Prevalence of preterm birth and risk factors associated with it at different gestational ages

A multicenter retrospective survey in China

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ABSTRACT

الأهداف: التحقق من انتشار الولادة المبكرة (PTB) وعوامل الخطر من المجموعات الفرعية الخدج في مختلف الأعمار في الصين.

المنهجية: أجرينا دراسة وصفية مقطعية شملت 215254 ولادة حية فردية (24^{+0}–41^{+6} أسابيع) في 23 مقاطعة من 2010م إلى 2017م في الصين. قارنا كلاً من مجموعة الخدج (24^{+0}–36^{+6} أسابيع) والمجموعات الفرعية الخدج (<32 أسابيع، 32^{+0}–33^{+6} أسابيع، و34^{+0}–36^{+6} أسابيع) مع مجموعة المدى (37^{+0}– 41^{+6} أسابيع). جمعنا المعلومات المتعلقة بخصائص الأم والجنين من السجلات الطبية. تم استخدام الانحدار اللوجستي.

النتائج: كان معدل انتشار PTB 7.4% في الولادات المفردة. بعد تعديل عمر الأم، والتكافؤ، وعوامل الخطر المحتملة في التحليل أحادي المتغير، كانت العوامل عالية الخطورة لـ PTB في أقل من 32 أسبوعًا هي انفصال المشيمة (aOR=41.523؛ 95% CI، 25.892–66.589)، المشيمة المنزاحة (aOR=40.043؛ 95% CI، 32.006–50.099)، التهاب المشيمة والسلى (aOR=11.069؛ 95% CI، 8.738–14.021)، واضطرابات ارتفاع ضغط الدم أثناء الحمل (aOR=3.564؛ 95% CI، 2.930–4.335). ارتبط الركود الصفراوي داخل الكبد (ICP) بشكل كبير مع PTB في 34–36 أسبوعًا (aOR=5.763؛ 95% CI، 5.049–6.577)، خاصة مع PTB العفوي (aOR=10.04؛ 95% CI، 8.79–11.47). ارتبط داء سكري الحمل (GDM) بشكل كبير مع PTB في 34–36 أسبوعًا فقط (aOR=1.156؛ 95% CI، 1.054–1.267).

الخلاصة: انفصال المشيمة، المشيمة المنزاحة، التهاب المشيمة والسلى، وHDP كانت أكثر تنبؤيه لـPTB المبكر: كان GDM وICP أكثر تنبؤًا ب PTB متأخر.

Objectives: To investigate the prevalence of preterm birth (PTB) and the risk factors for different gestational age subgroups of preterm birth in China.

Methods: We carried out a descriptive cross-sectional study encompassing all singleton live births (24^{+0} to 41^{+6} weeks) with completed data in 23 provinces in China from 2010 to 2017 during investigation period. We compared both the preterm group (24^{+0} to 36^{+6} weeks) and preterm subgroups (<32 weeks, 32^{+0} to 33^{+6} weeks, and 34^{+0} t0 36^{+6} weeks) with the term group (37^{+0} to 41^{+6} weeks). We collected information on maternal and fetal characteristics from medical records. Logistic regression was use.

Results: The prevalence of PTB was 7.4% (15,833/215,254) in singleton births. After adjusting for maternal age, parity, and potential risk factors in univariate analysis, the high-risk factors for PTB at <32 weeks were placental abruption (aOR=41.52; 95% CI, 25.89–66.58), placenta previa (aOR=40.04; 95% CI, 32.00–50.09), chorioamnionitis (aOR=11.06; 95% CI, 8.738–14.02), and hypertension disorders in pregnancy (HDP) (aOR=3.564; 95% CI, 2.930–4.335). Intrahepatic cholestasis of pregnancy (ICP) was significantly associated with PTB at 34–36 weeks (aOR=5.763; 95% CI, 5.049–6.577), particularly with spontaneous PTB (aOR=10.04; 95% CI, 8.79–11.47). Gestational diabetes mellitus (GDM) was significantly associated with PTB at 34–36 weeks only (aOR=1.156; 95% CI, 1.054–1.267).

Conclusion: Placental abruption, placenta previa, chorioamnionitis, and HDP were more predictive of early PTB; GDM and ICP were more predictive of late PTB.

Keywords: preterm birth, risk factors, pregnancy, prenatal care

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Preterm birth (PTB) is defined as delivery before 37 completed weeks of gestation. Preterm births are divided into iatrogenic PTBs and spontaneous preterm births, which include spontaneous preterm labor and births with preterm premature rupture of membranes, based on the involvement of clinical intervention.[1] Preterm birth is a global health issue, and its prevalence was 8%-13% across 194 countries in 2014.[2] The rate has continued to increase in the last 20 years. Preterm birth is the leading cause of child under-5 and neonatal mortality and a major cause of long-term adverse prognoses in children.

Owing to its large population, the number of preterm infants born yearly in China ranks second in the world.[2] In China, the rate of preterm birth was 7%-8% in 2014, which is almost double that in the 1990s (4%-5%).[2-4] This continued increase has become an urgent health problem in China. Notwithstanding the significant progress in the care of premature infants, the prevalence of PTB has not decreased. Therefore, determining the risk factors for PTB is critical for developing new intervention strategies to reduce PTB.

