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Challenges in defining and classifying the preterm birth syndrome

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In 2009, the Global Alliance to Prevent Prematurity and Stillbirth Conference charged the authors to propose a new comprehensive, consistent, and uniform classification system for preterm birth. This first article reviews issues related to measurement of gestational age, clinical vs etiologic phenotypes, inclusion vs exclusion of multifetal and stillborn infants, and separation vs combination of pathways to preterm birth. The second article proposes answers to the questions raised here, and the third demonstrates how the proposed system might work in practice.

Key words: classification, phenotype, preterm birth

Preterm birth, defined by the World Health Organization (WHO) as birth prior to 37 complete weeks (259 days) after the first day of the last menstrual period preceding the pregnancy,[1] is a major global public health problem.[2,3] Recent systematic reviews by WHO[4] and the March of Dimes[5] have estimated that in 2005, 13 million infants were born preterm worldwide. The majority of these preterm births (85%) occur in Africa and Asia: the former because of high rates, the latter because of the large number of births. For several decades, preterm birth has been the focus of research and public health intervention in many developed countries because of the associated high risks of infant mortality and long-term neurocognitive, visual, and pulmonary sequelae and because rates have been stable or increasing.[2,6]

In low- and middle-income countries, attention to preterm birth has been more recent, largely because gestational age (GA) at birth is not routinely recorded in noninstitutional deliveries and is often unknown.[3-5] The longstanding emphasis on low birthweight, rather than preterm birth, naturally led to a primary emphasis on maternal under nutrition, which does not appear to be a major contributor to preterm birth.[7]

In 2009, more than 200 participants attended the International Conference on Prematurity and Stillbirth convened by the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), hosted by Seattle Children's Hospital with support from the Bill and Melinda Gates Foundation, March of Dimes, Save the Children, World Health Organization, United Nations Children's Fund, and Program for Appropriate Technology in Health. A Global Action Agenda was developed (an agenda) that, in part, highlighted the need for a comprehensive, consistent, and uniform classification system for preterm birth.[3]

The authors of this paper and the following two in the series were brought together as a direct result of the GAPPS meeting, with instructions to determine the need for such a classification system, to define the issues related to creating a preterm birth classification system, and to present a prototype classification system for general consideration.

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Measurement issues

The earlier international definition of prematurity (birthweight ≤2500 g) did not distinguish between infants born early from those born small for their GA.[8] For that reason, WHO changed the term from prematurity to preterm birth and defines the latter (preterm birth) based on GA only: a birth before 37 completed weeks (259 days) after the first day of the last menstrual period (LMP).[1] That GA, a cutoff that was entirely arbitrary, however, is an issue that will be discussed later in this article.

First, it is important to consider how GA is measured. In the past, the GA estimate on a population-wide scale was primarily based on the LMP, an estimate that assumes that conception occurs on the same day of ovulation and that ovulation and conception occur 14 days after the onset of the LMP. Differences in the duration of the menstrual cycle, however, and particularly on the day of the menstrual cycle on which ovulation occurs, account for considerable variability in the day of conception vis-à-vis the first day of the LMP.[9,10] In addition, LMP reporting is subject to error in recall and can be influenced by spotting or frank bleeding (which may reflect early miscarriages of clinically unrecognized pregnancies).[11,12]

Historically, obstetricians and other prenatal care providers often used uterine fundal height as a check to validate the estimated duration of gestation, but more recently, clinical GA estimates have been based on ultrasound fetal measurements in the first half of the pregnancy.[12] These are usually calculated from the biparietal diameter in the second trimester (13-20 weeks) or crown-rump length before 14 weeks of gestation.

