Original Investigation

# The Distribution of Clinical Phenotypes of Preterm Birth Syndrome
## Implications for Prevention

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**IMPORTANCE** Preterm birth has been difficult to study and prevent because of its complex syndromic nature.

**OBJECTIVE** To identify phenotypes of preterm delivery syndrome in the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.

**DESIGN, SETTING, AND PARTICIPANTS** A population-based, multiethnic, cross-sectional study conducted at 8 geographically demarcated sites in Brazil, China, India, Italy, Kenya, Oman, the United Kingdom, and the United States. A total of 60 058 births over a 12-month fixed period between April 27, 2009, and March 2, 2014. Of these, 53 871 had an ultrasonography estimate of gestational age, among which 5828 were preterm births (10.8%). Pregnancies were prospectively studied using a standardized data collection and online data management system. Newborns had anthropometric and clinical examinations using standardized methods and identical equipment and were followed up until hospital discharge.

**MAIN OUTCOMES AND MEASURES** The main study outcomes were clusters of preterm phenotypes and for each cluster, we analyzed signs of presentation at hospital admission, admission rates for neonatal intensive care for 7 days or more, and neonatal mortality rates.

**RESULTS** Twelve preterm birth clusters were identified using our conceptual framework. Eleven consisted of combinations of conditions known to be associated with preterm birth, 10 of which were dominated by a single condition. However, the most common single cluster (30.0% of the total preterm cases; n = 1747) was not associated with any severe maternal, fetal, or placental condition that was clinically detectable based on the information available; within this cluster, many cases were caregiver initiated. Only 22% (n = 1284) of all the preterm births occurred spontaneously without any of these severe conditions. Maternal presentation on hospital admission, newborn anthropometry, and risk for death before hospital discharge or admission for 7 or more days to a neonatal intensive care unit, none of which were used to construct the clusters, also differed according to the identified phenotypes. The prevalence of preterm birth ranged from 8.2% in Muscat, Oman, and Oxford, England, to 16.6% in Seattle, Washington.

**CONCLUSIONS AND RELEVANCE** We identified 12 preterm birth phenotypes associated with different patterns of neonatal outcomes. In 22% of all preterm births, parturition started spontaneously and was not associated with any of the phenotypic conditions considered. We believe these results contribute to an improved understanding of this complex syndrome and provide an empirical basis to focus research on a more homogenous set of phenotypes.

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Preterm birth (<37 completed weeks' gestation) is the leading cause of perinatal mortality worldwide, and the second largest cause of deaths for children younger than 5 years.[1,2] Global estimates suggest that preterm birth is more prevalent than previously estimated[3,4] and increasing, especially in some developed countries.[5,6] In 2010, an estimated 14.9 million babies were born preterm, 11.1% of all live births worldwide.[2]

However, preterm birth is a complex syndrome[7,8] with multiple etiological factors requiring different preventive strategies.[6] Hence, interventions have had limited effect because each only improves outcomes in a subset of cases.[9]

To promote more targeted interventions, we have proposed subclassifying preterm birth syndrome based on separate phenotypes that have 5 components: (1) maternal conditions before presentation for delivery, (2) fetal conditions before presentation for delivery, (3) placental pathologies, (4) signs of initiation of parturition, and (5) pathway to delivery. Risk factors and mode of delivery are not included. This system does not force preterm births into predefined phenotypes and allows all relevant conditions to be part of the phenotype.[10-12]

To identify these new phenotypes, we prospectively enrolled all deliveries among 8 geographically demarcated populations into the Newborn Cross-Sectional Study (NCSS), one component of the INTERGROWTH-21st Project.[13-15]

## Methods

### Study and Participant Descriptions

A detailed description of the study appears elsewhere.[13] In brief, the NCSS was a multicenter, multiethnic, population-based study conducted between April 27, 2009, and March 2, 2014, in the cities of Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, England; Seattle, Washington; Shunyi County, a suburb of Beijing, China; Central Nagpur, India; and Parklands suburb, Nairobi, Kenya. The 27 participating institutions (41% tertiary, 52% secondary, and 7% primary care) covered more than 80% of all deliveries in each urban area. Data collection continued for 12 consecutive months at each site or until the target of more than 7000 deliveries per site was attained.

The Oxfordshire Research Ethics Committee C (08/H0606/139) approved the study protocol, as well as the research ethics committees of participating institutions and corresponding health authorities. Oral consent was obtained from parents/guardians.

