in this commentary, but offers a clue regarding causal connections between antecedents and consequences of preterm birth. The implications for potential interventions are limited, however, because we have no way to directly influence the course of pregnancy that precedes preterm birth. What the results do suggest, though, is that the combination of being early and unanticipated is a big part of the problem, implying that efforts to extend gestation are likely to have health benefits due to some combination of maturation and obstetrical intervention.
REFERENCES