Neonatal outcomes are closely associated with gestational age at delivery. Preterm births typically fall into these subgroups based on gestational age: late preterm (34^{+0} to 36^{+6} weeks), moderate preterm (32^{+0} to 33^{+6} weeks), very preterm (28^{+0} to 31^{+6} weeks), and extremely preterm (<28 weeks).[2] Some international studies have reported different risk factors for different subgroups with different effects on preterm births.[5,6] Conversely, investigations of risk factors in China have primarily been based on comparisons between preterm and term births,with few studies focusing on the risk factors for preterm subgroups.[7,8]

The risk factors for PTB reportedly differ depending on the developmental status of countries and the race of the individuals.[9-10] Despite considerable studies on the causes of PTB being carried out in developed countries, few studies have been carried out in developing countries involving Asian individuals. China is a large, developing country, and most Chinese individuals are Asian. The Chinese childbearing policy has been different from that of other countries and has changed since October 2015, and perinatal examinations and medical technologies have improved quickly. Although studies on risk factors for preterm birth are being increasingly reported in China, the sample size of most such studies is often restricted to only one hospital or one area in China. In addition, studies carried out across preterm categories are insufficient.[8,11,12] Therefore, it is necessary to carry out a study to investigate the prevalence of preterm birth and the specific risk profiles for 3 preterm subgroups (<32 weeks, 32^{+0} to 33^{+6} weeks, and 34^{+0} to 36^{+6} weeks) under current medical and social living conditions to implement prevention and intervention measures to reduce the incidence of preterm birth.

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Methods. The current study was a multicenter, hospital-based, retrospective study carried out in 70 hospitals in 23 provinces in China from 2010 to 2017. Children's Hospital of Fudan University, as the research center, was responsible for the coordination and integration of information. Data on births were collected from the obstetric birth database of the Chinese Neonatal Network (ChinaNeoNet: http://www.chinaneonate.net). All singleton live births (gestational age between 24^{+0}~40^{+6} weeks) during the investigation period in each hospital were included. We excluded multiple births, postterm births (≥42^{+0} weeks), and births with missing data for the potential affecting factors. If the obstetrics department of a hospital had fewer than 5000 deliveries annually, data for all live births were collected; conversely, for hospitals with an obstetrics department having more than 5000 deliveries annually, live birth data were collected only for 4 months during one year (any one month in a season). The data collected from medical records included gestational age, birth weight, maternal age (<20 years, 20~35 years, ≥35 years), parity, maternal illnesses during pregnancy (hypertension disorders in pregnancy [HDP], intrahepatic cholestasis of pregnancy [ICP], gestational diabetes mellitus [GDM], anemia, and chorioamnionitis), maternal pregnancy complications (placental abruption and placenta previa), and fetal distress. This study was approved by the Ethics Committee of Children's Hospital of Fudan University Hospital, Shanghai, China (committee's reference number Children's Hospital of Fudan University) and ethics committees of the participating hospitals.

Gestational age is defined as, completed weeks of gestation, was determined by the duration of amenorrhea or confirmed by an early ultrasound scan during pregnancy.[13] Hypertension disorders in pregnancy (HDP) included chronic hypertension, gestational hypertension, preeclampsia, and eclampsia.[14] We followed the definition of GDM recommended by the International Association of Diabetes and Pregnancy Study Groups.[15] Anemia during pregnancy

was defined as a hemoglobin level of less than 110 g/L.[16] Chorioamnionitis was diagnosed within 24 hours before delivery if more than 2 conditions among clinical indicators and more than one condition among infection indicators were met. Clinical indicators included: i) central temperature >37.8 °C, ii) maternal heart rate >110 beats/minutes [min] or fetal heart rate >160 beats/min for unexplainable reasons, iii) respiratory rate>24 beats/min, iv) purulent amniotic fluid, and v) uterine tenderness. Infection indicators included: i) peripheral blood leukocyte count >15 × 109/L or <4 × 109/L or immature granulocyte >10%, ii) C-reactive protein levels increased to greater than 2 standard deviations of the normal standard, iii) procalcitonin levels increased to greater than 2 standard deviations of the normal standard, iv) amniotic fluid pictures or culture were positive for an infection, and v) intrauterine tissue examination showed a positive inflammatory reaction.[17]

Fetal distress could be diagnosed before labor onset as the continuous recording of the fetal electrocardiogram showing abnormal fetal heart rates, such as a persistent nonreactive and "fixed" fetal heart rate, a substantial rise in baseline heart rate (>160 beats per minute), a loss of variability and repetitive severe variable or late decelerations, or fetal baseline heart rate <110 beats per minute.[17] The diagnoses of ICP, placental abruption, and placenta previa were also based on criteria used in China until 2017.[17]

Statistical analysis. Stata V.13.0 (StataCorp, College Station, Texas, USA) was used to perform statistical analyses. The χ^2 test was used to compare the frequencies among categorical data, and data were analyzed using logistic regression analyses. Maternal age, parity, and other factors that were identified to be associated with preterm births in the univariate logistic regression model (p<0.05 and odds ratio>1) were entered into a multivariate logistic regression model (Model A), which was used to estimate adjusted odds ratios (aORs). Confidence intervals (CIs) were calculated at the 95% level. A variable found to be significant at the 0.05 level with an aOR>1 in Model A was considered an independent risk factor for preterm birth. Mother's age, parity, and other independent risk factors for PTB were entered into a multinomial multivariate logistic regression model (Models B, C, and D), which was run to estimate aORs for preterm subgroups (<32 weeks, 32^{+0} to 33^{+6} wks, and 34^{+0} to 36^{+6} weeks) using term births as the reference. Model C compared spontaneous preterm birth subgroups with the term group. Model D compared iatrogenic preterm birth subgroups with the term group. For Models B, C, and D, a p-value of <0.05 was considered statistically significant. Missing data were deleted.