Gestational age was estimated at the first antenatal visit by performing an ultrasonographic examination to measure fetal crown-rump length at $9^{+0}$ to $13^{+6}$ weeks' gestation or head circumference at a later visit. These estimates were used to define preterm birth between 16 and 24 weeks' gestation.[10,12,16] If the scan was performed at more than $24^{+0}$ weeks' gestation, the estimate was considered reliable only if it was within 1 week of the gestational age based on the last menstrual period.[17]

Information about maternal clinical and demographic characteristics and the pregnancy/delivery outcomes were obtained from medical records, health care providers, and mothers, if records were incomplete. All newborns, including those admitted to the neonatal intensive care unit (NICU), special care, or another referral-care level, were assessed daily until hospital discharge to document mortality and morbidity. All data were entered locally directly onto a web-based system; the averages of repeated anthropometric measures were used in the analyses. A detailed description of the data monitoring, quality-control system, and data reliability appears elsewhere.[18]

Preterm phenotypes were classified using a new conceptual framework[12] based on severe maternal, fetal, and placental conditions causally associated with preterm birth (**Table 1**). Information about cervical length and dilation (signs of initiation of parturition) was unavailable; therefore, we evaluated signs of presentation on hospital admission: (1) regular contractions only; (2) preterm prelabor rupture of membranes (PPROM) with or without regular contractions; (3) bleeding with or without PPROM; and (4) no documented record of initiation of parturition. The last cases were considered caregiver initiated through labor induction/cesarean delivery. Caregiver-initiated cases were subdivided based on the indication for induction/cesarean delivery into (1) *mandatory*, if based on 1 or more diagnoses: vaginal bleeding, antepartum fetal distress, fetal death, severe pre-eclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome or (2) *discretionary* for any of the following indications: pregnancy-induced hypertension, nonsevere pre-eclampsia, suspicion/diagnosis of intrauterine growth restriction (IUGR), fetal anomaly, fetal hemolytic disease, sexually transmitted disease including human immunodeficiency virus/AIDS, any infection requiring treatment, or any other maternal/fetal indication not in the data collection form (eg, gestational diabetes). Cases with PPROM induced for that indication were not considered caregiver initiated but were classified as PPROM with or without contractions. We had no information on maternal trauma, invasive intrauterine procedures, and polyhydramnios. We recognized that some discretionary conditions at diagnosis could have become mandatory had the pregnancy continued.

We considered as *iatrogenic* any preterm birth if the caregiver induced labor or performed a cesarean delivery for maternal request, breech presentation, cephalopelvic disproportion, or previous cesarean delivery without another clinical indication. Finally, we created a *no discernible reason* category in caregiver-initiated cases without mandatory, discretionary, or iatrogenic causes. The rationale appears elsewhere.[10] This proposed framework[10-12] excluded upstream determinants lacking a clear biological pathway (eg, socioeconomic status, race/ethnicity, or parity).

Newborn anthropometric measures were obtained within 12 hours of birth using standardized procedures based on World Health Organization recommendations[19] and identical equipment.[20] The detailed methods appear elsewhere.[21] All neonatal diagnoses and treatments were standardized,[22] as was neonatal care using a protocol of evidence-based practices.[21,22] Primary perinatal outcomes were NICU admission for 7 or more days and newborn death before hospital discharge.[17] The data

