GOCM Gynecology and Obstetrics Clinical Medicine

Risk factors and birth outcomes of preterm birth subtypes: a case-control study of singleton natural pregnancy

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To cite: Jiang Y, Zhou F, Zhang H, *et al*. Risk factors and birth outcomes of preterm birth subtypes: a case-control study of singleton natural pregnancy. *Gynecology and Obstetrics Clinical Medicine* 2024;**4**:e000027. doi:10.1136/gocm-2024-000027

Received 02 April 2024
Accepted 20 August 2024

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ABSTRACT

Objective The objective of the study was to identify the risk factors correlated with spontaneous preterm birth (SPTB) and iatrogenic preterm birth (IPTB), as well as to compare the pregnancy outcomes between SPTB and IPTB.

Materials and methods A total of 1676 (343 SPTB, 144 IPTB and 1189 full-term control group) cases were collected from the International Peace Maternity & Child Health Hospital of Shanghai between August 2018 and October 2020. A case-control study was conducted to explore the risk factors and pregnancy outcomes of SPTB and IPTB.

Results The study identified a set of risk factors for SPTB and IPTB, as well as differences in pregnancy outcomes. Reproductive tract infections and myoma of the uterus were the risk factors for SPTB ($p<0.05$). Fetal growth restriction, pre-eclampsia, intrahepatic cholestasis of pregnancy, fetal distress, placenta abnormality, oligohydramnios and scarred uterus were the risk factors for IPTB ($p<0.05$). Antenatal haemorrhage and placental abruption were the risk factors both for SPTB and IPTB ($p<0.05$). The pregnancy outcomes of the two PTB subtypes differed, and birth weight, length and 1-minute Apgar score of newborns were significantly lower in IPTB than in SPTB ($p<0.05$).

Conclusion The risk factors of SPTB and IPTB are different, and IPTB is associated with a higher incidence of worse pregnancy outcomes than SPTB.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Research has shown some differences in the aetiology and pregnancy outcomes between spontaneous preterm birth (SPTB) and iatrogenic preterm birth (IPTB).

WHAT THIS STUDY ADDS

⇒ The impact of SPTB and IPTB due to factors such as obstetric history, scarred uterus, uterine fibroids and other pregnancy complications was investigated.

⇒ Statistical analysis was conducted on neonatal length, placental weight and gestational age distribution at delivery as pregnancy outcomes for both types of preterm birth.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To thoroughly and accurately delineate the etiological differences and disparities in pregnancy outcomes between SPTB and IPTB, it is recommended that future research endeavors focus on distinguishing between these two distinct categories of preterm birth.

INTRODUCTION

The WHO defines *preterm birth (PTB)* as births before 37 completed weeks of pregnancy.[1] It has been estimated that PTB occurs in 10.6% of worldwide deliveries.[2] A recent prospective cohort study showed that PTB incidence in China stood at 5.2% from 2017 to 2018.[3] PTB represents the leading cause of perinatal morbidity and mortality.[2 4] Furthermore, PTB has been linked to long-term health conditions, such as poorer neurodevelopmental outcomes, higher rates of hospital admissions, and behavioural, social-emotional and learning difficulties in childhood, consuming prodigious health resources and placing a heavy burden on society.[5–7]

Risk factors associated with PTB include multiple medical, genetic, environmental and socioeconomic factors.[4] However, certain results from epidemiological studies have been inconsistent. PTB can be divided into spontaneous preterm birth (SPTB) and iatrogenic preterm birth (IPTB). SPTB refers to the spontaneous initiation of regular uterine contractions during labour and cervical changes, independent of premature rupture of membranes. IPTB, including labour induction and caesarean delivery without spontaneous labour, mainly results from maternal or fetal complications. The proportion of IPTB varies between regions and countries, ranging from 11.8% to 31.7%.[8] Existing studies have shown that IPTB is associated with poorer neonatal outcomes than SPTB.[9–14] In addition, differences between aetiologies for PTB have been investigated.[15 16] Black race, smoking, nulliparity, body mass index (BMI) and prior

caesarean birth were significant risk factors for SPTB but had a small or insignificant effect on IPTB. For IPTB, multiple clinical conditions (eg, pre-eclampsia, chronic hypertension) were the primary influencing factors, while other risk factors had much smaller or inconsistent contributions. The above evidence has identified that IPTB and SPTB might represent a different aetiological or causal pathway resulting in preterm delivery. Thus, the failure to focus on the distinction between PTB subtypes may explain the inconsistencies in previous epidemiological studies.

