The preterm birth syndrome: a prototype phenotypic classification

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Preterm birth is a syndrome with many causes and phenotypes. We propose a classification that is based on clinical phenotypes that are defined by ≥1 characteristics of the mother, the fetus, the placenta, the signs of parturition, and the pathway to delivery. Risk factors and mode of delivery are not included. There are 5 components in a preterm birth phenotype: (1) maternal conditions that are present before presentation for delivery, (2) fetal conditions that are present before presentation for delivery, (3) placental pathologic conditions, (4) signs of the initiation of parturition, and (5) the pathway to delivery. This system does not force any preterm birth into a predefined phenotype and allows all relevant conditions to become part of the phenotype. Needed data can be collected from the medical records to classify every preterm birth. The classification system will improve understanding of the cause and improve surveillance across populations.

Key words: phenotype, preterm birth

The epidemiologic factors, consequences, and suggested preventive strategies for preterm delivery have been reviewed extensively.[1-3] In these and other articles, it is recognized increasingly that our understanding of preterm delivery has been limited by the failure to accept the idea that preterm birth is a syndrome with a number of etiologic factors and phenotypic characteristics, many of which are independent of each other.[4-6] "What seems certain is that any progress in our understanding and prevention of preterm birth requires acknowledgement that it is not one disease with a single solution or cure, but rather the product of overlapping factors."[7]

As shown in the first 2 articles of this series, other than the categorization by gestational age, there are considerable challenges when one moves to classify cases of preterm birth by any system, including cause or phenotype.[8,9] The authors of this series were brought together as a direct result of the Global Alliance to Prevent Prematurity and Stillbirth meeting in 2009 with instructions to determine the need for such a classification system, to define the issues that are related to creating a preterm birth classification system, and to present a prototype classification system. The aim of this article is to propose a classification system for clinical and research purposes for general consideration.

The preterm birth phenotype

A *phenotype* can be defined as "any observable characteristic or trait of an organism such as its morphology, development, biochemical or physiological properties, or behavior. Phenotypes of a disease result from the expression of an organism's genes, as well as the influence of environmental factors and often interactions between the two."[10] In relationship to preterm birth, environmental factors might include exposure to infectious organisms, toxins, or stressful events. However, it is extremely unlikely that a single gene will be identified as responsible for more than a few cases of preterm birth. The inconsistencies that are reported in genetic studies could be explained by the involvement of multiple genes that leads to a

