Commentary

Quantifying the risk of different types of perinatal death in relation to gestational age: Researchers at risk of causing confusion

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One of the most basic concepts in epidemiology is the risk of an event, defined as the probability that an individual will experience the event of interest in a given time frame. We estimate the risk by studying populations of similar individuals. We calculate the proportion of individuals within the population who experience the event relative to the total size of the population who were at risk of the event (using methods to take into account the time of exposure as required). What, then, is the correct denominator for the risk of perinatal death at a given week of gestational age? The problem in answering this simple question is that perinatal deaths occur secondary to diverse different types of event, and the denominators may differ depending on the cause.

Broadly, we consider three major categories of perinatal death: (i) antepartum stillbirth, i.e. stillbirth where fetal death took place prior to the onset of labour, (ii) intrapartum stillbirth, i.e. stillbirth where death occurred after the onset of labour but before delivery, and (iii) neonatal death, i.e. death of a live born infant (strictly, perinatal death only includes early neonatal deaths). One of the key factors which we study in relation to perinatal death is gestational age. A problem when studying the risk of perinatal death at a given week of gestational age is that each of the three main categories of death has different populations at risk of the given event in the given week. It has been proposed (see Smith 2005 for review[1]) that (i) the population at risk of antepartum stillbirth is the total number of pregnancies in the population which were undelivered at the start of the week; (ii) the population at risk of intrapartum stillbirth is the total number of women in labour at that week where the fetus was alive at the onset of labour; and (iii) the population at risk of neonatal death is the total number of livebirths in the given week. This summary raises two problems. First, given three different denominators, it is clearly problematic to summarise the net risk of perinatal death associated with delivery at a given week of gestational age (this has previously been addressed[1]). Second, in reality, the denominators for intrapartum stillbirth and neonatal death are more complex.

The complexity can be demonstrated by considering a specific example: placental abruption. If there is a massive placental abruption it will frequently trigger labour or medically

indicated delivery. Massive abruption leads to acute, severe asphyxia of the infant, which can lead to death of the baby prior to labour (antepartum stillbirth), during labour (intrapartum stillbirth), or death of an extremely sick but live born baby shortly after birth (neonatal death). At any given week of gestational age, every on-going pregnancy is at risk of massive abruption. Hence, all on-going pregnancies at the given week seems the appropriate denominator for estimating this risk, whatever the timing of the death of the infant in relation to labour and delivery. However, small placental abruptions can also lead to labour.[2] If this occurs at 24 weeks, preterm delivery would lead to a high chance of neonatal death due to very early (preterm) delivery. In contrast, a small abruption at term would rarely result in a neonatal death. The difference in the outcomes despite the same initiating event is explained by the gestational age at birth: death following the small abruption at 24 weeks occurred because it led to preterm delivery, rather than as a direct result of the placental abruption. Preterm birth is the cause of about half of neonatal deaths.[3] The majority of these deaths are related to the consequences of developmental immaturity. Another major determinant of neonatal death is congenital anomaly, accounting for about a quarter of the total.[3] In many such cases (i) the death was inevitable due to an anomaly determined in the first trimester; and (ii) the fetus can survive in utero but the risk of death becomes manifested on delivery. Examples of the latter are causes of pulmonary hypoplasia, such as massive congenital diaphragmatic hernia. Therefore, deaths associated with preterm delivery and anomalies at a given week of gestational age are frequently conditional on delivery at that week.

The paper by Basso[4] addressed whether events following livebirth (such as neonatal death) should be analysed on the basis of "fetuses at risk", i.e. the denominator of all on-going pregnancies at the given week of gestational age. As discussed above, neonatal death can be due to antepartum, intrapartum or neonatal events. Hence, there is no single perfect denominator for the risk of neonatal death at a given week of gestational age. However, as about 75% of neonatal deaths are due to prematurity or anomalies,[3] and many of the remainder are also not due to antepartum events, using the denominator of all livebirths at a given week better captures the population at risk of neonatal death than the number of fetuses alive at the start of that week. Hence, when analysing the risk of neonatal death,

neither denominator (livebirths nor fetuses at risk) perfectly captures the population at risk. But perhaps we can conclude that analysis of neonatal events in relation to the number of livebirths is less flawed than analysis on the basis of fetuses at risk.

The complexity of classifying causes of perinatal death is reflected by the plethora of systems which have been developed.[5] The multiple causes of perinatal death, and the potential for a single cause to lead to perinatal death through different mechanisms (such as the example of placental abruption) mean that it would be extremely difficult to create a summary statistic that perfectly captures the risk of all events in relation to the correct denominator at a given week of gestational age. Future research could try and differentiate between antepartum causes of deaths, and those conditional on the occurrence of labour and delivery at the given week. The problem is that the analysis and the output would be highly complex. And if it is difficult for epidemiologists to conceptualise numerators, denominators and summary values of risk, how much more difficult is it for clinicians trying to understanding the relationship between gestational age and the overall risk of perinatal death?

About the author

Gordon Smith is Professor and Head of the Department of Obstetrics and Gynaecology, Cambridge University, UK, and works clinically in Maternal-Fetal Medicine at The Rosie Hospital, Cambridge. His research focuses on developing novel predictors of adverse pregnancy. His current work is largely focused on a prospective cohort, the Pregnancy Outcome Prediction study.

References

(1) Smith GC. Estimating risks of perinatal death. *Am J Obstet Gynecol* 2005; 192(1):17-22.

(2) Gargano JW, Holzman CB, Senagore PK, Reuss ML, Pathak DR, Williams MA et al. Evidence of placental haemorrhage and preterm delivery. *BJOG* 2010; 117(4):445-455.

(3) Healthcare Improvement Scotland. Scottish perinatal and infant mortality and morbidity report. 2014. Edinburgh, Common Services Agency, NHS Scotland.

(4) Basso O. Implications of using a fetuses-at-risk approach when fetuses are not at risk. *Paed Perinat Epidemiol* 2015;In press.

(5) Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011; 377(9778):1703-1717.