

The preterm birth syndrome: issues to consider in creating a classification system

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In the first article of this series, the potential benefits of a classification system for preterm birth were articulated and a brief history of attempts to classify preterm birth was presented.¹ In this article, our goal is to raise many of the issues that need to be addressed and the decisions that need to be made to create a preterm birth classification system. As in the other articles in this series, the authors were brought together as a direct result of the Global Alliance to Prevent Prematurity and Stillbirth (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.

A comprehensive classification system for preterm birth requires expanded gestational boundaries that recognize the early origins of preterm parturition and emphasize fetal maturity over fetal age. Exclusion of stillbirths, pregnancy terminations, and multifetal gestations prevents comprehensive consideration of the potential causes and presentations of preterm birth. Any step in parturition (cervical softening and ripening, decidual-membrane activation, and/or myometrial contractions) may initiate preterm parturition, and should be recorded for every preterm birth, as should the condition of the mother, fetus, newborn, and placenta, before a phenotype is assigned.

Key words: classification, phenotype, preterm birth

In addition to discussing the issues that need to be resolved before a classification system can be created, we also intend to cause readers to consider conceptual issues that may have hindered progress toward better understanding preterm birth. These include

the assumption that the clinical presentation for delivery defines distinct causes and acceptance of the arbitrary gestational age boundaries that define prematurity. In writing this commentary, we began with many diverse opinions regarding the development of a classification system for preterm birth. We found that, by isolating each issue and posing a specific question regarding the issue, we could better understand the principles on which to base a classification system and, eventually, came to a consensus on each of the issues. We have tried to identify and emphasize clearly superior options among the possible choices, although noting other potential options and the rationale for our choices.

What is the reason for creating this classification system for preterm birth?

There are many reasons to classify preterm births and to consider various systems of classification. In this article, we focus on the decisions involved in creating a classification system for use in both population surveillance and research, so that when specific types of preterm births are discussed, studied, or compared across populations or over time, categories have consistent definitions that are widely understood and accepted.

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What should the gestational age boundaries in a classification of preterm births be?

The lower and upper gestational age boundaries for defining preterm birth are variably defined. Although most geographic areas base their preterm birth rates on live births (usually excluding stillbirths), the boundaries at both ends are arbitrary. For example, if a lower gestational age boundary for defining a preterm birth is used at all, the cutoffs range from 20^{0/7} to 22 or even 28 weeks. However, as demonstrated in the first paper in this series, the risk factors, causes, and recurrence risks for spontaneous births at 16-19 weeks do not differ substantially from those births occurring at 20-24 weeks.²⁻¹¹ Thus, if the objective is to explore the full range of preterm birth, there is no reason to exclude births at 16-19 weeks from the classification system. Regardless of the lower cutoff chosen, for comparison purposes across sites or over time, some clearly defined, scientifically sound, lower gestational age cutoff that defines preterm birth should be used.

Similarly, there is now abundant evidence that many infants born at 37 or 38 weeks of gestation experience increased neonatal mortality and even lifetime morbidity related to immaturity of one or more organs as compared with infants born at ≥ 39 weeks.¹²⁻¹⁵ The historical choice of 37 weeks as the upper gestational age cutoff for defining a preterm birth was arbitrary and may no longer serve a useful purpose, because it does not coincide with functional maturity. For this reason, we believe that defining a preterm birth as any occurring before 39 weeks would be more appropriate. For research and reporting purposes, extending both the lower and upper boundaries of preterm birth should be considered.

Regardless of the final gestational age cutoffs for defining preterm birth, there was universal agreement (the authors agreed) that gestational age data should be collected and recorded in narrow categories (eg, no more than 1 week) to allow flexibility in later categorization. Dividing the preterm births into several

gestational age groups may also be useful.¹⁶⁻¹⁸ The exact thresholds matter less than the common use of a universal system of gestational age groupings, so that differences in the gestational age distribution of preterm birth can be understood. Finally, because menstrual dating of gestational age is often inaccurate, we believe gestational age estimation should, whenever possible, be corroborated by an early, high quality ultrasound and the best obstetric estimate be used for all gestational age determinations in the classification system.¹⁹

What information will be collected in this preterm birth classification system?