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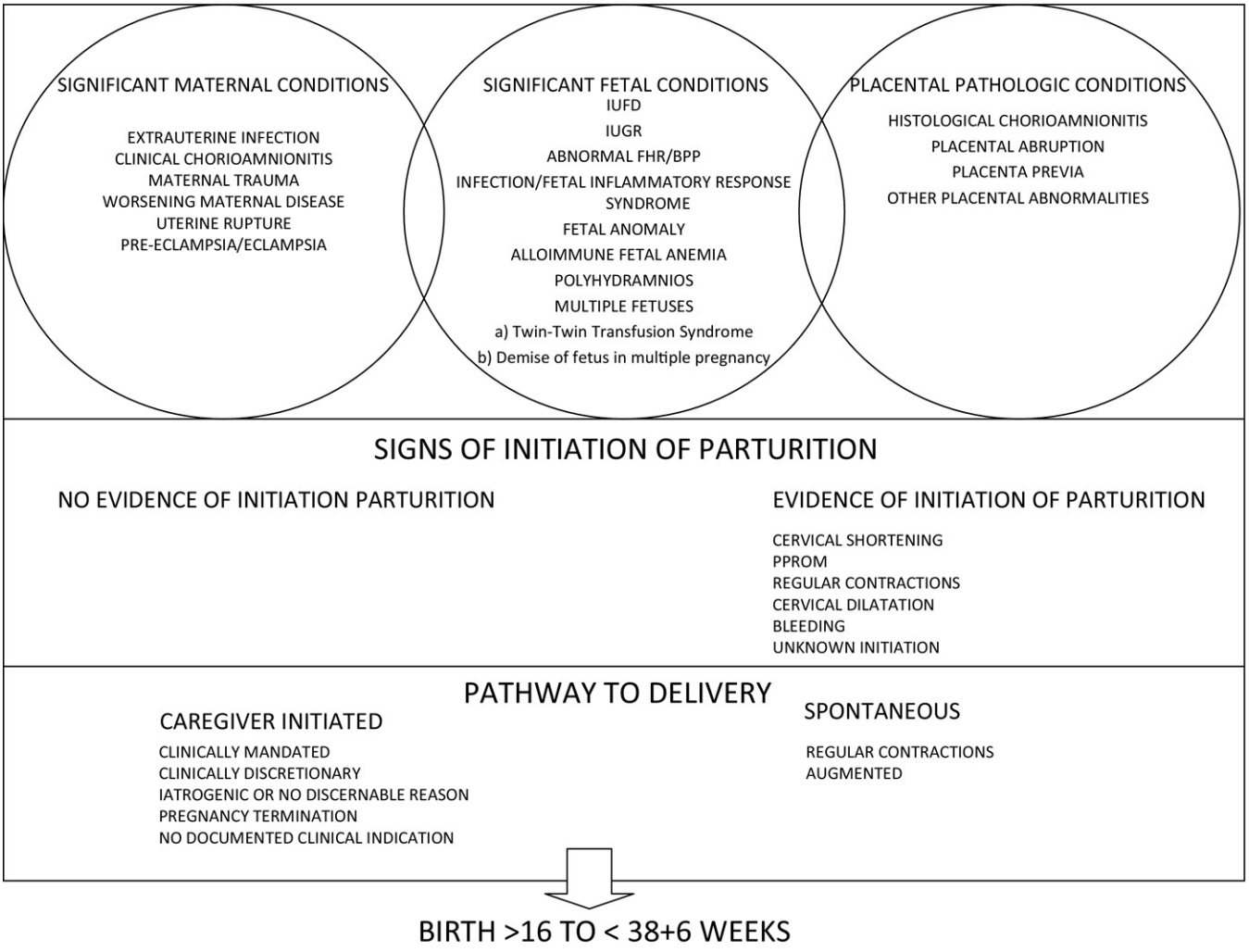
FIGURE
Phenotypic components of the preterm birth syndrome



BPP, biophysical profile; *FHR,* fetal heart rate; *IUGR,* intrauterine growth restriction; *PPROM,* preterm premature rupture of membranes.
Villar. The preterm birth syndrome. Am J Obstet Gynecol 2012.

wide range of phenotypic expression. Based on current knowledge, a specific cause is hard to discern for most cases of preterm birth. The authors therefore have decided that, at the present time, the most useful classification of preterm births would be by phenotype. However, because of its heterogeneous etiologic, pathophysiologic, and parturition event sequence, preterm birth is a "complex phenotype."[11] If and when specific phenotypes within the preterm birth syndrome are agreed on more universally, causes and appropriate preventive interventions can be developed for each preterm birth phenotype.

How the collected data are used to drive the new classification

Referring to discussions in the first 2 articles of this series, we shall consider as a preterm birth any birth (which includes stillbirths and pregnancy terminations) that occurs after 16 weeks' gestation and before term (ie, 39 weeks' gestation). The complete population of preterm deliveries within the gestational range as described earlier includes live births, stillbirths, multiple pregnancies, pregnancy terminations, and newborn infants with congenital malformations. The proposed classification is based on clinical phenotypes that are defined as ≥1 characteristics of the mother, fetus, and placenta, the presence or absence of signs of parturition, and the pathway to delivery (Figure).

The phenotypic classification does not include risk factors for preterm birth. We have adopted the concept of including only conditions that are found in the index pregnancy. For example, previous preterm birth is considered a risk factor and not a phenotype of the preterm birth under consideration. We recognize, however, that this is a complex issue and that when and how a risk factor becomes a phenotype needs further evaluation. How these permutations of risk factors and significant conditions relate to clinical phenotypes

should be explored during validation of our classification.