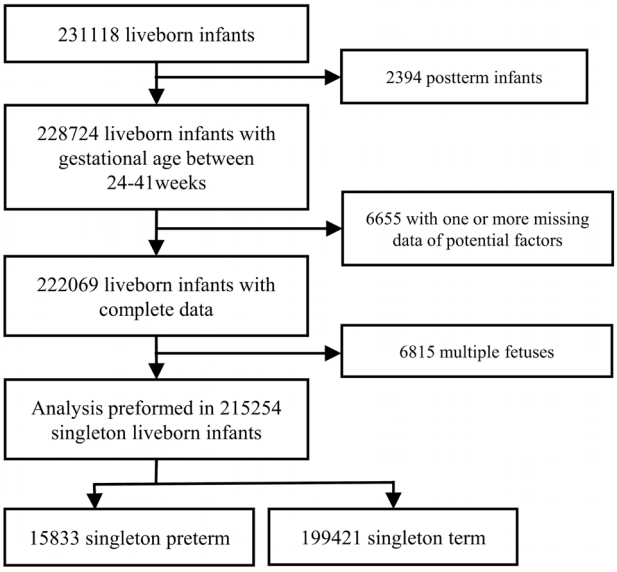

Figure 1 - Flowchart showing the recruitment process for participants.

Results. In the final analysis, 215,254 singleton newborns were included, including 15,833 (7.4%) singleton preterm infants (Figure 1). The total incidence of preterm births was 8.5% (19,532/231,118). Of the singleton preterm births, 10.8% were early preterm births (<32 weeks), 14.8% were moderate preterm births (32 to 33 weeks), and 74.4% were late PTBs (34 to 36 weeks). Of the singleton preterm births, 65.1% (10309/15833) were spontaneous preterm births, 33.5% (5303/15833) were spontaneous preterm births with intact membranes, and 31.6% (5006/15833) were births with preterm premature rupture of membranes (PPROM).

Table 1 shows the general characteristics of the singleton preterm and term groups. These groups had very different maternal ages, parities, and neonatal outcomes. The mean maternal age in the preterm group was higher than that in the term group. Furthermore, the preterm group had higher parity than the term group. The proportion of male infants was greater in the preterm group. Preterm group cases more frequently showed adverse perinatal outcomes, such as lower neonatal birth weight and Apgar score at 5 min of <7 (p<0.05; Table 1), compared with the term group.

Univariate and multivariate logistic regression analyses for singleton preterm birth. Table 2 shows the results of univariate logistic regression analyses. The results showed that the potential risk factors (OR>1, p<0.05) for preterm birth were placental abruption, placenta previa, ICP, hypertension disorders in

Table 1 - General characteristics of the study group.

Characteristics	Total group (n=215254)	Preterm group (n=15833)	Term group (n=199421)	*P*-value
Gestational age (weeks)*	38±2	34±2	39±1	<0.001
Birth weight (g)*	3262±500	2419±583	3329±4263	<0.001
Male †	114084 (53.0)	9212 (58.0)	105094 (52.7)	0.001
Maternal age (years) †	27.4±4.9	27.7±5.6	27.4±4.8	<0.001
Parity †				<0.001
1	149951 (69.7)	9949 (62.8)	140002 (70.2)	
≥2	65303 (30.3)	5884 (37.2)	59419 (29.8)	
Apgar score at 5 min of <7	600 (2.8)	335 (2.1)	265 (1.3)	<0.001

*Mean±SD, $p<0.05$ was considered significant. †n (%), $p<0.05$ was considered significant.

Table 2 - Univariate and multivariate analyses of risk factors for singleton preterm births.