Because the system we envision will be used for research and population surveillance, we propose to classify the preterm birth at some time after delivery, with as much information available as possible. The clinical record should be the primary source of information. This record should include antepartum and intrapartum data, a record of all prior pregnancies, medical history, a patient and physician interview when preterm birth has been scheduled and where the reason for delivery is not completely clear, and finally, a gross and microscopic placental evaluation and, for stillbirths, an autopsy or pathology report. Without examining each of these sources, an important potential cause or phenotype might be missed.

Should a classification system be based on phenotype or cause?

Because the cause of a specific case of preterm birth is rarely known with any degree of certainty, the authors agreed that the optimal classification system should primarily be based on the clinical phenotype, defined in this study as one or more characteristics of the mother, fetus, placenta, and the presentation for delivery. We also agree that more than 1 phenotype may be present in a single case of preterm delivery and that each phenotype present should be recorded so that the choice of a single category is not forced. Finally, the actual method of delivery (spontaneous or instrumental vaginal or cesarean birth) should not be part of the phenotypic classification sys-

tem. Data about method of delivery should be noted and collected separately.

One question raised in relation to those preterm births considered as "spontaneous" in many prior studies is whether the findings at initial clinical presentation (eg, contractions, preterm premature rupture of membranes [P-PROM], bleeding, or advanced dilation), or the likely pathway leading to the final presentation (eg, short cervix or polyhydramnios), should be primary. In this matter, we were influenced by evidence suggesting that a common "phenotype" of spontaneous preterm birth is primarily characterized by progressive cervical effacement, after which P-PROM, persistent mild contractions, prolapsed membranes, or bleeding could be the acute reason for seeking care.²⁰ Based on this consideration, we believe that the most useful classification system will not only capture information about the clinical presentation on admission (contractions, P-PROM, bleeding, advanced cervical dilation without P-PROM or significant contractions, or none of these for a provider initiated delivery), but will also be based on conditions and observations during pregnancy, including significant maternal infection, short cervical length, increased or decreased amniotic fluid volume, as well as relevant clinical, laboratory, and placental findings.

Should risk factors be part of the classification system?

The next issue is whether risk factors should be part of the classification system. We believe that distal determinants that have no clear causal pathway to preterm birth, such as low socioeconomic status, ethnicity, smoking, or illicit drug use, should be collected in a systematic way, but should not be part of the classification system. Some classification systems include potential causes, like stress, unspecified immune, or allergic pathways, with no clear means of defining how a specific case gets so classified.²¹ At this point, unless a condition can be clearly defined and there is a reasonably clear pathway from that condition to the preterm birth, we believe it should be considered a potential risk factor but should not constitute a phenotype in a

classification system. One such example is whether the method of conception (assisted reproductive technologies [ART] vs spontaneous) should be considered a risk factor for preterm birth or merit a separate phenotypic category? Because there is no clear etiologic pathway linking ART to increased risk of preterm birth among singleton or even multifetal gestations, we believe that the method of conception should be considered as a risk factor for preterm birth but should not constitute a phenotype.

Should pregnancy terminations and stillbirths be included?

The issue of whether to include pregnancy terminations (live born or stillborn), occurring at or above the lower gestational age limit in the classification, is controversial. Various stillbirth classification systems handle these cases differently, with many systems excluding them.²² An important question in this study is whether the reason for the termination makes a difference. Terminations occur electively but also for diverse reasons, such as severe growth retardation, absence of amniotic fluid, P-PROM, advanced cervical dilatation, or a major anomaly detected at a previsible gestational age above the lower threshold for defining preterm birth. Some of these fetuses are either live born or die before delivery. Should these deliveries be included in the classification system at all, and if so, should some be considered spontaneous, indicated, or elective terminations? Our preference is to include all births above the lower gestational age threshold for preterm birth, whether it was a termination or not, and within the system, to classify terminations of pregnancy by the phenotypes used for all other preterm births. A system that includes some terminations but not others would likely be confusing for all.

Stillbirth is also a difficult issue. In many data sets used to study preterm birth, stillbirths are not combined with the live births. Preterm births are reported only for live born infants. This is an important consideration because, in developed countries, as many as 50% of stillbirths occur before 28 weeks and 80% or more of stillbirths are preterm.^{23,24} Also, the pathologic processes leading to preterm stillbirths are of-

ten similar to those for live born preterm births (eg, chorioamnionitis or abruption).²⁵⁻²⁷ In fact, many intrapartum stillbirths occur during preterm labor after a decision that a live fetus in distress is too immature to salvage by cesarean delivery. Further confusion is added when a stillbirth that occurs in the antepartum period presents in preterm labor or with P-PROM. With these considerations in mind, the authors agreed that the classification system for *preterm birth* should include all preterm stillbirths.

