Invited Commentary

Invited Commentary: The Hidden Population in Perinatal Epidemiology

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Several recent papers have argued that understanding of pathologic perinatal processes may be advanced by considering, in varying ways, the population of fetuses still in utero. Initially invoked by Yudkin et al. (Lancet 1987;1:1192–4) as the optimum denominator for intrapartum stillbirths, fetuses in utero (or “fetuses at risk”) have also been of interest because of their patterns of growth, especially in comparison to infants born after varying durations of gestation. The paper by Hutcheon and Platt (Am J Epidemiol 2008;167:786–792) extends work that compares growth in infants born prematurely with that in infants continuing in utero and investigates the biases in analyses that can emerge from failure to consider the selection for impaired fetal growth characteristic of many prematurely born infants. Although the conceptual basis of this perspective is sound, in-utero fetal growth standards from serial ultrasonographic measurements in pregnancy are often based on small and highly selected samples. Some authors have proposed “fetuses at risk” as the appropriate denominator for postnatal phenomena related to premature birth, such as neonatal mortality and cerebral palsy. This application is problematic; in such situations, the denominator population differs from infants with the outcome in not having experienced adjustment to postnatal life, a potentially important determinant of outcome, especially in premature infants. The fetuses-at-risk concept is important in perinatal epidemiology and has implications for obstetric practice, but it must be handled with caution.

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THE VEIL OF PREGNANCY

The central difficulty of perinatal epidemiology is that so much is hidden from view by the veil of pregnancy. Of the embryonic population that is formed at conception, as many as a third may be lost within a few weeks, often without the mother’s awareness (1). The processes that govern these fetal losses, or even the later fetal losses that occur when pregnancy is under medical surveillance, are poorly understood (2). Nor can we directly observe the way in which the fetus grows and develops; even so simple a measure as fetal weight can be inferred only indirectly from other measures. Many of our inferences in perinatal epidemiology are thus derived from what is observable after pregnancy is over. At that point, we can enumerate the number of livebirths and fetal deaths, and we can ascertain deaths occurring in the first month of life. From these three populations, and the relationships among them, we construct the perinatal mortality statistics that we use to monitor maternal and child public health.

This end-of-pregnancy approach has been widely used to assess the mortal pregnancy outcomes at any gestational age. The neonatal mortality rate for babies born between 32 and 33 weeks of gestation is generally derived from all livebirths in that interval and the number of newborn deaths occurring among them. Similarly, stillborn infants born in that gestational week are conventionally denominated to all births occurring in that week (livebirths plus stillbirths), generating a “stillbirth rate,” which, as most “rates” in epidemiology, is not a measure of change over time, but a proportion. However, pregnancies ending prematurely can also be viewed as part of a cohort of births most of whose members are still in utero. From this perspective, it makes sense to consider the population of fetuses not yet
delivered at any given gestational week as the denominator population at risk of stillbirth in that week. This compelling argument was first put forth by Yudkin et al. (3) in 1987. These authors appear to have been the first to suggest that in addition to livebirths, fetal deaths, and neonatal deaths, a fourth population—fetuses still in utero—needs to be considered in at least some perinatal analyses. They used the term “stillbirth risk” as contrasted to “stillbirth rate” to describe their approach.

An interesting finding emerged from Yudkin et al.’s (3) approach. Stillbirth rates decrease with gestational age, but stillbirth risks increase with gestational age. This observation alerts clinicians to anticipate that the risk of stillbirth, especially unexplained stillbirth, rises as term approaches. The appeal of this way of thinking about risk of stillbirth is strong, since stillbirths by definition do not arise from the population of livebirths. As we shall see, however, the concept of fetuses at risk is more applicable to stillbirths than it is to some other perinatal outcomes.

FETAL GROWTH

Hutcheon and Platt (4), in this issue of the Journal, take a parallel stance in relation to fetal growth. The hidden population of fetuses still in utero is also viewed as a reference population of interest, but the situation here is more complicated, requiring not just enumeration but measurement. Serial ultrasonographic measurements of fetuses in utero have shown what many clinicians have long suspected, that premature births are selected for poor fetal growth from among the population of fetuses. Moreover, as Hutcheon and Platt show, this selection bias increases with decreasing gestation, making fetal growth restriction and gestational age inversely correlated with each other. They thus have the potential to confound each other in analyses of perinatal health outcomes. Their paper empirically demonstrates this bias, showing how pregnancy phenomena that are inversely correlated with gestational age at birth—preeclampsia, for example—have stronger associations with fetal growth restriction when that growth is assessed on the basis of standards derived from fetuses in utero rather than on standards derived from livebirths, because the latter group is biased toward fetal growth restriction when gestational duration is curtailed.

The authors (4) show, although perhaps do not emphasize quite enough, that, in their data, selection for premature birth is unevenly distributed across the spectrum of fetal weight. Thus, while the median fetal/birth weight at 32 weeks differs between the two weight standards by 120 g, the difference between the 10th percentiles is 300 g, a value that would be even larger were it expressed as standard deviations from the means being compared. Indeed, if we compare the two weight distributions plotted by the authors (their figure 1), we see that it is not the entire weight distribution that is shifted to the left in the liveborn compared with the fetal sample; rather, those fetuses destined to be born early are selectively removed from the lower 75 percent of the distribution. Above that percentile, the two distributions seem nearly identical. It is good to be reminded that we cannot predict the shape of two distributions from their mean or median difference.

