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Original Article

A case control study of risk factors and neonatal outcomes of preterm birth

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ABSTRACT

Objective: The aim is to examine risk factors and neonatal outcomes of preterm birth and to provide basis in preventing preterm birth.
Materials and methods: we carried out our study on 1328 term controls and 1328 preterm birth cases. By using multivariable logistic regression procedures we estimated odds ratio (OR) of potential preterm birth risk factors. T-test and chi-square test were used to estimate differences between groups.
Results: Maternal age, prior history of pregnancy and abortion, prenatal care, complications of pregnancy (includes hypertension, intrahepatic cholestasis of pregnancy (ICP), fetal growth restriction (FGR), premature rupture of the membranes (PROM), placenta previa, abnormal presentation, abnormal S/D ratio et al.) were significantly associated with preterm birth. Several factors emerged as being statistically significant risk factors for preterm birth, such as prior history of pregnancy, hypertension, ICP, FGR, PROM, placenta previa and abnormal presentation. The time of prenatal care was shown to be a protective factor. Additionally, we observed evidence suggested that male babies are known to have a significant higher risk of preterm birth than female babies.
Conclusion: Prior history of pregnancy, hypertension, ICP, FGR, PROM, placenta previa and abnormal presentation were covariates identified in this study as risk factors for preterm birth. Preterm birth is an important reason of neonatal poor prognosis and death.

Introduction

Preterm birth, defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation [1], is the leading cause of perinatal morbidity and mortality in both developed and developing countries [2,3]. It is associated with short-term and long-term adverse outcomes as well as increased healthcare costs [4–6]. The incidence of preterm birth ranges from 5% to 13% in Europe, Australia, Northern America, Asia and Africa [3,7–10]. No data have been published on the global incidence of preterm birth. There are worrying trends that the incidence of preterm birth is on the increase [9,11]. The events leading to preterm birth are still not completely understood, although the etiology is thought to be multifactorial. Till now it's unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Efforts to predict and prevent the occurrence of preterm birth are difficult because of our lacking in understanding the biochemical mechanism of labor and the multiplicity of medical and socioeconomic factors associated with preterm birth.

Putative preterm birth risk factors include predisposing genetic attributes, preterm premature rupture of the membranes, a prior history of preterm birth, vaginal infections, pregestational hypertension or diabetes, multiparity, multiple births, greater use of assisted reproduction techniques, greater use of elective Caesarean section, psychosocial stress, psychiatric disorders, and lifestyle habits such as smoking, alcohol and illicit drug use during pregnancy [9,12–16]. Despite intensive research efforts, the underlying causes of preterm birth remain elusive.

Evidence-based clinical intervention and effective educational programs aiming to reduce preterm birth rates require accurate identification and evaluation of the risk factors of preterm birth. Although the risk factors for preterm birth have been widely studied on European and North American populations, they have not been as extensively characterized in China. This information is

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necessary to guide further research in this area. We, therefore, sought to evaluate risk factors and neonatal outcomes of preterm birth. In this study, we have carried out a detailed comparison of preterm and term deliveries in a relatively homogeneous obstetric population attending a tertiary referral hospital, to highlight areas where further research or intervention is needed in order to prevent preterm birth and improve perinatal outcome.

Materials and methods

Study population

This survey was done at Northern Jiangsu Province Hospital, Yangzhou Jiangsu, China. This is a tertiary referral hospital with approximately 3200 deliveries a year; preterm deliveries accounted for approximately 8% of all births. We obtained lists of deliveries before completed 37 weeks and after 28 weeks of gestation (n = 1328) between August 2012 and August 2017. Preterm delivery cases were identified by daily monitoring of all new deliveries at postpartum wards of this hospital. A case control study using one control for each case of preterm delivery was conducted among women who delivered at term (≥37 weeks of gestation) and were selected from the same hospital of delivery in this period. We used computer generated random numbers to draw separate samples from lists of all term babies delivered. An eligible control, delivering immediately after a case patient, was approached and recruited for the study. Gestational age was based either on certain dates or a dating scan. Antenatal care was undertaken by an obstetrician and followed standard practice.