Accurate phenotypic classification is essential to epidemiological study and developing effective methods for preventing PTB. So far, a comprehensive comparison of aetiological heterogeneity between SPTB and IPTB is still lacking. Therefore, the study aims to identify the difference between SPTB and IPTB in terms of the aspects of associated risk factors and pregnancy outcomes. It seeks to investigate the varying degrees of association between multiple risk factors and SPTB versus IPTB, the differences in risk factor profiles for each PTB subtype, and the variations in the severity of adverse pregnancy outcomes between the two forms of PTB.

Materials and methods

Study design and population

A case-control design was used for this study. Patients were recruited at the International Peace Maternity & Child Health Hospital of Shanghai (IPMCH), China, a tertiary obstetrics and gynaecology hospital, which was conducted in October 2020. Inclusion criteria were as follows: patients were singleton natural pregnancies delivery from August 2018 through October 2020, the case group delivered before 37 weeks, and controls were randomly selected at IPMCH by matching the time of first inspection with the cases, with a ratio of 2 controls per case, for deliveries between $37^{0/7}$ and $41^{0/7}$ weeks. The enrolled subjects were from Shanghai Province and shared the same ethnic background. Patients who met one of the following criteria were excluded: (1) cases with multiple pregnancies; (2) in vitro fertilisation; (3) stillbirths; and (4) missing information. Finally, a total of 1676 eligible samples were recruited (1189 controls with 487 preterm deliveries). In the case of preterm deliveries, 343 were SPTB and 144 were IPTB. All included samples were neither smokers nor drinkers.

Definition and data collection

The primary outcome was the type of preterm birth: spontaneous preterm birth (SPTB, due to preterm labour with regular uterine contractions and cervical changes, with or without preterm membrane rupture) or indicated preterm birth (IPTB, due to any maternal or fetal medical complication necessitating early delivery). Gestational age was established based on first-trimester ultrasound estimations for the majority of patients and a small minority of patients by last menstrual bleeding prior to pregnancy. The characteristics that were chosen for investigating the relationship between two subtypes of PTB included non-medical and medical factors that were available in the sample: maternal age, education level, fetal sex, BMI at the beginning of pregnancy, previous obstetric history (gravida, para, miscarriage), scarred uterus, myoma of uterus, hypertension, pre-eclampsia, gestational diabetes mellitus (GDM), anaemia in pregnancy, intrahepatic cholestasis of pregnancy (ICP), reproductive tract infections, fetal growth restriction (FGR), fetal distress, oligohydramnios, placenta abnormality(placenta previa, placenta implantation, velamentous placenta and battledore placenta unified), placental abruption, antenatal haemorrhage. Secondary outcomes included newborn birth weight, fetal macrosomia, 1-minute Apgar score, placenta weight and delivery mode.

Statistical analysis

Data were analysed using SPSS V.17 software. Categorical data were compared using either the χ^2 test or Fisher's exact test, and continuous data were analysed with Student's t-tests. Two multivariable logistic regression models were generated, which included all the variates of non-medical and medical factors mentioned above to calculate ORs of each subtype of PTB for each risk factor. To check for multicollinearity among the factors included, two linear regression models were constructed, and the variance inflation factors (VIFs) for all factors were calculated. The results showed that all VIF values were less than 2, indicating that there is no multicollinearity issue among the included factors. P value <0.05 was considered statistically significant.

RESULTS

The characteristics of research participants with term birth, SPTB and IPTB are shown in table 1. PTB research participants in the parent study were classified as SPTB (n=343; 70.4%) or IPTB (n=144; 29.6%). Age, educational level, fetal sex and BMI at the beginning of pregnancy of SPTB and IPTB were similar to the control.