Finally, it is recognized that, in any single case, >1 phenotype may exist because of overlapping conditions or presentations. We expect that, with more advanced diagnostic methods or a better understanding of the parturition process, it may become possible to reduce such overlaps.

We have identified 5 components that should be part of any preterm birth phenotype: (1) significant maternal conditions that are present before presentation for delivery, (2) significant fetal conditions that are present before presentation for delivery, (3) placental pathologic conditions that are associated with preterm birth, (4) signs of the initiation of parturition, and (5) the pathway to delivery (Figure). We believe that these 5 components can be used to classify every preterm birth and that the data could be collected on a short standard form with the use of routine medical records.

We envision using this classification system in the following manner: When all appropriate data are at hand, the classifier will note which, if any, of the maternal, fetal, or placental conditions on the lists were present. The requirement that the placentas of all preterm births be studied both macro- and microscopically may be a challenge in many settings and could be included initially in the context of research projects. The classifier will then note and describe, if possible, which (if any) signs of initiation of parturition were present or no evidence of initiation of parturition. Furthermore, a judgment about the pathway to delivery will be made; if the pathway was caregiver initiated, a judgment will be made about whether the delivery was mandated clinically, clinically discretionary, no documented clinical indication to suggest that it was initiated for social reasons, or no discernible reason for "iatrogenic" delivery. The decision to terminate the pregnancy will also be noted (Figure).

Preterm birth phenotypes that can be identified by the 5 components

The preterm birth phenotypes can best be illustrated by several examples:

Example 1

A patient delivered at 29 weeks' gestation might have an abnormal fetal heart rate (from the fetal list), evidence of abruption (from the placental list), no signs of spontaneous parturition, with a pathway to delivery that was initiated by the provider because of fetal distress and suspected abruption.

Example 2

A case of preterm birth at 32 weeks' gestation might include polyhydramnios and esophageal atresia (from the fetal list) and no finding from the placental or maternal lists. There might be signs that there were spontaneous initiation of parturition and that the pathway to delivery was judged spontaneous.

Example 3

A case of preterm birth at 30 weeks' gestation might include, from the maternal list: no conditions; from the fetal list: no conditions; from the placental list: no conditions. Signs of spontaneous parturition (eg, cervical shortening, contractions, bleeding) were noted, and the pathway to delivery was judged spontaneous.

Example 4

A case of preterm birth at 33 weeks' gestation might include no conditions (from the maternal list), no conditions (from the fetal list), and chorioamnionitis (from the placental list). Signs of spontaneous parturition were noted, and the pathway to delivery was judged spontaneous.

Example 5

Finally, a preterm birth case at 37 weeks' gestation with no maternal, fetal, or placental conditions and with no evidence of spontaneous parturition was delivered by cesarean section by maternal request because of an "extremely valuable fetus."

What became obvious as we developed these and other examples is that a large number of scenarios could be created. This finding emphasizes the fact that we are dealing with many potential phenotypes and also explains the reason that it has been so difficult to develop a simple, but useful, classification system. Attempts in the past to simplify the categorization (such as splitting all preterm births into spontaneous and indicated groups) were easy to adopt but have not proved particularly useful in the identification of causes or preventive interventions. It is for this reason that the proposed system should improve the specificity of each preterm birth phenotype. Defining each phenotype by the presence or absence of maternal, fetal, and placental conditions, signs of parturition, and a pathway to delivery provides more of that specificity. Not requiring the 5 components to be linked a priori to a single phenotype means that this classification system does not require any particular case to be forced into a predefined phenotype and allows all the relevant conditions that are present to become part of the phenotype. We understand the temptation to make the classification more manageable by reducing the number of phenotype categories; however, at present we believe such "lumping" will lessen our ability to have a clear understanding of the contribution of specific phenotypes to the overall picture of preterm birth and ultimately will hinder our efforts to determine causes and to develop effective preventive interventions.

The way forward: empiric validation of the new system

Until this classification system actually is used in practice, we will not know for certain whether several phenotypes predominate. But we suspect that only a small number will be relatively common. For example, a common phenotype will likely be 1 with no maternal or fetal conditions but with placental inflammation and signs of spontaneous parturition. Another will be similar but with no placental inflammation. Therefore, the next step would be to categorize a large number of preterm births with this system to compare the approximate frequency of different preterm birth phenotypes in various clinical settings.