Ultrasound-based estimates of GA have been shown to yield GA estimates that are 2-3 days earlier than LMP-based estimates (corresponding to ovulation on day 16-17 vs day 14), on average, and yield slightly higher rates of preterm birth.[13-16] Ultrasound-based estimations may also have errors related to insufficient standardization and quality control of the operators, are based on equations derived from small samples (especially at early GAs) from different selected populations, do not provide variability around the GA estimates, and assume that all fetuses with the same measurement have the same GA (ie, they do not account for true differences in fetal growth in early gestation).[17,18] Data entry errors can arise with either LMP or ultrasound GA estimates and can lead to an apparent bimodal or upwardly skewed distribution of birthweight at preterm GAs (especially at 27-32 weeks), owing to inclusion of term or near-term births.[19-23]

In the United States and the United Kingdom, official estimates of preterm birth rates are based on LMP GA estimates. Despite the evidence from clinical and hospital-based study samples that ultrasound-based estimates are slightly shorter than LMP-based estimates,[13,14] preterm birth rates based on the menstrual estimates in the United States have been shown to be considerably higher than those based on the clinical estimate, which, as in other countries, is increasingly based on ultrasound-derived GA estimates.[12,22,24] US and Canadian preterm birth rates, for example, have been shown to be closer when the US rate is based on the clinical estimate.[25] The higher US preterm birth rate based on the LMP GA estimate may reflect errors in recalling the date of the LMP, particularly among women with late onset of prenatal care.

The neonatal mortality rates among preterm births are very similar in Canada and the United States when the US rate is based on the clinical estimate but considerably lower when based on the menstrual (LMP) estimate, suggesting the inclusion of some term births among those classified as preterm based on LMP.[25] Similarly, relative risks (vs infants born ≥37 weeks) are also very similar in Canada and the United States when based on the US clinical GA estimate but are considerably lower in the United States when based on the LMP-based estimate. Postterm rates (GA ≥42 weeks) are virtually identical in the United States (including both US whites and blacks) and Canada when the US rates are based on the clinical estimate but much higher in the United States when based on the menstrual estimate.[25] In summary, these measurement differences can lead to substantial disparities in the GA distribution, and specifically the preterm birth rate, for different populations.

Finally, postnatal examination of the newborn infant has also been used to estimate GA, based on physical and neurological criteria. These estimates are far less satisfactory than early ultrasound-based prenatal estimates, however, because they are influenced by race, pregnancy complications, delivery complications, and birthweight for GA.[26,27]

Phenotypic heterogeneity

Preterm birth is an unusual entity because it is defined by time, not by a distinctive clinical phenotype. Consider the hypothetical analogy of premature death. Premature death (ie, death occurring at an age earlier than expected; eg, <65 years) would consist largely of deaths from cancer, coronary heart disease, unintentional injury, and suicide.

Imagine the etiological research based on such an entity. Risk factors differ vastly for cancer, coronary heart disease, unintentional injury, and suicide. A genome-wide association study, study of biomarkers, or investigation of physiological/biochemical mechanisms underlying premature death would be meaningless and uninterpretable. This is a similar situation to that currently faced by preterm birth and at least partly explains why we have not made much headway in understanding its etiology.[2,6]

Existing phenotypic classifications or subdivisions include subdivisions by GA (early vs late); clinical presentation (spontaneous preterm labor, preterm prelabor rupture of membranes [PPROM], and iatrogenic [indicated] preterm birth); and pathology or presumed pathophysiological pathways (infectious/inflammatory, vasculopathic, and stress-induced).

Subdivision by GA usually separates early preterm birth (variably defined but often <32 completed weeks) vs late preterm births, those between 32 and 36 (or 34-36) completed weeks.

Subdivision by clinical presentation distinguishes cases of preterm birth presenting with spontaneous preterm labor, those with PPROM, and iatrogenic (indicated) preterm birth.[28]

Finally, placental pathology or postulated physiological mechanisms have also been used to subdivide preterm birth into infectious/inflammatory, vasculopathic, and stress-induced pathways to preterm birth.[2,6,29-31]

Studies have been consistent in showing that early preterm births are more frequently associated with infection/inflammation, as revealed by leukocytosis or high levels of inflammatory cytokines in the amniotic fluid, histological chorioamnionitis, or even cultured organisms from the genital tract.[32] Other features of the subdivision, however, have been less robust. For instance, distinguishing preterm labor from PPROM by history can be difficult. Women often present with preterm labor already underway and membranes already ruptured. It is often impossible to determine which occurred first, even on careful questioning. The criteria used to make this distinction also vary from study to study, as do the relative proportions between the 2 presentation categories.[33-37]