Two independent logistic regression models calculated the adjusted ORs for influence factors of SPTB and IPTB. As presented in table 2, the logistic regression analysis showed that antenatal haemorrhage (OR 23.9, 95% CI 4.2 to 135.7), placental abruption (OR 20.0, 95% CI 4.2 to 96.0), reproductive tract infections (OR 2.4, 95% CI 1.1 to 5.1) and myoma of the uterus (OR 1.6, 95% CI 1.0 to 2.4) were independent risk factors for SPTB. Antenatal haemorrhage (OR 49.8, 95% CI 9.3 to 267.7), FGR (OR 40.5, 95% CI 10.6 to 154.5), pre-eclampsia (OR 32.5, 95% CI 16.1 to 65.4), ICP (OR 24.9, 95% CI 7.6to 81.9), placental abruption (OR 12, 95% CI 1.5 to 103.2), fetal distress (OR 8.9, 95% CI 5.1 to 15.4), placenta abnormality (OR 6.7, 95% CI 3.3 to 13.7), oligohydramnios (OR 3.5, 95% CI 1.3 to 9.7) and scarred uterus (OR 3.6, 95% CI 1.8 to 7.2) were significant risk factors for IPTB. Antenatal haemorrhage and placental abruption were both associated with significantly increased risk for SPTB and IPTB. Reproductive

Table 1 Clinical characteristics of the study population

Variable	Controls (n=1189)	SPTB (n=343)	P value	IPTB (n=144)	P value
Maternal age ≥35 years	361 (30.4)	87 (25.4)	0.073	42 (29.2)	0.768
Education level			0.621		0.993
High school or less	58 (4.9)	19 (5.5)		7 (4.9)	
College diploma or higher	1131 (95.1)	324 (94.5)		137 (95.1)	
Fetal sex			0.881		0.454
Male	740 (62.2)	215 (62.7)		85 (59.0)	
Female	449 (37.8)	128 (37.3)		59 (41.0)	
BMI at the beginning of pregnancy (kg/m^2)			0.528		0.150
Underweight (<18.5)	142 (139.8)	43 (12.5)		12 (8.3)	
Normal (18.5–24)	863 (72.6)	239 (69.7)		102 (70.8)	
Overweight or obesity (≥24)	184 (15.5)	61 (17.8)		30 (20.8)	
Gravida			0.054		0.346
0	522 (43.9)	173 (50.4)		62 (43.1)	
1–2	555 (46.7)	135 (39.4)		63 (43.8)	
≥3	112 (9.4)	35 (10.2)		19 (13.2)	
Para			0.007		0.987
0	748 (62.9)	236 (68.8)		90 (62.5)	
=1	423 (35.6)	96 (28.0)		52 (36.1)	
≥2	18 (1.5)	11 (3.2)		2 (1.4)	
Previous abortion			0.094		0.082
0	717 (60.3)	224 (65.3)		76 (52.8)	
≥1	472 (39.7)	119 (34.7)		68 (47.2)	
Maternal complications					
Scarred uterus	229 (19.3)	47 (13.7)	0.018	40 (27.8)	0.016
Myoma of uterus	85 (7.1)	34 (9.9)	0.092	23 (16.0)	<0.001
Hypertension	49 (4. 1)	13 (3.8)	0.784	16 (11.1)	<0.001
Pre-eclampsia	25 (2.1)	1 (0.3)	0.022	44 (30.6)	<0.001
GDM	203 (17.1)	68 (19.8)	0.239	27 (18.8)	0.615
Anaemia in pregnancy	207 (17.4)	40 (11.7)	0.011	24 (16.7)	0.824
ICP	8 (0.7)	2 (0.6)	0.856	11 (7.6)	<0.001
Reproductive tract infections	20 (1.7)	13 (3.8)	0.018	4 (2.8)	0.350
Fetal complications					
FGR	4 (0.3)	2 (0.6)	0.519	22 (15.3)	<0.001
Fetal distress	143 (12.0)	37 (10.8)	0.530	57 (39.6)	<0.001
Other					
Oligohydramnios	33 (2.8)	4 (1.2)	0.087	9 (6.3)	0.024
Placenta abnormality	46 (3.9)	19 (5.5)	0.176	30 (20.8)	<0.001
Placental abruption	2 (0.2)	11 (3.2)	<0.001	7 (4.9)	<0.001
Antenatal haemorrhage	2 (0.2)	10 (2.9)	<0.001	14 (9.7)	<0.001

Values are means±SDs or numbers (percentages).
BMI, body mass index; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; IPTB, iatrogenic preterm birth; SPTB, spontaneous preterm birth.