Whereas Yudkin et al. (3) used fetuses as the sole denominator for stillbirth risk, Hutcheon and Platt (4) conclude that a hybrid growth standard, based on both fetuses and livebirths, would best be used to determine infants who suffer from “intrauterine growth restriction.” Doing so would greatly expand the number of babies defined as experiencing intrauterine growth restriction, from the conventional lightest 5 percent or 10 percent of the distribution, to a considerably higher figure that increases with decreasing gestational age, reaching as high as 70 percent in the very earliest gestations at which infant viability occurs.

DIFFICULTIES TO CONSIDER

The technique of prenatal ultrasonography has proven reasonably good at estimating birth weight from in-utero measurements, but it is not without its flaws. For one thing, gestational age is itself often estimated from the same source, at times creating a circularity in the logic of fetal-weight-for-gestational-age estimation (5, 6). Second, fetal weight is estimated from formulas based on one-dimensional measures such as femoral length or biparietal diameter, whose measurement errors must be magnified when extrapolated to a measure based on three dimensions, such as weight. Third, because repeated ultrasonographic measurements in pregnancy are not simple to arrange, most longitudinal fetal growth standards are based on small and selected samples. The fetal growth standard used by Hutcheon and Platt (4) is from Norway and is based on 634 pregnancies, each scanned three times on average (7). The births are also Norwegian, but they cover a much longer period of time, during which birth weight for gestational age changed, probably as the result of more liberal use of cesarean section (8). More problematic are comparison studies in which, for example, the births are British and the fetuses Swedish (9) or the births are Canadian and the fetuses Texan (10). In these latter two examples, the sample sizes used to establish the fetal growth standards were, respectively, 86 (11) and 392 (12). One has to consider the possibility that the disparate sources of such comparisons might bear some relation to their divergent findings.

Hutcheon and Platt (4), like most authors in this area, echo the clinical focus on one extreme tail of the distribution—weight below the 5th or the 10th percentile for gestational age. However, there is little to suggest that the effects of impaired growth suddenly become manifest below a fixed threshold. More likely, the entire range of growth is of interest, especially when dealing with infants already deemed to be at risk because of preterm birth. I suspect that both clinicians and scientists interested in the preterm infant would gain more useful information from describing each infant’s status in relation to the entire spectrum of growth, whether based on fetal, neonatal, or hybrid standards. The full spectrum of fetal growth can be represented as a ratio of the infant’s weight to the median for his or her gestational week (termed the fetal growth ratio) (13) or as standard deviations units (z scores) away from the mean weight for the gestational week (14).
BEYOND FETAL LIFE

The two illustrations of the fetuses-at-risk approach discussed thus far—stillbirths and fetal growth—are both intrauterine phenomena determined before birth. However, the suggestion has been made to use this approach for phenomena occurring after birth, such as neonatal death, and even phenomena of perinatal origin diagnosed much later, such as cerebral palsy (15). The difficulty here is that neonatal death and cerebral palsy occur in liveborn infants only. This is not just a technical matter but a recognition that certain experiences are key predisposers to risk, and, absent those experiences, any comparison of risk may be biased.

The traditional assumption, implicit in gestational growth curves based on livebirths, is that premature birth is a random event occurring in an otherwise normal pregnancy that ended too early. We now know that assumption is untenable. On the other hand, the “fetus-at-risk” approach carries the assumption that neonatal death or disability would have occurred with equal probability, and at the same point in time, whether the infant was born early or had stayed in utero. That assumption is likewise untenable. The truth must lie somewhere between these two extremes. For neonatal death and disability linked to preterm birth, the manifold problems associated with successful transition to postnatal life require us to place our marker much closer to the traditional assumption that delivery and birth dramatically alter risk. The imperfect ability of postnatal medical care to mimic the environment of the womb in severely preterm infants means that, even with the best of care, the death and disability rate for infants born at 28 weeks of gestation is orders of magnitude higher than for those remaining in utero. That risk difference cannot entirely be due to birth selection for preexisting damage.

Consider a parallel. Livebirths arise from the denominator population of fetuses, but fetuses themselves arise from a denominator population of women of childbearing age. The fetuses-at-risk concept might thus be enlarged to include women at risk as the denominator population. Would we be interested in the rate of preeclampsia in women of childbearing age, ignoring the fact of pregnancy? Obviously not. Just as pregnancy is a requirement for risk of preeclampsia, so is livebirth a requirement for risk of neonatal death and cerebral palsy.

WHY ALL THIS MATTERS

The limitations of prenatal growth standards noted above have deterred some neonatologists from using them to replace birth standards (16), but, in any case, clinicians who care for premature infants will, for the purpose of defining a high-risk group, want to compare growth among their liveborn charges. The growth of these infants compared with their more fortunate peers remaining in utero is not really relevant. Nonetheless, clinicians should recognize that the more premature a baby, the more likely he or she is to deviate in growth from fetuses in utero of the same gestational age.

Obstetricians almost certainly incorporate the fetuses-at-risk model into their decision making, whether consciously or not. The concern that further time in the womb might produce a stillbirth or a severely compromised infant implies a recognition that certain risks increase with increasing gestation, the hallmark of the fetuses-at-risk calculation. It is this concern that motivates the principal obstetric intervention, the decision to hasten birth by induction or operative delivery. A more formal model of this thinking has been provided by Joseph (17).

For epidemiologists, recognition and acknowledgment of the hidden perinatal population—the fetuses quietly biding their time in utero and not coming to our attention as vital events—can at times lead to a more precise understanding of the determinants of perinatal health.

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REFERENCES