Table 1. Definitions of Maternal, Fetal, and Placental Conditions

| Condition | Definition |
|---|---|
| **Maternal** | |
| Extrauterine infection during the index pregnancy | Presence of at least 1 of the following: malaria, pyelonephritis. sexually transmitted diseases (including syphilis and HIV/AIDS), and other clinically documented infections that required use of antibiotics or other treatments during pregnancy, except when antibiotics were used for PPROM |
| Clinical chorioamnionitis | Cases where antibiotic treatment was specifically indicated for PPROM. Suspected chorioamnionitis cases with intact membranes were not possible to identify in this data set |
| Severe maternal disease clinically active during the index pregnancy | Cases with a relevant clinical condition documented in the medical records in which birth was caregiver initiated because of the severity or complications related to these conditions. This excludes cases in which there was also an obstetric reason for induction/cesarean delivery. Clinical conditions associated with caregiver-initiated preterm birth included diabetes mellitus, thyroid disease, other endocrine diseases, cardiac disease, hypertension previous to pregnancy, chronic respiratory disease (including chronic asthma), renal disease, cancer, lupus erythematosus, any coagulopathy (including falciparum anemia), tuberculosis, severe intestinal malabsorption (including Crohn and celiac diseases), maternal congenital abnormality or genetic disease (eg, cystic fibrosis or cardiac congenital defects), epilepsy, or any other clinical condition that required surgery or referral to specialized care |
| Pre-eclampsia | Defined as elevated blood pressure (≥140/90 mm Hg), 30 mm Hg increase of systolic pressure, or 15 mm Hg increase of diastolic pressure in relation to basal measurements observed at least twice, the interval of the measurements being >4 h but <168 h and proteinuria >2+ by dipstick |
| Eclampsia | Defined as the occurrence of seizures (grand mal type) and/or coma, not related to cerebral problems, in women who presented with signs of pre-eclampsia. Symptoms might have occurred before or during labor or within 48 h after delivery |
| HELLP syndrome | HELLP or any other coagulation abnormalities reported from a pregnant woman with pre-eclampsia or eclampsia |
| **Fetal** | |
| Antepartum stillbirth | All fetal deaths occurring before the clinically reported start of labor |
| Suspicion or diagnosis of intrauterine growth restriction | Suspicion of impaired fetal growth during pregnancy based on ultrasonography examinations or physical examination and specifically stated in the medical record |
| Fetal distress | Diagnosis based on: (1) abnormal antepartum nonstress test reported in the medical record as indication for induction of labor or elective cesarean delivery or (2) severe intrapartum electronic fetal monitoring pattern equivalent to category 3 of NICHD as indication for intrapartum cesarean delivery |
| Fetal inflammatory response syndrome or perinatal sepsis | Signs, symptoms, and laboratory results compatible with perinatal sepsis documented by the neonatologist (systemic illness with bacteremia) |
| Multiple pregnancy | ≥2 Fetuses in the same pregnancy |
| Fetal anomaly | Severe anomalies diagnosed through pregnancy ultrasonography or on neonatal examination |
| Fetal anemia | For example, due to fetal hemolytic disease; Rhesus negative |
| **Placental** | |
| Early bleeding | Vaginal bleeding <$15^{+0}$ weeks' gestation |
| Mid-/late-pregnancy bleeding | Vaginal bleeding ≥$15^{+0}$ weeks' gestation without the diagnosis of pre-eclampsia, eclampsia, or HELLP syndrome |
| Third trimester bleeding and pre-eclampsia | Vaginal bleeding occurring >$27^{+0}$ weeks' gestation in women diagnosed as having severe pre-eclampsia, eclampsia, or HELLP syndrome |

Abbreviations: HELLP, hemolysis, elevated liver enzymes, low platelet; HIV, human immunodeficiency virus; NICHD, National Institute of Child Health and Human Development; PPROM, preterm premature rupture of membranes.

collection system is described elsewhere[18]; the forms and operation manuals are available online (http://www.intergrowth21.org.uk).

## Statistical Analysis

Because many births entailed more than 1 maternal, fetal, or placental condition, we used 2-step cluster analysis to identify phenotypes. This entailed a precluster step to form numerous subclusters with very similar newborns, then a second step to pool the preclusters into the specified number using a hierarchical, agglomerative approach combining individual cases into clusters as different from one another as possible. Between-group linkage was used as the cluster method, with squared Euclidian distance as the interval measure.

This approach was designed to cluster large numbers of cases according to the variables in Table 1. The analyses were

Table 2. Distribution of the 12 Clusters of Preterm Births According to Main Individual Maternal, Fetal, or Placental Conditions