We believe that this classification system should now be piloted and altered as necessary and that a final version should be agreed on by those healthcare practitioners who are interested in preterm birth. When the system is used, each of the components

must have a clear and accepted definition so that comparisons can be made between users; a list of working definitions is provided in the Appendix for this initial phase. Future etiologic studies can examine whether the categories show robust specificity for genetic and environmental risk factors. The system may also be useful for surveillance across populations and to explain variations in time and place overall and among phenotypes of preterm birth. The classification system presented here should facilitate the comparisons and metaanalysis of data from different institutions and countries and should help us to understand differences between populations.

Research implications of the use of a phenotypic classification system of preterm birth

It is important to consider the implications for study design, sample size calculations, and data analysis for the use of the identified phenotypes of preterm birth as outcome measures in randomized controlled trials and epidemiologic studies. When focusing on a given phenotype, it is expected that its incidence will be considerably lower than the total preterm delivery rate or even the "spontaneous" preterm delivery rate. This has major implications for sample size and statistical power, which may explain the reason that many previous epidemiologic and intervention studies have used the total preterm delivery rate as the primary outcome measure. In any case, the balance between incidence and specificity should be considered carefully when one is designing future studies of preterm birth. Finally, data that are collected from studies of preterm birth should be standardized ideally to include the relevant covariates on which data should be ascertained.

In summary, the use of the new classification system should lead to the following improvements: (1) clarification of the phenotypes of preterm birth, (2) the conduct of meaningful comparisons of preterm birth incidence (overall and by phenotype) between different locations and institutions, and (3) assurance that studies of preterm birth cause (genetic or environmental) and interventions are based on consistent phenotypes. ■

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APPENDIX

Definitions

Significant maternal conditions

Extrauterine infection. Significant maternal infective illness that is associated with pyrexia and the corresponding clinical manifestations (eg, bacteremia, malaria, and pyelonephritis).

Clinical chorioamnionitis. Clinically suspected intrauterine infection, manifest by maternal fever and rupture of the membranes, plus 2 features from maternal tachycardia, uterine tenderness, purulent amniotic fluid, fetal tachycardia, and maternal leukocytosis.

Maternal trauma. A serious or critical bodily injury, wound, or shock (in turn defined as a failure of the circulatory system to maintain adequate blood flow.

Worsening maternal disease. Examples include worsening maternal cardiac, respiratory, or renal disease or hemodynamic instability that poses immediate, significant, or life-threatening risk to the mother/fetus.

Uterine rupture. A defect that occurs in the uterus and that involves the entire uterine wall; this is symptomatic and requires surgical intervention.

Preeclampsia. Gestational hypertension with proteinuria of ≥300 mg in a 24-hour period or 2 readings of at least "++" on dipstick analysis of midstream or catheter urine specimens, if no 24-hour collection is available.

Eclampsia. Convulsions (seizures) that occur in the presence of preeclampsia and have no other cause.

Significant fetal conditions

Antepartum intrauterine fetal death. Intrauterine fetal death before the onset of labor (we recognize that, in some cases, it will be difficult to distinguish between recent antepartum and intrapartum deaths; however, in the consideration of the etiologic differences, efforts must be made to establish the timing of the death).

Intrauterine growth restriction. Growth restriction (estimate fetal weight <10th percentile) with abnormal umbilical artery blood flow, abnormal fetal heart rate, or abnormal biophysical profile.

Abnormal fetal heart rate. Antepartum persistently reduced short-term variability or decelerations.

Abnormal biophysical profile. Biophysical profile of ≤6/10.

Infection. Usually the presence of clinical chorioamnionitis with fetal tachycardia or neonatal sepsis.

Fetal inflammatory response syndrome. Systemic fetal inflammation and elevated fetal plasma interleukin-6 levels.

Invasive intrauterine procedures. Invasive procedures that include prenatal diagnosis (eg, amniocentesis, chorionic villus sampling), fetal blood sampling, and endoscopic procedures (eg, laser ablation of placental vessels, fetoscopy).