Factors	Singleton preterm (n=15833)	Singleton term (n=199421)	OR (95% CI)*	*P*-value	aOR (95% CI) (Model A)†	*P*-value
Maternal age (years)						
<20	609 (3.8)	4584 (2.3)	1.796 (1.647–1.958)	<0.001	1.963 (1.796–2.145)	<0.001
20–34	13124 (82.9)	177395 (89.0)	1.000		1.000	
≥35	2100 (13.3)	17442 (8.7)	1.627 (1.550–1.708)	<0.001	1.318 (1.250–1.390)	<0.001
Parity						
1	9949 (62.8)	140002 (70.2)	1.000		1.000	
≥2	5884 (37.2)	59419 (29.8)	1.393 (1.347–1.441)	<0.001	1.423 (1.372–1.476)	<0.001
HDP						
Yes	1007 (6.4)	3486 (1.7)	3.818 (3.552–4.103)	<0.001	3.978 (3.691–4.288)	<0.001
No	14826 (93.6)	195935 (98.3)	1.000		1.000	
GDM						
Yes	723 (4.6)	7020 (3.5)	1.311 (1.213–1.418)	<0.001	1.216 (1.122–1.319)	<0.001
No	15110 (95.4)	192401 (96.5)	1.000		1.000	
ICP						
Yes	347 (2.2)	973 (0.5)	4.570 (4.039–5.172)	<0.001	5.520 (4.860–6.270)	<0.001
No	15486 (97.8)	198448 (99.5)	1.000		1.000	
Anemia						
Yes	288 (1.8)	2407 (1.2)	1.516 (1.341–1.71)	<0.001	1.261 (1.108–1.436)	<0.001
No	15545 (98.2)	199421 (98.2)	1.000		1.000	
Chorioamnionitis						
Yes	196 (1.2)	787 (0.4)	3.164 (2.703–3.703)	<0.001	2.834 (2.406–3.340)	<0.001
No	15637 (98.8)	198634 (99.6)	1.000		1.000	
Placenta previa						
Yes	284 (1.8)	392 (0.2)	9.27 (7.95–10.81)	<0.001	10.09 (8.60–11.83)	<0.001
No	15549 (98.2)	199029 (99.8)	1.00		1.00	
Placental abruption						
Yes	96 (0.6)	66 (0.0)	18.42 (13.46–25.21)	<0.001	17.20 (12.35–23.95)	<0.001
No	15737 (99.4)	199355 (100.0)	1.000		1.000	
Fetal distress						
Yes	832 (5.3)	8018 (4.0)	1.324 (1.230–1.425)	<0.001	1.249 (1.157–1.348)	<0.001
No	15001 (94.7)	191403 (96.0)	1.000		1.000	

Values are presented as number and percentages (%). *OR (odds ratio) value and 95% CI (confidence interval) of univariate logistic analysis model, $p<0.05$ was considered significant. †aOR (adjusted odds ratio) value and 95% CI after adjusting for other confounders in Model A (including maternal age, parity, HDP, GDM, ICP, anemia, chorioamnionitis, placenta previa, placental abruption, and fetal distress); $p<0.05$ was considered significant. HDP: hypertension disorders in pregnancy, ICP: intrahepatic cholestasis of pregnancy, GDM: gestational diabetes mellitus

pregnancy, chorioamnionitis, anemia, younger maternal age (<20 years) and advanced maternal age (≥35 years), higher parity, GDM, and fetal distress compared to term birth.

Table 2 also shows the results of the multivariate logistic regression model (Model A), which included all the statistically significant risk factors in the univariate analyses. After adjusting for confounders, the independent risk factors for preterm birth were placental abruption (aOR=17.20; 95%CI, 12.35–23.95), placenta previa (aOR=10.09; 95%CI 8.60–11.83), ICP (aOR=5.520; 95%CI, 4.860–6.270), HDP (aOR=3.978; 95%CI, 3.691–4.288), and chorioamnionitis (aOR=2.834; 95%CI, 2.406–3.340). Mothers with GDM, anemia, fetal distress, advanced age (≥35 years), younger age (<20 years), and higher parity (≥2) had a slightly increased risk of PTB, with aORs ranging from 1.216 to 1.963.

Multinomial multivariate logistic regression comparing preterm subgroups with the term group. Appendix 1 shows the distribution of all independent risk factors for preterm births across the gestational age spectrum. The distributions of all risk factors were significantly different across gestational age categories. Advanced maternal age (≥35 years), higher parity (≥2), chorioamnionitis, placenta previa, placental abruption, and fetal distress were most common among early preterm births and showed a downward trend as age increased. Intrahepatic cholestasis of pregnancy and GDM were the most frequent among late preterm

Table 3 - Risk factors associated with each preterm subgroup compared to the term group in multinomial multivariate logistic regression analysis.