| Cluster | No. (%) | Main Condition (%) | Most Frequent Associated Conditions (%) |
|---|---|---|---|
| 1 | 1747 (30.0) | None | None |
| 2 | 689 (11.8) | Pre-eclampsia (100) | Third-trimester bleeding and pre-eclampsia (72.6), extrauterine infection (28.6), and suspected IUGR (24.4) |
| 3 | 607 (10.4) | Multiple births (100) | Extrauterine infection (21.9) and suspected IUGR (21.3) |
| 4 | 450 (7.7) | Extrauterine infection (100) | Mid-pregnancy bleeding (20.4), chorioamnionitis (12.7), and severe maternal conditions (12.7) |
| 5 | 443 (7.6) | Chorioamnionitis (100) | Multiple births (25.1), perinatal sepsis (14.7), and suspected IUGR (9.7) |
| 6 | 362 (6.2) | Mid-/late-pregnancy bleeding (100) | Chorioamnionitis (21.8), perinatal sepsis (16.0), and multiple births (14.9) |
| 7 | 337 (5.8) | Suspected IUGR (100) | Fetal distress (18.4), severe maternal conditions (18.4), and mid-/late-pregnancy bleeding (7.7) |
| 8 | 319 (5.5) | Perinatal sepsis (68.0) | Congenital anomalies (41.4), multiple births (30.1), and fetal anemia (23.8) |
| 9 | 280 (4.8) | Early bleeding (100) | Multiple births (27.9), extrauterine infection (25.0), and mid-/late-pregnancy bleeding (22.5) |
| 10 | 213 (3.7) | Antepartum stillbirth (100) | Severe maternal condition (23.9), extrauterine infection (13.6), and mid-/late-pregnancy bleeding (13.1) |
| 11 | 200 (3.4) | Fetal distress (100) | Severe maternal conditions (7.5), congenital anomalies (6.5), and chorioamnionitis (4.5) |
| 12 | 181 (3.1) | Severe maternal conditions (100) | Multiple births (28.7), chorioamnionitis (24.3), and congenital anomalies (8.3) |
| All | 5828 (100) | | |

Abbreviation: IUGR, intrauterine growth restriction.

performed with the SPSS (version 19) TwoStep cluster algorithm (IBM), which defines clusters using a model-based distance measure derived from previous approaches.[23-25] The method produces results consistent with other procedures[26] and has been used in several publications.[26-30] We tried a range of cluster number options: a 12-cluster model provided a categorization of phenotypes highly consistent with our a priori conceptual classification.[12]

Cluster quality was assessed based on silhouette measures of cohesion and separation. The value of the silhouette statistic over all data of a cluster reflects how tightly grouped are the observations in that cluster, and the overall average of this measure across the 12 clusters indicates the extent of clustering. Clustering is considered satisfactory if the silhouette statistic is 0.6 or greater on a −1.0 to +1.0 range.[31] To explore the robustness of our cluster analysis, we conducted 5 random selection procedures producing 2 subsamples, each containing approximately half the preterm births, and performed separate cluster analyses in each of these 10 subsamples.

For each cluster, to evaluate their independence as clinical entities, we calculated the admission rates to the NICU for 7 or more days and neonatal mortality with and without adjustment for gestational age and birth weight using multivariable logistic regression models. All analyses were stratified by country.

## Results

From the 60 058 births in the study period, we selected 53 871 (89.7%) with reliable ultrasonographic estimates of gestational age. Of these, 5828 (10.8%) who constituted our study newborns were preterm births (≥$16^{+0}$, <$37^{+0}$ weeks' gestation). The prevalence of all preterm (including multiple) births ranged from 8.2% in Muscat, Oman, and Oxford, England, to 16.6% in Seattle, Washington. eTable 1 in the Supplement shows the mean (SD) values for gestational age, birth weight, birth length, and head circumference. Gestational age and birth weight are also shown stratified; overall, nearly 74% of all preterm babies were between $34^{+0}$and $36^{+6}$ weeks' gestation; 15.2% were less than $32^{+0}$weeks' gestation and 2.3% were less than $24^{+0}$ weeks' gestation. Among the preterm births, the mean (SD) gestational age was 33.8 (3.3) weeks and the mean (SD) birth weight was 2265 (708) g.

**Table 2** summarizes the distribution of preterm births into the 12 clusters identified in the analysis (all row and column percentages for each cluster appear in eTable 2 in the Supplement). The largest cluster (No. 1), comprising 30.0% of all preterm births, had none of the conditions strongly linked with preterm birth in the conceptual framework. Table 2 shows that in 10 clusters, 1 condition dominated the distribution. Thus, in cluster 3, all cases included multiple births, but other related conditions (eg, extrauterine infections and suspected IUGR [defined in the medical records or as the indication for induction of labor/cesarean delivery]) were also observed. Similar patterns occurred in 9 other clusters (eg, in cluster 2, all women selected in the analysis were diagnosed as having pre-eclampsia or eclampsia and a quarter also had suspected IUGR, a condition clinically related to pre-eclampsia).