Multiple fetuses. Multiple pregnancy, subdivided into the number of fetuses and by chorionicity: (1) twin-twin trans-

fusion syndrome, at any stage that is diagnosed on ultrasound scanning; (2) death of a fetus in multiple pregnancy; intrauterine death of ≥1 of the fetuses with live co-multiple fetuses that is confirmed by ultrasound scanning.

Fetal anomaly. Fetal structural abnormality by ultrasound scanning or during neonatal examination.

Fetal anemia. Fetal anemia that is caused by immune factors that are suggested by (1) hematocrit or hemoglobin concentration >2 SD below the mean for gestational age or (2) middle cerebral artery Doppler peak systolic velocity of >1.5 multiples of the median.

Polyhydramnios. Excess amniotic fluid subjectively or objectively that is measured as amniotic fluid index above the 95th percentile for gestational age or a maximum vertical pool of at least 8 cm.

Oligohydramnios. Reduced amniotic fluid subjectively or objectively measured as amniotic fluid index below the 5th percentile for gestational age or a maximum vertical pool of <2 cm.

Placental conditions

Histologic chorioamnionitis. The presence of inflammatory infiltrate of neutrophils in the chorionic plate and extra placental membranes. (The *inflammation of amnion and chorio-decidua* is defined as the presence of at least 1 focus of >5 neutrophils and is considered as severe inflammation if there is diffuse neutrophil infiltration. The *inflammation of the chorionic plate* is defined as the presence of at least 1 focus of ≥10 neutrophil foci or diffused inflammation in the subchorionic fibrin and is considered to be severe inflammation if there is diffuse and dense infiltration of neutrophils into the connective tissue of the chorionic plate, or placental vasculitis.)

Histologic evidence of vasculitis/infarction/necrosis.

Other histologic/microscopic findings (eg, villitis, thrombosis).

Abruption. Premature separation of the placenta from the uterine wall that is diagnosed by a combination of vaginal bleeding, maternal abdominal pain, and retroplacental blood clot at delivery.

Placenta previa. Implantation of the placenta over the internal os of the cervix.

Fetal-Maternal Hemorrhage. Evidence of fetal-maternal hemorrhage on the Kleihauer test.

Other placental abnormalities. Placental abnormalities that may lead to or necessitate delivery (eg, placental giant chorioangioma, circumvallate placenta).

Evidence of parturition

Cervical shortening. Shortening of the uterine cervix on clinical and/or ultrasound examination.

Preterm prelabor rupture of the membranes. Rupture of the amniotic membranes before the onset of labor at <39 weeks' gestation

Regular contractions. Regular uterine contractions that lead to cervical effacement or dilation.

Cervical dilation. Dilation of the uterine cervix on clinical examination.

Bleeding. Any evidence of bleeding from the uterus or cervix.

Unknown initiation. Cases in which it is not possible to establish the initial step in the parturition process.

Pathway to delivery

Caregiver initiated

Clinically mandated. Cases in which the caregiver initiates delivery because there is an immediate and significant or life-threatening risk to the mother/fetus (eg, preterm delivery for severe maternal preeclampsia).

Clinically discretionary. Cases in which the caregiver initiates delivery although there is no immediate or significant risk to the mother/fetus but in which there may be some evidence that delivery may be associated with a better outcome.

No clinical indication. Cases in which the caregiver initiates delivery for reasons (such as errors in gestational age estimation, convenience of timing, precious fetus, maternal request) that were stated on or inferred from the medical records.

Pregnancy termination. Cases in which termination is caused for reasons such as fetal abnormality, medical contraindication to pregnancy, or maternal request.

No discernable reason. Cases in which the caregiver initiates delivery, but there is no documentation of any indication or supporting information of any indication, including a range of several less-well understood social and personal factors that are seldom documented that could motivate a preterm birth.

Spontaneous

Regular contractions. Regular uterine contractions that lead to cervical effacement or dilation.

Augmented. Augmentation or stimulation of uterine contractions by oxytocin without spontaneous contractions.