Table 2 Risk factors of SPTB and IPTB

SPTB	OR (95% CI)	IPTB	OR (95% CI)
Antenatal haemorrhage	23.9 (4.2 to 135.7)**	Antenatal haemorrhage	49.8 (9.3 to 267.7)**
Placental abruption	20.0 (4.2 to 96.0)**	FGR	40.5 (10.6 to 154.5)**
Reproductive tract infections	2.4 (1.1 to 5.1)*	Pre-eclampsia	32.5 (16.1 to 65.4)**
Para		ICP	24.9 (7.6 to 81.9)**
1	1 (reference)	Placental abruption	12 (1.5 to 103.2)*
0	1.1 (0.7 to 1.6)	Fetal distress	8.9 (5.1 to 15.4)**
≥2	2.1 (0.9 to 5.1)	Placenta abnormality	6.7 (3.3 to 13.7)**
Myoma of uterus	1.6 (1.0 to 2.4)*	Oligohydramnios	3.5 (1.3 to 9.7)*
FGR	1.3 (0.2 to 7.2)	Scarred uterus	3.6 (1.8 to 7.2)**
Gravida		Hypertension	1.8 (0.7 to 4.4)
1–2	1 (reference)	Maternal age ≥35	1.8 (1.0 to 3.3)
0	1.2 (0.8 to 1.6)	Gravida	
≥3	1.2 (0.8 to 2.0)	1–2	1 (reference)
Placenta abnormality	1.2 (0.7 to 2.3)	0	1.4 (0.7 to 2.8)
BMI		≥3	1.7 (0.8 to 3.6)
Normal (18.5–24)	1 (reference)	Previous abortion	1.6 (1.0 to 2.6)
Underweight (<18.5)	1.1 (0.7 to 1.6)	High school or less education	1.3 (0.5 to 3.7)
Overweight or obesity (≥24)	1.2 (0.9 to 1.7)	GDM	1.2 (0.6 to 2.2)
GDM	1.2 (0.9 to 1.7)	Myoma of uterus	1.1 (0.5 to 2.4)
Male baby	1.0 (0.8 to 1.3)	Para	
Previous abortion	0.9 (0.7 to 1.1)	1	1 (reference)
High school or less education	0.8 (0.5 to 1.5)	0	0.9 (0.4 to 2.0)
Fetal distress	0.8 (0.5 to 1.2)	≥2	1.1 (0.2 to 6.4)
Hypertension	0.8 (0.4 to 1.6)	Male baby	1.0 (0.6 to 1.6)
Maternal age ≥35	0.8 (0.6 to 1.1)	Reproductive tract infections	1.0 (0.2 to 6.0)
ICP	0.8 (0.2 to 4.0)	BMI	
Scarred uterus	0.7 (0.5 to 1.1)	Normal (18.5–24)	1 (reference)
Anaemia in pregnancy	0.7 (0.4 to 0.9)*	Underweight (<18.5)	0.7 (0.3 to 1.6)
Oligohydramnios	0.4 (0.2 to 1.3)	Overweight or obesity (≥24)	0.9 (0.5 to 1.7)
Pre-eclampsia	0.1 (0.01 to 0.9)*	Anaemia in pregnancy	0.9 (0.5 to 1.6)

The ORs for each risk factor were calculated using two independent logistic regression models. Statistical significance was defined as p<0.05. *p<0.05; **p<0.01.
BMI, body mass index; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; IPTB, iatrogenic preterm birth; SPTB, spontaneous preterm birth.

tract infections (OR 2.4, 95% CI 1.1 to 5.2) and myoma of the uterus (OR 1.6, 95% CI 1.0 to 2.5) were important risk factors for SPTB but not IPTB. However, FGR, pre-eclampsia, ICP, fetal distress, placenta abnormality, oligohydramnios, scarred uterus and previous abortion were significant risk factors for IPTB but not SPTB. Anaemia in pregnancy (OR 0.7, 95% CI 0.4 to 0.9) was associated with a decreased risk of SPTB, but not with IPTB. The pre-eclampsia (OR 0.1, 95% CI 0.01 to 0.9) was also associated with a decreased risk of SPTB, but there was only one case of SPTB.

Pregnancy outcomes for control, SPTB and IPTB are shown in table 3. The gestational ages of the three groups were 39.1±1.0, 35.2±1.9 and 35.1±1.9 weeks, respectively. The average gestational ages between SPTB and IPTB were similar, but neonates who underwent IPTB revealed a higher proportion of moderate prematurity (32–33 weeks) and severe prematurity (<32 weeks). In addition, newborn birth weight, newborn length and 1-minute Apgar score were significantly lower in IPTB than in SPTB. There was no significant difference in placenta weight between SPTB and IPTB. The above four indexes were greater in the control group than two subtypes of PTB.