	<32 weeks		32–33 weeks		34–36 weeks	
Factors	aOR (95% CI)*	*P*-value	aOR (95% CI)*	*P*-value	aOR (95% CI)*	*P*-value
Maternal age (years)						
<20	**2.084 (1.650–2.632)**	<0.001	**2.197 (1.810–2.666)**	<0.001	**1.437 (1.289–1.601)**	<0.001
20–34	1.000		1.000		1.000	
≥35	**1.396 (1.213–1.606)**	<0.001	**1.167 (1.024–1.330)**	0.020	**1.204 (1.132–1.280)**	<0.001
Parity						
1	1.000		1.000		1.000	
≥2	**1.369 (1.238–1.514)**	<0.001	**1.332 (1.220–1.455)**	<0.001	**1.218 (1.169–1.269)**	<0.001
HDP						
Yes	**3.564 (2.930–4.335)**	<0.001	**4.418 (3.774–5.173)**	<0.001	**3.044 (2.786–3.326)**	<0.001
No	1.000		1.000		1.000	
GDM						
Yes	1.113 (0.886–1.399)	0.358	1.092 (0.893–1.336)	0.392	**1.156 (1.054–1.267)**	<0.001
No	1.000		1.000		1.000	
ICP						
Yes	1.384 (0.766–2.499)	0.282	**3.056 (2.147–4.348)**	<0.001	**5.763 (5.049–6.577)**	<0.001
No	1.000		1.000		1.000	
Anemia						
Yes	1.240 (0.896–1.715)	0.195	**1.582 (1.207–2.074)**	0.001	1.096 (0.939–1.279)	0.246
No	1.000		1.000		1.000	
Chorioamnionitis						
Yes	**11.06 (8.738–14.02)**	<0.001	**3.023 (2.119–4.314)**	<0.001	**2.247 (2.153–2.344)**	<0.001
No	1.000		1.000		1.000	
Placenta previa						
Yes	**40.04 (32.00–50.09)**	<0.001	**13.85 (10.28–18.65)**	<0.001	**9.37 (7.77–11.29)**	<0.001
No	1.000		1.000		1.00	
Placental abruption						
Yes	**41.52 (25.89–66.58)**	<0.001	**32.06 (20.27–50.70)**	<0.001	**11.67 (7.99–17.02)**	<0.001
No	1.000		1.00		1.00	
Fetal distress						
Yes	**1.487 (1.230–1.799)**	<0.001	**1.477 (1.250–1.746)**	<0.001	**1.061 (0.969–1.161)**	0.201
No	1.000		1.000		1.000	

*aOR (adjusted odds ration) value and 95% CI (confidence interval) after adjusting for other confounders in Model B (including maternal age, parity, HDP, GDM, ICP, anemia, chorioamnionitis, placenta previa, placental abruption, and fetal distress). The reference group was the term group. *P*<0.05 was considered significant. Bold values are significant. Bold numbers are significant. HDP: hypertension disorders in pregnancy, ICP: intrahepatic cholestasis of pregnancy, GDM: gestational diabetes mellitus

births. Hypertension disorders in pregnancy anemia and younger maternal age (<20 years) were the most common among moderate preterm births.

Table 3 shows the results of a multinomial multivariate logistic regression model (Model B), which included all the independent risk factors for singleton preterm birth and compared 3 preterm subgroups (<32 weeks, 32^{+0} to 33+6 weeks, and 34^{+0} to 36^{+6} weeks) with the term group.

After adjusting for confounding factors, placenta previa, placental abruption, HDP, chorioamnionitis, advanced maternal age (≥35 years), younger maternal age (<20 years), and higher parity were significantly associated with the 3 preterm subgroups compared with the term group (aOR>1; p<0.05). The high-risk factors for preterm birth at <32 weeks were placental abruption (aOR=41.52; 95%CI, 25.89–66.58), placenta previa (aOR=40.04; 95%CI, 32.00–50.09), and chorioamnionitis (aOR=11.06; 95%CI, 8.738–14.02). The OR of placenta previa, placental abruption, chorioamnionitis, and higher parity decreased with increasing gestational age. The highest odds ratio of advanced maternal age was for birth at <32 weeks. The highest odds ratios of HDP and younger maternal age were for birth at 32-33 weeks.

Notably, GDM, ICP, anemia, and fetal distress were not related to all the categories of PTB but were only related to one or 2 subgroups of preterm birth. Herein, GDM was only significantly associated with late PTB. In addition, mothers with ICP had an increased risk

Table 4 - Risk factors associated with each spontaneous preterm subgroup compared to the term group in multinomial multivariate logistic regression analysis.

	<32 weeks		32–33 weeks		34–36 weeks	
Factors	aOR (95% CI)*	*P*-value	aOR (95% CI)*	*P*-value	aOR (95% CI)*	*P*-value
Maternal age (years)						
<20	1.088 (0.757–1.564)	0.649	1.328 (1.004–1.756)	0.047	0.950 (0/868–1.163)	0.950
20–34	1.000		1.000		1.000	
≥35	**1.585 (1.357–1.851)**	<0.001	**1.299 (1.127–1.498)**	<0.001	**1.252 (1.166–1.343)**	<0.001
Parity						
1	1.000		1.000		1.000	
≥2	**1.391 (1.237–1.563)**	<0.001	**1.391 (1.258–1.453)**	<0.001	**1.218 (1.161–1.278)**	<0.001
HDP						
Yes	**8.518 (7.099–10.221)**	<0.001	**7.924 (6.797–1.538)**	<0.001	**4.303(3.917–4.727)**	<0.001
No	1.000		1.000		1.000	
GDM						
Yes	1.185 (0.922–1.523)	0.184	**1.293 (1.047–1.596)**	0.017	**1.286 (1.162–1.424)**	<0.001
No	1.000		1.000		1.000	
ICP						
Yes	1.384 (0.766–2.499)	0.282	**3.875 (2.595–5.786)**	<0.001	**10.04(8.79–11.47)**	<0.001
No	1.000		1.000		1.000	
Anemia						
Yes	1.240 (0.896–1.715)	0.195	**1.862 (1.392–2.489)**	0.001	1.221 (1.027–1.452)	0.240
No	1.000		1.000		1.000	
Chorioamnionitis						
Yes	**33.30 (27.29–40.63)**	<0.001	**3.863 (2.620–5.694)**	<0.001	**1.835 (1.405–2.397)**	<0.001
No	1.000		1.000		1.000	
Placenta previa						
Yes	**36.75 (26.02–51.92)**	<0.001	**22.71 (16.36–31.517)**	<0.001	**16.05 (13.29–19.36)**	<0.001
No	1.000		1.000		1.00	
Placental abruption						
Yes	**63.75 (37.49–108.4)**	<0.001	**49.59 (30.66–80.21)**	<0.001	**17.31 (11.76–25.48)**	<0.001
No	1.000		1.00		1.00	
Fetal distress						
Yes	**1.735 (1.414–2.130)**	<0.001	**1.654 (1.378–1.986)**	<0.001	**1.016 (1.050–1.286)**	0.004
No	1.000		1.000		1.000	