How do we deal with multiple births?

Should multiple births be combined with singletons in the same classification system, or should they be considered separately? And if separately, should twins and higher-order multiples be considered together? If multiples are considered separately, should they be classified using the same system used for singletons? If a single system were used for classifying both singleton and multiple preterm births, multiplicity could be part of a preterm birth phenotype. Thus, there are many questions related to the inclusion or exclusion of multiples in this system. Perhaps the most important influence on the group was the sentiment that all preterm births should be included in this *preterm birth* classification system. Therefore, our recommendation is to create a single classification system, with multiples included in the system as 1 potential phenotype for preterm birth. The number of fetuses should, of course, be noted. In addition, there are issues related to multiples that do not apply to singletons that could be considered subcategories within the multiples phenotype, including vanishing twin, twin/twin transfusion, fetal demise of 1 of multiples, and the type of placentation. These characteristics could be considered fetal and placental conditions in association with the multiples phenotype.

What should the definition of indicated and spontaneous births be and how do we draw a distinction between them?

The most common classifications divide all live born preterm births into sponta-

neous vs indicated deliveries.²⁸⁻³³ However, review of papers using these categories reveals that these terms are neither well defined nor consistently used. An indicated preterm birth is often defined as one that occurred because continuation of the pregnancy risked the health of the mother and/or fetus, but the degree of risk is variably defined, affected by local circumstances, and may arise from a complication of pregnancy that had a “spontaneous” onset (eg, infection after ruptured membranes). Thus, these terms need further exposition for any classification system to be acceptable to most users. We believe that coming to a clear consensus on this issue is one of the most important requirements to create a widely accepted classification system.

How do we classify P-PROM, spontaneous dilation, and bleeding?

Classification of preterm (<37 weeks) premature (before the onset of labor) rupture of the fetal membranes (P-PROM) is a particularly difficult issue.^{31,34} Most women with confirmed P-PROM enter spontaneous preterm labor within several hours or days, depending on the gestational age and cause of rupture, but some remain undelivered for many days without infection or other complications. In women who do not labor spontaneously, labor might be induced or a cesarean delivery performed for many reasons, most commonly because of clinical or laboratory evidence or fear of infection. Should births in the latter category be classified as “indicated” (because the mothers were not in spontaneous labor), or instead be classified as “spontaneous” (because the process that led to the preterm delivery—the P-PROM—was spontaneous)? To understand preterm birth, it seems clear that the phenotypic classification system should include information about the presentation at delivery, and this would include P-PROM, regardless of whether it was followed by spontaneous labor or an induction. Forcing it into a spontaneous or indicated category will likely reflect a physician management decision and, thus would not help to define a preterm birth phenotype.

A spontaneously dilating cervix without contractions may lead to delivery

with few or no contractions, usually at early gestational ages. At later—but still preterm—gestational ages, the finding of advanced cervical dilatation may be followed by a cesarean delivery because of fear of spontaneous membrane rupture, followed by head entrapment in cases of breech presentation or a prolapsed cord. In both instances, parturition is present without any indication of active labor. Should these cases be classified as spontaneous, because the dilation occurred spontaneously, or as indicated, because active labor was not present? As with P-PROM, for the purposes of phenotypic classification, the important information is that the patient presented with a dilated cervix, not that she be forced into a specific spontaneous or indicated category. These discussions suggest that categorical assignment of all preterm births into one of the traditional categories as spontaneous or indicated contributes to confusion rather than clarity in the creation of a useful classification system.