Caesarean section rates varied across the three groups. Almost all research participants (97.9%) in the IPTB

Table 3 Comparison of pregnancy outcomes among study groups

Variable	Controls (n=1189)	SPTB (n=343)	IPTB (n=144)	P value
Gestational age (weeks)	39.1±1.0	35.2±1.9**	35.1±1.9**	0.427
Subcategory of gestational age (weeks)				0.328
Near term (34–36 weeks)	–	286 (83.4)	112 (77.8)	
Moderate prematurity (32–33 weeks)	–	32 (9.3)	19 (13.2)	
Severe prematurity (<32 weeks)	–	24 (7.3)	13 (9.0)	
Newborn birth weight (g)	3378.4±397.9	2580.8±482.8**	2391.4±605.7**	<0.001
Subcategory of newborn birth weight (g)		**	**	0.003
Fetal macrosomia (≥4000 g)	68 (5.7)	0 (0)	0 (0)	
Normal birth weight (~2500 g)	1108 (93.2)	209 (60.9)	67 (46.5)	
Low birth weight (<2500 g)	13 (1.1)	134 (39.1)	77 (53.5)	
Newborn length (cm)	50.0±1.2	47.1±3.2**	46.2±3.6**	0.013
1-minute Apgar score	9.9±0.6	9.6±1.1**	9.2±1.6**	0.010
A subcategory of 1-minute Apgar score		**	**	0.030
Normal (8–10)	1175 (98.8)	324 (94.5)	128 (88.9)	
Asphyxia (0–7)	12 (1.2)	19 (5.5)	16 (11.1)	
Placenta weight (g)	633.7±106.8	529.7±103.9**	511.0±137.9**	0.146
Delivery mode		**	**	<0.001
Vagina	556 (46.8)	233 (67.9)	3 (2.1)	
Caesarean	633 (53.2)	110 (32.1)	141 (97.9)	

Values are means±SDs or numbers (percentages). **Compared with controls, p<0.001; p value: SPTB compared with IPTB.
IPTB, atrogenic preterm birth; SPTB, spontaneous preterm birth.

group had caesarean section, while SPTB had the lowest (32.1%) caesarean section rate.

DISCUSSION

In this study, we analysed the data from this case-control study of singleton natural pregnancy women in a tertiary referral hospital in China. We revealed the set of risk factors differentiating SPTB from IPTB and discovered that IPTB represented worse pregnancy outcomes than SPTB.

Reproductive tract infection is a risk factor for SPTB. Amniotic fluid interleukin-6 (IL-6) levels are considered an excellent marker of intrauterine inflammation that can be evaluated prenatally. One previous study demonstrated that, compared with the full-term group, the mean of second-trimester amniotic fluid IL-6 level was significantly elevated for SPTB (1.6±3.2 ng/mL vs 0.8±1.2 ng/mL, p=0.01) but was not statistically different for IPTB (1.4±4.0 vs 0.8±1.2 ng/mL, p=0.12).[17] In addition, some studies found an association between *Chlamydia trachomatis* infection and preterm premature rupture of membranes.[18] This suggests that infection conditions contribute to SPTB and primarily result in premature rupture of membranes. However, our study did not further separate preterm premature rupture of membranes from spontaneous labour with intact membranes, for which further research is needed.

Previous studies found that the myoma of the uterus was associated with PTBs.[19 20] In this study, multivariate logistic regression analysis confirmed that women with myoma of the uterus had a higher risk of SPTB but discovered no significant association with IPTB.

Our study found that placental abruption and prenatal haemorrhage were risk factors for both SPTB and IPTB, but that incidences of the two complications, particularly prenatal haemorrhage, were significantly higher in the IPTB group than in the SPTB group.

Prenatal haemorrhage and placental abruption are common indicators of a medical intervention resulting in PTB. Our results suggest that placental abruption and prenatal haemorrhage are further important reasons for SPTB. Consistent with previous studies, FGR, pre-eclampsia, ICP, fetal distress, placenta abnormality and oligohydramnios were important risk factors for IPTB in the present study.[21–23]

In addition, our study has clarified that scarred uterus is a risk factor for IPTB. A scarred uterus is mainly the result of a previous caesarean delivery causing pathological changes in the myometrium and endometrium in the uterus. Previous studies have demonstrated that a scarred uterus was strongly associated with ruptured uterus and

placental abruption,[24 25] with the latter known as a critical induction for IPTB. Thus, it is biologically plausible that a scarred uterus is associated with IPTB. This finding suggests that encouraging women to deliver vaginally may be an essential step in lowering the risk of IPTB in later pregnancy.