*aOR (adjusted odds ration) value and 95% CI (confidence interval) after adjusting for other confounders in Model B (including maternal age, parity, HDP, GDM, ICP, anemia, chorioamnionitis, placenta previa, placental abruption, and fetal distress); the reference group was the term group. P<0.05 was considered significant. Bold values are significant. HDP: hypertension disorders in pregnancy, ICP: intrahepatic cholestasis of pregnancy, GDM: gestational diabetes mellitus

for moderate and late PTB. Intrahepatic cholestasis of pregnancy was a stronger predictor for late PTB (aOR=5.763; 95% CI, 5.049–6.577) than other preterm subgroups. Anemia was only significantly associated with moderate PTB. Fetal distress was significantly associated with early PTB and moderate PTB.

Table 4 shows the results of a multinomial multivariate logistic regression model (Model C), which included all the independent risk factors for singleton preterm birth and compared 3 spontaneous preterm subgroups with the term group.

After adjusting for other confounding factors, placenta previa, placental abruption, hypertension disorders in pregnancy, chorioamnionitis, fetal distress, higher parity, and advanced maternal age (≥35 years) were identified to be significantly associated with the 3 spontaneous preterm subgroups when compared to the term group (aOR>1; $p<0.05$), and their odds ratios decreased with increasing gestational age. The high-risk factors for spontaneous early PTB were placental abruption (aOR=63.75; 95%CI, 37.49–108.4), placenta previa (aOR=36.75; 95%CI, 26.02–51.92), chorioamnionitis (aOR=33.30; 95%CI, 27.29–40.63), and hypertension disorders in pregnancy (aOR=8.518; 95% CI, 7.099-10.221).

Notably, GDM, ICP, and anemia were not related to all the subgroups of spontaneous preterm birth but only to one or 2 subgroups of preterm birth. Herein, GDM and ICP were significantly associated with spontaneous

Table 5 - Risk factors associated with each iatrogenic preterm subgroup compared to the term group in multinomial multivariate logistic regression analysis.

	<32 weeks		32–33 weeks		34–36 weeks	
Factors	**aOR (95% CI)***	***P*-value**	**aOR (95% CI)***	***P*-value**	**aOR (95% CI)***	***P*-value**
Maternal age (years)						
<20	2.103 (1.663–2.660)	<0.001	2.221 (1.826–2.701)	<0.001	1.449 (1.299–1.615)	<0.001
20–34	1.000		1.000		1.000	
≥35	1.390 (1.207–1.600)	<0.001	1.161 (1.018–1.324)	0.027	1.198 (1.126–1.274)	0.001
Parity						
1	1.000		1.000		1.000	
≥2	1.331 (1.238–1.514)	<0.001	1.287 (1.177–1.406)	<0.001	1.181(1.133–1.231)	<0.001
HDP						
Yes	3.405 (2.799–4.143)	<0.001	4.176 (3.566–4.892)	<0.001	2.900 (2.655–3.168)	<0.001
No	1.000		1.000		1.000	
GDM						
Yes	1.119 (0.889–1.408)	0.339	1.098 (0.896–1.347)	0.368	1.162 (1.059–1.274)	0.001
No	1.000		1.000		1.000	
ICP						
Yes	1.280 (0.709–2.312)	0.413	2.775 (1.949–3.950)	<0.001	5.299 (4.646–6.044)	<0.001
No	1.000		1.000		1.000	
Anemia						
Yes	1.235 (0.891–1.711)	0.204	1.575 (1.199–2.070)	0.001	1.092 (0.935–1.275)	0.269
No	1.000		1.000		1.000	
Chorioamnionitis						
Yes	11.89 (9.391–15.07)	<0.001	3.317 (2.319–4.743)	<0.001	2.025 (1.630–2.516)	<0.001
No	1.000		1.000		1.000	
Placenta previa						
Yes	3.786 (1.682–8.523)	0.001	1.228 (0.305–4.940)	0.773	2.276 (1.398–3.706)	0.001
No	1.000		1.000		1.00	
Placental abruption						
Yes	23.68 (10.21–654.9)	<0.001	11.236 (23.52–35.87)	<0.001	2.404(0.755–7.654)	0.138
No	1.000		1.00		1.00	
Fetal distress						
Yes	1.487 (1.230–1.799)	<0.001	1.479 (1.263–1.779)	<0.001	1.071 (0.978–1.173)	0.141
No	1.000		1.000		1.000	

*aOR (adjusted odds ration) value and 95% CI (confidence interval) after adjusting for other confounders in Model B (including maternal age, parity, HDP, GDM, ICP, anemia, chorioamnionitis, placenta previa, placental abruption, and fetal distress); the reference group was the term group. *P*<0.05 was considered significant. Bold values are significant. HDP: hypertension disorders in pregnancy, ICP: intrahepatic cholestasis of pregnancy, GDM: gestational diabetes mellitus.

moderate and late PTB. Intrahepatic cholestasis of pregnancy was a stronger predictor of spontaneous late PTB (aOR=10.04; 95%CI, 8.79–11.47) than other subgroups. Anemia was only significantly associated with spontaneous moderate PTB.