Similar issues arise when bleeding is the initial or dominant manifestation of parturition. Bleeding may be associated with a placental abruption, placenta previa, or no obvious pathology. Each condition may have different bleeding patterns in timing and volume over the course of pregnancy. As with P-PROM, induction of labor, or cesarean birth for bleeding because of an ongoing abruption or a placenta previa might be classified as a spontaneous or indicated preterm birth. Because there was no labor and delivery was accomplished after a prelabor cesarean delivery or induction of labor, the preterm birth could be considered medically indicated. Conversely, should it be considered spontaneous, because the precipitating event followed a spontaneously occurring maternal condition? The discussion surrounding this issue again led the authors to conclude that attempts to assign preterm births related to bleeding into spontaneous and indicated groups would be artificial. Women who present for delivery with bleeding, either with an abruption or a previa or without a clearly defined cause, can be characterized phenotypically as having one of those clinical con-

ditions, as well as having either signs of spontaneous initiation of parturition (contractions, cervical effacement, or P-PROM) or a nonspontaneous initiation of parturition (induction or prelabor cesarean birth). This discussion emphasized the need for the classification system to have several potential phenotypic components, including the maternal condition, the fetal condition, and the presentation at delivery.

How should we define and classify indicated preterm births?

For this classification system, maintenance of the existing terminology related to what are customarily called indicated preterm births, proved confusing.³⁵⁻³⁷ Thus, we chose to define a category of (indicated) preterm birth as one in which parturition was *initiated* by the caregivers. This designation would apply to a preterm birth in which there was no evidence that any part of the parturitional process had begun (ie, little cervical shortening or effacement and no fluid leakage, persistent contractions or bleeding, and specifically, little likelihood that birth would have occurred within the next several days, unless initiated by the obstetric care giver).

However, even if this definition is accepted, other questions remain. For example, should medically indicated preterm births be defined as those following a cesarean delivery or induction of labor only for urgent maternal or fetal indications (eg, clearly defined maternal or fetal distress as evidenced by severe preeclampsia or a dangerously abnormal fetal heart rate pattern)? If so, how do we classify physician-initiated deliveries with “softer” indications, such as mild preeclampsia or mild fetal growth restriction, in which there is clearly some discretion in timing of the delivery? Are these preterm births as “indicated” as those in the prior group, or should we call these deliveries “discretionary”? What are the threshold events that demarcate the boundary between indicated and discretionary, and how are they affected by the gestational age and availability of neonatal care?³⁸

Classification of scheduled births before 39 weeks that lack any obvious med-

ical indication, regardless of the mode of delivery, is also an issue of recent concern.³⁹ Should these still be considered “indicated,” because the physician chose to deliver and there was no spontaneous maternal process leading to labor or delivery? Should these be called “iatrogenic” or designated as being performed for “social reasons”? In any case, we agreed that, for this classification system, provider initiated deliveries be subdivided into 3 or 4 groups, with headings such as urgent, discretionary, iatrogenic, and/or social.

There were a number of remaining questions. For example, how do we classify preterm deliveries where the mother entered the hospital before term with contractions or slight cervical change but without active labor? If her labor was “augmented” by amniotomy or oxytocin or a cesarean birth performed, is this to be categorized as a spontaneous preterm birth or an indicated, discretionary, or iatrogenic preterm birth? For the classification system, we must be able to distinguish between (1) essentially social or convenience inductions of labor in women with minimal signs of active labor and (2) appropriate augmentation of spontaneous dysfunctional labor. Thus, an important issue is whether the classification system should attempt to determine the reason and perhaps appropriateness for the physician’s decision to initiate delivery? We agree that both the type of indication, such as urgent, discretionary, and iatrogenic or social, and the medical or social conditions leading to the decision to initiate a preterm delivery should be captured in this classification system.

Other important issues

At times, signs of spontaneous parturition will occur in pregnancies complicated by preeclampsia, maternal illness, fetal growth restriction, and fetal distress, although these conditions might not be part of another obvious phenotype that led to the preterm birth.⁴⁰ If preeclampsia is present in a preterm birth that follows spontaneous onset of labor, should this birth be still be classified as a spontaneous preterm birth? We agree that these births should still be clas-

sified as having signs of spontaneous parturition, but the type of information discussed previously should be collected, as it will allow an examination of the link between various maternal and fetal conditions and different preterm delivery presentations.

Another important issue is how to best integrate placental pathologic and other laboratory information into a classification system based on phenotype. For the placenta, if histologic chorioamnionitis, signs of abruption, or of placental dysfunction (as might be indicated by large areas of infarction or necrosis) are present, how should these findings affect the classification? For laboratory tests, would an elevated white count or a positive blood or amniotic fluid culture be included in an infection-related phenotype? These questions must also be considered before a classification system can be developed. Discussion surrounding this issue led us to recommend that the placental findings be included as part of the phenotype of preterm birth with 4 potential components: infection, hemorrhage, infarction, or no pathology. Important laboratory findings, such as evidence of infection/inflammation on amniocentesis, would become part of the phenotype within the category on important maternal pregnancy-related conditions.