With the highest neonatal mortality and morbidity, cluster 8 was the only exception to this pattern of clusters being led by 1 dominant factor. It contained a mixture of conditions (eg, multiple births [30%], fetal anemia [24%], and

Table 3. Signs of Presentation on Hospital Admission According to Phenotype Clusters

| Phenotype Cluster | Patients, % | | | | |
|---|---|---|---|---|---|
| | | | | Caregiver Initiated | |
| | Regular Contractions | PPROM ± Contractions | Bleeding ± PPROM | Mandatory or Discretionary | Iatrogenic |
| 1. No severe maternal, fetal, or placental conditions detected (n = 1747) | 56.7 | 16.8 | 0 | 14.5 | 12.0 |
| 2. Mostly pre-eclampsia/eclampsia (n = 689) | 9.3 | 6.7 | 7.7 | 76.3 | 0 |
| 3. Mostly multiples (n = 607) | 39.4 | 13.5 | 4.1 | 43.0 | 0 |
| 4. Mostly extrauterine infections (n = 450) | 30.0 | 30.2 | 20.4 | 19.3 | 0 |
| 5. Mostly chorioamnionitis (n = 443) | 1.6 | 96.8 | 0.7 | 0.9 | 0 |
| 6. Mostly mid- or late-pregnancy bleeding (n = 362) | 0 | 0 | 100.0 | 0 | 0 |
| 7. Mostly suspected IUGR (n = 337) | 27.3 | 5.6 | 7.7 | 59.3 | 0 |
| 8. Mostly mixed conditions (n = 319) | 35.4 | 25.1 | 7.8 | 31.7 | 0 |
| 9. Mostly early bleeding (n = 280) | 27.1 | 22.1 | 22.6 | 28.2 | 0 |
| 10. Mostly stillbirths (n = 207) | 16.9 | 7.7 | 13.5 | 61.8 | 0 |
| 11. Mostly fetal distress (n = 200) | 24.5 | 19.5 | 0 | 66.0 | 0 |
| 12. Mostly severe maternal disease (n = 181) | 0 | 32.6 | 1.1 | 66.3 | 0 |
| All cases (N = 5822) | 30.9 | 21.7 | 11.7 | 32.2 | 3.6 |

Abbreviations: IUGR, intrauterine growth restriction; PPROM, preterm premature rupture of membranes.

suspected IUGR [22%], although 2 were more common [68% had perinatal sepsis, 41% had congenital anomalies, and 50 of 319 had both]).

The column percentages in eTable 2 in the Supplement show the distribution of conditions across clusters. For example, pre-eclampsia/eclampsia cases constituted 100% of cases in cluster 2, representing 99.0% of all pre-eclampsia/eclampsia cases in the overall study. Conversely, although multiple births constituted all 607 cases in cluster 3,there were another 543 in other clusters, mainly in clusters 2 and 5. Stillbirth is another example: although stillbirths constituted all cases in cluster 10 (91.8% of all stillbirths in the sample), a large number were included in cluster 2.

In the third largest cluster (10.4% of all preterm births), all cases were multiple births but other conditions were also present (eg, suspected IUGR and extrauterine infections). The next largest phenotype (cluster 4, 7.7% of all preterm births) comprised all cases with extrauterine infections but also included mid- and late-pregnancy bleeding affecting 20.4% of cases. In cluster 5 (7.6% of all preterm births), all cases presented with chorioamnionitis but 25.1% were also multiple births and 14.7% had perinatal sepsis.

In the sixth largest cluster (6.2% of all preterm births), all cases presented with mid- or late-pregnancy bleeding but a large number also had chorioamnionitis and perinatal sepsis. In cluster 7 (5.8% of all preterm births), all cases had suspected IUGR but 18.4% also had severe maternal disease or fetal distress.

**Table 3** shows the distribution of clinical signs on admission to the hospital across clusters. We separated admission with spontaneous regular contractions from PPROM, although both have similar mechanisms of initiation with a short cervix as a common pathway.[32]

Among women in the cluster with no detected severe maternal, fetal, or placental condition (30.0% of all preterm births), labor was caregiver initiated in 26.5% of cases (12% iatrogenic and 14.5% for an indication not causally linked in the literature and therefore not included in our list). Of the 209 newborns in this iatrogenic group, 201 (96.2%) were more than $34^{+0}$ weeks of gestation at birth, which represented 4.6% of all 4319 late-preterm births. In the remaining 73.5% of the pregnancies in this cluster, regular contractions occurred alone (56.7%) or with PPROM (16.8%). Among these cases (22.0% of all preterm births), 1.3% of those with contractions or PPROM were associated with nonproteinuric gestational hypertension, which we had not considered a severe maternal condition. For the remaining 20.7% of all preterm births, labor was initiated spontaneously without any detected severe maternal, fetal, or placental condition (**Table 4**).