Table 5 shows the results of a multinomial multivariate logistic regression model (Model D), which included all the independent risk factors for singleton preterm birth and compared 3 iatrogenic preterm subgroups with the term group.

After adjusting for other confounding factors, placental abruption, hypertension disorders in pregnancy, chorioamnionitis, younger maternal age (<20 years), advanced maternal age (≥35 years), and higher parity were significantly associated with the 3 iatrogenic preterm subgroups when compared with the term group (aOR>1; p<0.05). The odds ratios of placenta previa, placental abruption, and chorioamnionitis decreased with increasing gestational age. The high-risk factors for iatrogenic preterm birth at <32 weeks were placental abruption (aOR=23.68; 95% CI, 10.21–654.9) and chorioamnionitis (aOR=11.89; 95% CI, 9.391–15.07).

Notably, GDM, ICP, placenta previa, fetal distress, and anemia were not related to all the subgroups of iatrogenic preterm birth. Herein, GDM was only significantly associated with iatrogenic late preterm birth. In addition, ICP was significantly associated with iatrogenic moderate and late PTB. ICP was a stronger predictor of iatrogenic late PTB (aOR=5.299; 95% CI, 4.646–6.044) than other subgroups. Placenta previa was significantly associated with iatrogenic early and late PTB. Fetal distress was associated with an increased risk of iatrogenic early and moderate PTB. Anemia was only associated with iatrogenic moderate PTB.

Discussion. Our current study provides information on the risk factors associated with different gestational age subgroups of preterm birth in China. Our findings highlight different risk profiles and different magnitudes of association of risk factors with different gestational ages and are consistent with the hypothesized complex multifactorial etiology of preterm birth.[18] Therefore, we emphasize the need for developing interventions targeted at specific gestational ages rather than preterm birth as a whole to prevent preterm delivery.

The prevalence of preterm delivery (8.5% of total live births) in the current study was higher than the Chinese prevalence of preterm birth (7.8% of overall live births) in 2014.[2] This increasing incidence is concerning and has attracted interest in identifying the etiology and risk factors associated with preterm births.

The total incidence of spontaneous PTB with intact membranes was lower in our study than reported in other studies (33.5% vs. 45%).[1] However, the total incidence of PPROM in preterm births (31.6%) was in agreement with previous reports (25%-35%).[1]

Our comparison of preterm and term births identified the following 11 independent risk factors for preterm birth: placental abruption, placenta previa, ICP, HDP, chorioamnionitis, anemia, advanced maternal age (≥35 years) and younger maternal age (<20 years), higher parity, GDM, and fetal distress. Although these findings corroborate previous studies, previous studies have seldom investigated the risk associated with different factors for different gestational age PTB subgroups.[19-27]

In this study, mothers with placenta previa had a high risk for delivering infants belonging to all 3 subgroups of preterm birth and had the highest risk for delivering early preterm birth infants (40 times compared to mothers who did not have placenta previa). This can be explained by the abnormal position of the placenta, wherein uterine contraction can lead to heavy bleeding, thus warranting immediate delivery and consequently translating into a higher prevalence of placenta previa in the second trimester (2%–10%) than at term (0.3%–0.5%).[28,29] This study also found mothers with placental abruption to be associated with a high risk for all preterm births across all gestational ages, with the highest risk for early spontaneous preterm birth (63 times compared to mothers who did not have placental abruption) because placental abruption can cause fetal death and warrant emergency pregnancy termination before term. Taken together, placenta previa and placental abruption were the highest-risk factors for early PTB. Previous studies have not investigated the risk posed by placenta previa for different gestational age subgroups of preterm birth.

The current study showed that mothers with hypertension disorders in pregnancy had a high risk for delivering infants belonging to all 3 subgroups of preterm births and the highest risk for delivering moderate preterm birth infants (4 times compared to mothers who did not have HDP). A similar trend was observed by Butali et al[6] in their single-center study. We also found that mothers with HDP had an 8-fold increased risk of delivering early spontaneous preterm birth infants compared to mothers without HDP. Abnormal maternal blood pressure can cause insufficient placental blood supply and consequent chronic fetal hypoxia and poor growth. Our findings also showed the importance of detecting high blood pressure during pregnancy and indicated normalizing blood pressure before 32 weeks to prevent preterm birth.[30]

This study suggested that chorioamnionitis was a high-risk factor for early PTB, especially for early spontaneous PTB (33-fold), and the odds ratios decreased with increasing gestational age. This finding corroborated a previous study reporting that the incidence of histologic chorioamnionitis was inversely related to gestational age, with its effect decreasing from 66% of preterm births at 20-24 weeks to 16% of preterm births at 34 weeks.[31]

Our study found that mothers with ICP had an increased risk for delivering moderate and late PTB infants, and the odds ratios increased with increasing gestational age and had the strongest risk (aOR=10.04; 95% CI, 8.79–11.47) for spontaneous late PTB. This could be explained by the finding of Stulic et al,[32] who reported a significant association between higher bile acid levels and spontaneous preterm births. Furthermore, our observation is also in line with the pathophysiological process that ICP generally appears in the middle-to-late stage of pregnancy, with 80% of its incidence after 30 weeks of gestation and a gradually worsening trend with increasing gestational age.