Some studies have required a minimum duration of rupture of membranes prior to onset of regular contractions before classifying a case as PPROM,[33] whereas others base the distinction on questioning the mother of which event occurred first. Although early publications proposing this subdivision suggested that African-American women had higher relative risks vs whites for PPROM than for spontaneous preterm labor[38] and that PPROM was more often associated with an infectious etiology than was spontaneous preterm labor,[39] those findings have not been confirmed in more recent studies.[34,40] The observed black-white differences could theoretically reflect racial or cultural differences in the interval between onset of clinical symptoms and seeking of medical care or even bias in the type of questioning by health care providers or their belief in the accuracy of reporting.

The category of indicated preterm birth is etiologically and prognostically heterogeneous.[34] The category includes both fetal and maternal indications (eg, fetal growth restriction and nonreassuring tests of fetal well-being and pregnancy-induced hypertension and antepartum hemorrhage). Within the overall category of indicated preterm birth, some etiological risk factors can have opposite effects, depending on the indication. For example, maternal smoking and low maternal prepregnancy body mass index are risk factors for fetal growth restriction but are protective against preeclampsia, whereas maternal obesity is protective against fetal growth restriction but a risk factor for preeclampsia. Moreover, indicated preterm births have increased over time largely because the indication threshold has fallen as obstetric care has become more aggressive and interventive.[41] In the United States, this increase has been more prominent among whites than among blacks,[41] which may be partly responsible for the recent modest attenuation in the racial disparity in that country.

Phenotype vs etiology

Existing subdivisions of preterm birth often include presumed etiological or mechanistic pathways, as well as descriptive characteristics that might be preferable in definable a pure phenotype. Atherosclerotic coronary heart disease is a clinical, radiological, and/or pathological phenotypic entity that does not consider serum lipids, glucose tolerance, family history, blood pressure, smoking history, or genotype. Similarly, non–small-cell lung cancer is a combined clinical/pathological phenotype that is assigned based on clinical, radiological, and pathological characteristics present at the time of diagnosis, not on history of smoking, environmental exposure, or occupation.

Deciding on what characteristics should be included or excluded from the phenotypic classification of preterm birth, however, is far more difficult. It seems reasonable to exclude such potential risk factors as socioeconomic status and smoking from the list of phenotypic criteria. But what about documented amniotic fluid infection or inflammation, placenta previa, cervical shortening, or prior history of preterm delivery? Should these be considered risk factors (potential etiological determinants) or phenotypic features? These issues will be discussed in greater depth in the second paper of this series.

A further complication in defining phenotypic subtypes of preterm birth is the rapidly changing landscape. The falling threshold for obstetric intervention (labor induction or prelabor cesarean delivery) is a moving target.[42,43] We are not commenting here on the benefits or harms of these profound temporal changes for maternal, fetal, and neonatal health. But some of today's or tomorrow's preterm births would have been spontaneous term births or preterm stillbirths in the past. Clinical intervention makes it impossible to determine the natural phenotype (ie, the phenotype that would have been observed in the absence of the intervention, and prevents phenotypic stability over time, however desirable that might be for etiological or prognostic research). In other words, the entirety of the natural phenotype is unknowable because the visible phenotype is influenced by prenatal and peripartum care. This phenomenon will increasingly and unavoidably complicate etiological research on preterm birth.

Other definitional problems

It is often difficult or impossible to determine whether studies or population prevalence rates include or exclude stillbirths. Although stillbirths account for only around 5% of all preterm births, the majority of stillbirths occur prior to 37 completed weeks. Although few studies have examined whether the etiological risk factors, or their relative importance, differ in preterm stillbirths and preterm live births. Poor fetal growth is strongly associated with both.[44-48] Moreover, risk factors have been shown to strongly overlap for live vs stillborn births as early as 14-21 weeks of gestation.[49]

Late pregnancy terminations are a tiny fraction of all preterm births but a rising and important fraction of perinatal deaths. Studies from Canada indicate a temporal increase in stillbirths because of congenital anomalies at 20-25 weeks and a corresponding reduction in stillbirths because of congenital anomalies at 26-44 weeks and in infant mortality because of congenital anomalies.[50] The same study reported on an increase in

infant mortality because of congenital anomalies in the 20-25 week range but a corresponding decrease at 34 weeks or longer.