To explore the robustness of our cluster assignment, we conducted separate analyses on 10 randomly selected subsamples, each with about half of all cases. The results pro duced

Table 4. Clinical Characteristics of Preterm Births That Were Not Associated With Severe Maternal, Fetal, or Placental Conditions

| Characteristic | No. of Preterm Births | No. (%) | | Proportion of Total Participants With Spontaneous and/or PPROM and PIH/Others | No. (%) Initiated | |
|---|---|---|---|---|---|---|
| | | Spontaneous and/or PPROM | Spontaneous and PIH/Others | | Due to Clinical Conditions | Iatrogenic |
| Preterms of cluster 1 (no severe maternal, fetal, or placental conditions detected) | 1747 | 1206 (69.0) | 78 (4.5) | 73.5 | 254 (14.5) | 209 (12) |
| All preterms | 5828 | 1206 (20.7) | 78 (1.3) | 22.0 | 254 (4.4) | 209 (3.6) |

Abbreviations: PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes.

Table 5. Gestational Age, Birth Weight, Length, Head Circumference, and Severe Mortality and Morbidity According to Phenotype Clusters and Odds Ratios for Neonatal Mortality[a]

| Phenotype Cluster | Mean (SE) | | | | NICU ≥7 d, % | NMR/1000[b] | Neonatal Death, Odds Ratio (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| | Gestational Age, wk | Birth Weight, g | Length, cm | Head Circumference, cm | | | Adjusted[c] | Adjusted[d] |
| 1. No severe maternal, fetal, or placental conditions detected (n = 1747) | 34.9 (0.07) | 2608 (16) | 46.3 (0.08) | 32.1 (0.05) | 13.9 | 5 | 1 [Reference] | 1 [Reference] |
| 2. Mostly pre-eclampsia/ eclampsia (n = 689) | 33.6 (0.10) | 2019 (24) | 43.7 (0.14) | 30.5 (0.09) | 45.8 | 36 | 7.5 (3.3-17.0) | 2.5 (0.9-7.2) |
| 3. Mostly multiples (n = 607) | 34.4 (0.11) | 2156 (26) | 44.7 (0.14) | 31.2 (0.09) | 31.2 | 24 | 4.8 (2.0-11.6) | 3.4 (1.1-10.2) |
| 4. Mostly extrauterine infections (n = 450) | 34.2 (0.13) | 2456 (31) | 45.9 (0.17) | 31.8 (0.11) | 26.3 | 36 | 7.3 (3.1-17.4) | 3.9 (1.2-12.2) |
| 5. Mostly chorioamnionitis (n = 443) | 33.6 (0.13) | 2217 (30) | 44.6 (0.17) | 31.0 (0.11) | 37.3 | 43 | 9.7 (4.1-23.2) | 3.4 (1.1-10.5) |
| 6. Mostly mid- or late-pregnancy bleeding (n = 362) | 33.2 (0.14) | 2214 (33) | 44.6 (0.19) | 30.8 (0.12) | 38.9 | 27 | 5.3 (2.1-13.7) | 1.7 (0.5-5.8) |
| 7. Mostly suspected IUGR (n = 337) | 34.4 (0.15) | 2062 (35) | 43.8 (0.19) | 30.7 (0.13) | 42.4 | 28 | 5.7 (2.2-15.1) | 3.2 (0.9-11.5) |
| 8. Mostly mixed conditions (n = 319) | 32.6 (0.15) | 1917(36) | 42.8 (0.20) | 29.7 (0.13) | 66.8 | 99 | 20.1 (9.0-44.7) | 4.5 (1.6-12.6) |
| 9. Mostly early bleeding (n = 280) | 33.5 (0.16) | 2222 (38) | 44.4 (0.21) | 30.9 (0.14) | 31.8 | 68 | 14.5 (6.2-34.2) | 3.5 (1.1-11.6) |
| 10. Mostly stillbirths (n = 213) | 26.5 (0.19) | 1141 (49) | 36.9 (0.62) | 27.0 (0.53) | NA | NA | NA | NA |
| 11. Mostly fetal distress (n = 200) | 34.5 (0.19) | 2445 (34) | 45.5 (0.25) | 31.8 (0.16) | 26.6 | 45 | 10.5 (4.0-27.9) | 10.9 (3.1-37.9) |
| 12. Mostly severe maternal disease (n = 181) | 34.4 (0.20) | 2412 (46) | 45.4 (0.26) | 31.8 (0.17) | 22.4 | 37 | 7.2 (2.4-21.3) | 7.0 (1.9-25.8) |
| All cases (N = 5828) | 33.8 (0.42) | 2265 (94) | 45.0 (0.51) | 31.3 (0.33) | 29.5 | 30 | | |

Abbreviations: IUGR, intrauterine growth restriction; NA, not applicable; NICU, neonatal intensive care unit; NMR, neonatal mortality rate.