Our study also found that mothers with GDM had an increased risk for late preterm birth and for spontaneous moderate and late PTB. The results echoed the findings of a study by Wingate et al,[5] which indicated GDM as a risk factor for PTB at ≥32 weeks,as well as a study by Kong et al,[33] which reported that GDM was associated with spontaneous PTB. This observation could be attributable to the increased risk of preterm birth with progressive hyperglycemia and the gradual exacerbation of GDM along with the rapid growth of the fetus after 28 weeks.[34] In addition, GDM was associated with macrosomia and preeclampsia, which warrant medically-indicated termination.[35]

Our study demonstrated that mothers with higher parity (≥2) and advanced maternal age (≥35 years) had a significantly higher possibility of preterm birth across all gestational ages, the odds ratios of which decreased with increasing gestational age. This finding corroborates previous studies showing that women with a high parity (≥4) had a fourfold increased risk of delivering PTB infants.[36] Women with advanced maternal age and high parity are at a higher risk of adverse obstetrical and perinatal outcomes.[37] Health workers should pay more attention to women with these 2 risk factors to prevent early PTB. This study also found that women of younger ages (<20 years) had an increased risk for all preterm categories, particularly for moderate spontaneous preterm birth.

Previous systematic reviews on maternal anemia and the risk of preterm birth reported different results.[38,39] Our current study found that maternal anemia was significantly associated only with birth at 32–33 weeks, which could explain the difference in results.

This study first analyzed the risk factors for different gestational age subgroups in China. This study was more representative of the Chinese population because of its large sample size and coverage (23 provinces). In this study, we selected several globally identified and broadly acknowledged risk factors for preterm birth and used the classic regression model. These results were consistent with the previous model, which was selected from 174 identified intrauterine and extrauterine risks, including placenta previa, pregnancy-induced hypertension, and preeclampsia.[40]

Study limitations. This was a retrospective study, and we could not collect some data on other risk factors, such as in- vitro fertilization, intrauterine growth retardation, other infections in pregnancy, antiphospholipid antibody syndrome, maternal nutrition, adverse lifestyle during pregnancy and psychological factors. In addition, preterm births with gestational ages <28 weeks were not analyzed because of the small sample size. Further studies are warranted to address these limitations.

In conclusion, our data suggest that the occurrence of preterm births remains high in China. We found preterm birth to be caused by multifactorial etiologies. Placenta previa, placental abruption, chorioamnionitis, and hypertension disorders in pregnancy were more predictive of early preterm birth, and GDM and ICP were more predictive of late preterm birth. Different preterm subgroups had different risk profiles and different odds ratios of risk factors, thus emphasizing the need for different preventive strategies.

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Appendix 1 - Distribution of the risk factors in each group.

Variables	<32 weeks (n=1703)	32–33 weeks (n=2345)	34–36 weeks (n=11785)	37–41 weeks (199421)	*P*-value*
Maternal age (years)					<0.001
<20	83 (4.9)	123 (5.2)	403 (3.4)	4584 (2.3)	
20–34	1345 (79.0)	1915 (81.7)	9864 (83.7)	177395 (89.0)	
≥35	275 (16.1)	307 (13.1)	1518 (12.9)	17442 (8.7)	
Parity ≥ 2	704 (41.3)	905 (38.6)	4275 (36.3)	59419 (29.8)	<0.001
HDP	119 (7.0)	182 (7.8)	706 (6.0)	3486 (1.7)	<0.001
GDM	76 (4.5)	100 (4.3)	547 (4.6)	7020 (3.5)	<0.001
ICP	12 (0.7)	38 (1.6)	297 (2.5)	1973 (0.5)	<0.001
Anemia	37 (2.2)	61 (2.6)	190 (1.6)	2407 (1.2)	<0.001
Chorioamnionitis	48 (2.8)	35 (1.5)	113 (1.0)	787 (0.4)	<0.001
Placenta previa	47 (2.8)	46 (2.0)	191 (1.6)	6392 (0.2)	<0.001
Placental abruption	24 (1.4)	26 (1.1)	46 (0.4)	66 (0.0)	<0.001
Fetal distress	124 (7.3)	166 (7.1)	542 (4.6)	80718 (4.0)	<0.001

Values are presented as number and percentages (%). *P-value indicates results of $\chi 2$ test comparing proportions of the distribution of risk factors for preterm subgroups. HDP: hypertension disorders in pregnancy, ICP: intrahepatic cholestasis of pregnancy, GDM: gestational diabetes mellitus