These data suggest that an increasing number of late pregnancy terminations because of prenatal diagnosis and late pregnancy termination is responsible both for an increase in stillbirths and live births, the latter followed rapidly by infant death, between 20 and 25 weeks of gestation. Although most countries do not currently record such data for live births or stillbirths at 16-19 weeks, the increase in pregnancy termination at these GAs has probably been even more striking.

Unpublished data from the United States comparing 2002 with 1989 suggest an increase in infant mortality because of congenital anomalies from 17 to 24 weeks and a reduction at 25 weeks or longer (K. S. Joseph, unpublished data). The increase at 24 weeks or less has been most striking for chromosomal (relative risk, 3.0; 95% confidence interval [CI], 2.0–4.4), cardiovascular (relative risk, 1.6; 95% CI, 1.1–2.5), and neurological (relative risk, 1.5; 95% CI, 1.0–2.1) anomalies.

Other problems relate to the lower and upper GA boundaries for defining preterm birth. Although most countries base their preterm birth rates on live births (usually excluding stillbirths) from 20 (or 22) to 36 completed weeks, the etiological risk factors for births at 14-23 weeks do not appear to differ from those of preterm births at 20-25 weeks.[49,51] Bacterial vaginosis, a well-known risk factor for preterm birth,[52,53] has also been reported to be associated with second-trimester miscarriage.[54,55] Moreover, women who miscarry during the second trimester also have an increased risk of subsequent preterm birth.[51,56] Should these second-trimester births therefore not be included as preterm births?

At the other end of the gestational spectrum, the WHO cutoff of less than 37 completed weeks (ie, up to 36 weeks 6 days, or 258 days) is arbitrary.[8] Although infants born between 39 and 41 weeks have similar risks of neonatal and postneonatal mortality and morbidity, those born at 38 and especially 37 weeks have significantly higher risks.[57-59] Early term births have also been reported to be at increased risk of sudden infant death syndrome.[60] Finally, a recent study has reported lower IQ scores in children born at 37 and 38 weeks vs those born at 39-41 weeks.[61] The available evidence thus suggests a less arbitrary definition of preterm birth: all births (including live births and stillbirths) occurring from 16 weeks 0 days to 38 weeks 6 days (ie, 112-272 days).

Conclusions

Preterm birth is an unusual health outcome. It is defined by time, not by a distinct clinical phenotype. Preterm birth rates have increased in most developed and many developing countries at a time when other population perinatal health indicators have improved, including reduced rates of infertility, stillbirth, infant mortality, and more recently cerebral palsy and other sequelae of preterm birth. Infants born before 20 weeks or at 37 or 38 weeks share many features with births at 20-36 weeks, including etiological and prognostic features.

Reclassifying the phenotypes of preterm birth is likely to require both lumping and splitting.[31] Unless genetic or other etiological studies show distinct differences, splitting spontaneous preterm labor and PPROM may be difficult to justify; moreover, each may result from more than 1 etiological pathway. The indicated preterm birth category is probably too heterogeneous for etiological studies. Fetal growth restriction, nonreassuring signs of fetal well-being, pregnancy-induced hypertension or preeclampsia, and hemorrhage can occur together but may also be considered as separate clinical categories. Categories defined by placental pathology, such as inflammation/infection vs vasculopathy/infarction vs normal, also deserve further attention.

Future etiological research for preterm birth will benefit from improved measurement methods for estimating GA and narrower, more homogeneous case definitions. Etiological studies will therefore require larger study bases (populations) and more in-depth clinical and pathological investigations. Some of these investigations are available only after the birth. On the other hand, future preventive interventions may depend on our ability to predict specific preterm birth phenotypes based on information available prior to or early in pregnancy. The challenges ahead are daunting indeed. ■

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