[a] All analyses are stratified by country.

[b] Death during hospital stay (might have occurred beyond the neonatal period).

[c] Adjusted for country.

[d] Adjusted for country, gestational age, and *z* scores of birth weight for gestational age.

a set of stable clusters almost identical to those from the total population (results not shown). The same phenotypes were identified in all subsamples, with small variations in the proportional contribution of each phenotype to the total sample. The smallest cluster (severe maternal conditions, 181 cases) was a separate cluster in 8 of the 10 subsamples; in the other 2, it was combined with congenital anomalies.

Overall, the neonatal mortality rate was 30 per 1000 live births, and 29.5% stayed 7 or more days in a NICU (**Table 5**). There was a differential pattern of mortality and morbidity across clusters: for example, the highest mortality and morbidity rates were observed in clusters 8, 9, 11, 5, and 12. In general, the greater the birth weight, length, head circumference, and gestational age independently, the lower the mortality and morbidity rates in the clusters. These patterns were observed after adjusting by study site for possible differences, despite our standardization efforts,[22] in neonatal care.

We then repeated the same analysis adjusting also by gestational age at birth and birth weight-for-gestational age *z* scores[33] to explore whether the differences in neonatal mortality were mediated by a differential effect of the leading condition in each cluster on reducing gestational age or birth weight. We estimated odd ratios (95% CIs) using logistic regression analysis for the risk for neonatal mortality using cluster 1 as the reference group. After adjusting for gestational age and birth weight, the magnitude of most odds ratios was con-

siderably reduced, suggesting that the observed differences in neonatal mortality among clusters were largely mediated by these 2 variables. However, 2 clusters associated with mostly severe maternal disease and mostly fetal distress retained significantly higher risks for neonatal mortality independent of the gestational age and birth weight distributions; however, these findings were based on small numbers of neonatal deaths in each cluster (Table 5). The results were virtually identical when quadratic terms for birth weight and gestational age were used in the adjusted models.

## Discussion

The results of this primary analysis of the NCSS component of the INTERGROWTH-21st Project, using the a priori criteria of the new classification system,[12] clearly delineate homogeneous, phenotypic subgroups in up to 70% of all preterm births. Each is dominated by a principal condition and its related complications and is associated with differential patterns of presentation on hospital admission and mortality and morbidity outcomes. In 10 of 12 clusters, the effect on neonatal outcomes of each leading condition in individual clusters appeared to be partially mediated by their influence on gestational age and birth weight.

We explored the a priori hypothesis from our conceptual framework[12] describing preterm birth as a complex syndrome consisting of several phenotypes dominated by specific conditions. We used the data-driven, standard statistical approach of cluster analysis, grouping women with very similar characteristics, to form statistically constructed clusters as different from one another as possible.

The dominant condition in each cluster concurred with a set of related diseases/complications known to be associated with both the main condition and preterm birth, adding clinical validity to the results. However, as predicted in our conceptual model,[11,12] overlaps existed: for example, some stillbirths were included in the same cluster as pre-eclampsia/eclampsia cases, which occurred because the causal factors associated with pre-eclampsia/eclampsia, preterm birth, and fetal death overlap, and pre-eclampsia/eclampsia are major causal factors for stillbirth.

Only close to 20% of all preterm births could be considered an independent pathological entity (rather than the consequence of one) based on current scientific knowledge and available data. Hence, preterm birth is similar conceptually to premature adult death—not a single entity but the end point of multiple determinants.[10]

Our preterm birth population (including stillbirths and multiple births) of 5828 cases was derived from a population-based, multicenter study designed specifically to explore the phenotypic composition (rather than causes) of preterm birth syndrome. Its distinguishing features were that gestational age was reliably determined by ultrasonography, and a standardized protocol was adopted for data collection, quality control and management, clinical definitions, anthropometric evaluation (including the same equipment and measures), and neonatal care.[18,20-22] Preterm birth was defined from 16 weeks' rather than 20 weeks' gestation because the risk factors, causes, and recurrence risk for births between 16 and 20 weeks' gestation are very similar to those between 20 and 24 weeks' gestation.[10] We adjusted for possible site-specific effects that might influence care modalities and might be associated with differential mortality and morbidity across sites and preterm clusters.