Numerous studies have evaluated the relationship between anaemia and PTB. However, these studies did not consider clinical subtypes and reported conflicting results.[26–28] A large prospective cohort study by Zhang *et al*[29] found that anaemia in early pregnancy was associated with increased risk for preterm premature rupture of membranes, whereas exposure in late pregnancy was associated with reduced risk for SPTB. Data for anaemia collected in our study can represent the anaemia of mothers near the time of delivery. Our result was similar to Zhang *et al*, which indicated that adequate physiological hemodilution during mid-to-late pregnancy is associated with reduced risk for PTB. However, our study did not collect accurate haemoglobin levels of pregnant women and cannot further explore the impact of different severity of anaemia on PTB. The incidence of anaemia of IPTB was higher than that of SPTB, indicating that some severe anaemia might impact IPTB. Further study is needed.

We also observed a very low incidence of pre-eclampsia for SPTB. One explanation for this might be that pre-eclampsia is a severe complication and that medical treatment will be taken and frequently results in IPTB when occurring before 37 gestational weeks. Another reason might be that the small size of the SPTB group introduced the risk of a sampling bias.

Nuss *et al* found that IPTB was associated with worse psychomotor development than SPTB.[9] Chen *et al* noted the association between two PTB subtypes and different neonatal complications.[10] Based on an analysis of composite pregnancy outcomes, this study has confirmed that PTB, especially IPTB, results in adverse pregnancy outcomes with greater frequency.

Some limitations of this study should be noted. First, due to the limited size of our study sample, to improve the efficiency of analysis, our results were restricted to singleton natural pregnancy, which to some extent reduces the generalisability of the study results. Second, the clinical symptoms of anaemia and amniotic fluid pollution with serious levels are not distinguished by strict quantitative detection indicators, and it is impossible to judge the difference in the degree of influence of different degrees of disease on PTB. Finally, the PTB clinic subtype groups have a small sample size, which may be a factor that leads to low incidence complications such as PTB history with a large number of previous studies have proven as risk factors of PTB failed to show differences between the comparison groups in our study. Despite these limitations, this study has several strengths. The aetiological types of PTB could be classified according to the reason for delivery by consulting obstetric records and collecting neonatology records, which ensured the accuracy of the data to the greatest extent possible. By using a matching time for the first inspection of the pregnant individual, the comparability of groups was guaranteed. Furthermore, the study included both contributing factors and pregnancy outcomes, in an unambiguous chronological order that supported causal inference. Finally, a comparison of multiple aspects comprehensively revealed the heterogeneity of the two PTB subtypes under analysis. One additional point to note is that pregnancy outcomes are closely related to the gestational age at delivery. The influencing factors among early, mid and late PTBs are likely to differ, and their aetiologies and pregnancy outcomes deserve further investigation. However, due to the limitations in sample size, this study is unable to explore this further. In conclusion, combining multiple factor analysis and carefully defining SPTB and IPTB, this study has revealed the heterogeneity of risk factors and pregnancy outcomes of SPTB and IPTB. PTB continues to be a significant public health problem, and precisely understanding different subtypes of PTB is essential for effective intervention and prevention. Thus, our data might provide more guidance for future research.

Acknowledgements We would like to thank Xiaofeng Wang for providing a thorough discussion of the research topic in the article. We thank Yafei Tian for providing linguistic polishing to the article.

Contributors YJ designed the study, collected and analysed data, and drafted the manuscript. FZ designed the study, collected data and drafted the article. Haokun Zhang interpreted the data and rigorously edited the overall content of the article. Hui Zhang provided significant editing revisions for the explanation of results, statistical analysis and writing related to the results of the article. SC participated in the research design, and data collection, and made important additions to the results of the article. EA contributed to the execution of the research and made significant revisions to the article content. HC participated in the research design, and research execution, and made significant modifications to the content of the result tables. CX participated in the research design and acquisition of data, and made significant modifications to the overall content of the article. DL participated in the research design and made significant modifications to the overall content of the article. All authors have read and approved the final manuscript.YJ is the guarantor of this study, accepting full responsibility for the work and/or the conduct of the study, having access to the data, and controlling the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethical review committee of The International Peace Maternity & Child Health Hospital (Shanghai, China) and the Approval ID number is GKLW 2019-50.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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