In this study, we use polyhydramnios as an example of how the classification system might work. Women with apparently similar degrees of polyhydramnios may present with spontaneous contractions, develop P-PROM, or dilate their cervix.⁴¹ Still others will be induced or undergo cesarean delivery performed for fear of prolapsed cord or a ruptured uterus. In discussing whether all such cases should be considered spontaneous because the process started with a maternal or fetal condition or whether the spontaneous classification should be reserved for only those cases that presented with contractions or P-PROM, it became clear that the classification system should capture the presence of polyhydramnios, the presence or absence of a fetal anomaly, whether there was evidence of spontaneous parturition, and if not, whether the physician initiated de-

livery was urgent, discretionary, or iatrogenic. A classification system with these characteristics would allow analysis of all cases of polyhydramnios, for example, as a single group, regardless of whether the woman presented for delivery with P-PROM, labor, a spontaneously dilated cervix, or for one of many reasons was induced, had a termination, or had a cesarean birth before the appearance of signs of spontaneous parturition.

This discussion also led us to add a fourth component to the classification system, one dealing with the fetal condition. Thus, the presence of a fetal demise, fetal distress, fetal growth restriction, a congenital anomaly, multifetal pregnancy, and poly- or oligohydramnios may influence when a delivery occurs and should be included in the fetal component of the classification system.

Definitions

For this classification system to achieve its goals, virtually all of the maternal and fetal conditions, presentations at delivery, and placental findings that may comprise a phenotype must be rigorously defined. For example, how much hydramnios must occur and when must it occur for polyhydramnios to be considered a component of the phenotype of a preterm birth?

Moving toward a classification system

From the foregoing discussion, the issues and components of a preterm birth phenotypic classification system are coming more clearly into focus. After much discussion, we agree that a preterm phenotype could be defined as having the following 4 components: (1) the presence of important maternal pregnancy related conditions; (2) important fetal conditions; (3) clinical presentation for delivery, including evidence of spontaneous parturition; and (4) placental findings. Risk factors for preterm birth, such as smoking, could be collected but would not be part of the phenotype. We recognize that the dividing line between significant maternal conditions and maternal risk factors is not always clear and that various characteristics might be put in one or the other category with some degree of arbitrariness. The use of the words “spontaneous” and “indicated” to

categorize the presentation for delivery have not been used in a consistent fashion and would be better replaced by less confusing, more descriptive terms. Nevertheless, by carefully defining the presentation for delivery, the concept of 2 broad categories of preterm births—those following spontaneous signs of parturition and those cases where there was none—should be retained, with cases where the birth process is of maternal/fetal origin, including shortening cervix, P-PROM, contractions, and bleeding classified as spontaneous. All other births in which delivery would likely not have happened within several days without the intervention of a caregiver, should be placed in the second, provider-initiated group. Several broad categories of maternal conditions should be noted as part of the phenotypes, usually based on information available before presentation for delivery, including clinical categories, such as shortened cervix and polyhydramnios.

Conclusions

Preterm birth is a syndrome defined by time and clearly is not a distinct clinical phenotype. Births at gestational ages less than 20 weeks and many of those at 37 and 38 weeks share with births at 20–36 weeks several etiologic and prognostic features that suggest these boundaries are artificial and therefore, should be reconsidered.^{2–15,42,43} Because the cause of many preterm births is unknown, we also believe that, at least for the near future, preterm birth classification systems will need to focus on phenotype rather than suspected cause. These phenotypes, whenever possible, should be based, at least in part, on maternal and/or fetal antecedent events, such as a shortening cervix or fetal death, with the understanding that presentation at delivery, including P-PROM, bleeding, contractions, or cervical dilation, may all be symptoms of the underlying process and may not be primary in determining or labeling the pathway leading to the preterm delivery. Finally, when the caregiver initiates a preterm delivery, a distinction should be made between cases in whom such interventions are clearly indicated, those in whom the timing of intervention is discretionary, and those

without a clinical indication. Thus, creating a classification system for preterm birth involves making many choices, some of which are clearly controversial. The issues described in this article are some that should be considered in creating a classification system for preterm birth phenotypes. ■

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