We predicted that more than 1 phenotype may be present in individual cases,[11,12] which we have now observed. Multiple births were concentrated in 1 cluster but all other clusters were characterized by a leading condition associated with preterm birth. This observation is important for future validation of our classification system because it is consistent with the known increased risks for other conditions associated with multiple births. It would be interesting to extend the analyses by exploring the association between the identified factors with initiation of parturition modalities beyond the medically mandatory groups.

Our interpretation of these results was that up to 70% of preterm births were associated with underlying factors, which result in preterm birth because of the condition's direct effect on the initiation of parturition or because they are caregiver initiated due to clinical severity.

Conversely, 30% of all preterm births were not associated with any of our predefined severe fetal, maternal, or placental conditions—a proportion similar to the distribution of previously reported spontaneous preterm deliveries without pathology.[7] However, in 14.5% of these cases, delivery was caregiver initiated because of a less-severe condition, which depended on clinical judgment. In 12% of the cases, the delivery was considered iatrogenic because the practice was nonevidence based or, if indicated (eg, previous cesarean delivery without another clinical indication), it occurred preterm and therefore exposed the newborn to unnecessary risk. This involved nearly 5% of all late-preterm births in our overall population, a lower figure than in previous reports (up to 25%), although a more comprehensive definition of nonevidence-based practice has often been used (eg, induction of labor in PPROM).[34]

The remaining preterm births in cluster 1 (22% of all preterm births) presented with regular contractions with or without PPROM. We had no data on cervical changes preceding these births; however, 1.3% of these cases were associated with gestational hypertension, which might therefore have a direct effect on parturition. Overall, 20.7% of all preterm births were spontaneously initiated without any severe maternal (including gestational hypertension), fetal, or detectable placental condition; so these cases appeared genuinely idiopathic. They represent 2.2% of all deliveries (the preterm birth rate in our total population was 10.5%), which is close to the 3.0% to 3.5% rates in health-advanced countries.[35]

Other possibly causal conditions (eg, subclinical chorioamnionitis) were not detected by our methods nor are there yet biomarkers available.[36] Whether including additional conditions in the model might reduce the number of preterm births in this cluster is unclear. We only included conditions strongly associated with preterm birth rather than universal risk fac-

tors (eg, poor nutrition). If new conditions are to be added, there must be strong biological evidence of association.

We combined an a priori conceptual framework and a statistical approach to separate the population into different phenotypes, with distinct maternal characteristics and signs of presentation on hospital admission. Neonatal outcomes, not included in the cluster analysis, also differed across the phenotypes. The differences in neonatal mortality were largely mediated by reductions in gestational age and/or fetal growth. Knowledge about phenotypes remains essential for identifying effective preventive interventions because they have to be condition specific (ie, prevention of pre-eclampsia or multiple births). For example, additional information on initiation of parturition or placental characteristics may produce more subphenotypes.[10,11]

The study had limitations because neither placental histology nor other markers were available for a precise diagnosis of conditions such as chorioamnionitis or perinatal infection. For example, chorioamnionitis was defined by a combination of PPROM and antibiotics; therefore, we conceivably missed women with infection and intact membranes. Although we standardized antenatal and neonatal practices in the participating hospitals, considerable variability remained particularly in hospitals with large private practices. The lack of information about cervical dilation or effacement also precluded us from incorporating the actual initiation of parturition within the phenotypic characterization.

We opted for a 2-step cluster analysis among several approaches proposed for binary variables such as clinical conditions. The algorithm assumes that all categorical variables have a multinomial distribution and are independent, which is only partly fulfilled with some of the conditions studied. However, the statistical procedure is robust to violations of this assumption. Importantly, the method produced distinct and clinically sound clusters with different mortality and morbidity rates, supporting its usefulness in classifying our study population.

## Conclusions

In summary, our large, prospective, population-based study, implemented with the primary aim of exploring preterm birth phenotypes, demonstrated that nearly 80% of all preterm newborns are linked to specific, mostly independent, conditions. Some phenotypic overlap exists and the phenotypes may be rearranged when tested in different populations. Nevertheless, we believe these phenotypes should be considered separately in etiological research or when evaluating preventive or treatment modalities.

We have suggested possible explanations for the remaining 20% of the preterm births but it is clear they require considerable further investigation. In the meantime, greater effort should be made to prevent or treat the known conditions considered here including iatrogenic late-preterm births.

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