All participants provided informed consent and the research protocol was reviewed and approved by ethical committees of the Faculty of Medicine, Northern Jiangsu Province Hospital, Clinical Medical College, Yangzhou University.

Data collection

Initial maternal and newborn information was taken from the hospital computer databases. Participants' labor and delivery medical records and prenatal medical records were retrieved and analysed in detail by a trained research doctor using a structured proforma. The Recorded information was anonymized by assigning a unique project number to each delivery. Data on maternal and fetal characteristics at birth were recorded, including maternal age, gestational age at delivery, past obstetric history (including previous history of termination, miscarriage and preterm birth), complications of pregnancy and delivery, delivery mode, birth weight, Apgar score and gender of baby. Data was entered into a Microsoft Office excel 2007 database and imported into SPSS statistical software for analysis.

Analytical variable specification

The diagnosis of preterm delivery was made using Chinese Medical Association guidelines [1]. Gestational age was determined by a reliable collection of the last menstrual period (LMP), a positive urine β-HCG test before 6 weeks gestation, and ultra-sonographic examination within 20 weeks gestation. If both LMP and ultrasound dates were available and the dates were within 14 days, we used the former to assign gestational age. If the two dates differed by more than 14 days, we used the ultrasound date.

Statistical analysis

Comparisons between cases and controls were made using standard statistical procedures. Multivariable logistic regression procedures were employed to calculate odd ratios (OR) of potential risk factors associated with preterm birth. Confidence intervals (CI), at the 95% level were also reported for each unadjusted and adjusted OR. Confounding was assessed by entering potential co-founders into a logistic regression model one at a time, and by comparing the adjusted and unadjusted ORs. Final logistic regression models included covariates that altered unadjusted ORs by at least 10%. Continuous variables were summarized by mean (SD). Means were compared using Student's t-tests. For categorical variables Chi-squared tests were used. Statistical significance was achieved when *P* value was less than 0.05 throughout.

Results

The general characteristics of the control and preterm groups are shown in Table 1 (n = 1328). Gestational age of preterm group is 241.94 ± 14.32 days, while of control group is 276.45 ± 7.70 days. The control and preterm groups had very different maternal age and hospitalization days ($P = 0.000$) and, as expected, multiple births were more common in the preterm group ($P = 0.000$) (Table 1). Ninety-six of the multiple pregnancies were the result of assisted reproduction treatment (IVF). Since the obstetric management of multiple pregnancies differs from that of singleton pregnancies, we excluded all the multiple pregnancies from further analysis.

Maternal age

Table 2 displays maternal age of preterm cases and term controls. Women who were <20 years of age, compared to those who were 25–29 years old, had a 6.63-fold increased risk of preterm birth (95% CI: 2.22, 19.82) (Table 2). Advanced maternal age was associated with a 4.47-fold increased risk of preterm birth (OR = 4.47, 95% CI: 3.27, 6.13) (Table 2). Previous reports have indicated that extremes of maternal age predispose to preterm birth and we have confirmed that the incidence of preterm birth in women over 35 years of age remains significantly higher. Moreover, teenage mothers were also more common in the preterm group. We observed evidence of a U-shaped relationship of preterm birth risk in relation to maternal age.

Table 1
General characteristics of the study groups.

	Control group	Preterm group	*P* value
Number	1328	1328	
Gestational age (days)	276.45 ± 7.70	241.94 ± 14.32	Not applicable
Maternal age (days)	27.13 ± 3.78	28.49 ± 5.09	0.000
Hospitalization days	6.29 ± 3.13	8.73 ± 7.76	0.000
Multiple births	11	159	0.000

Table 2
Maternal age in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		OR (95%CI)
	n	%	n	%	
Maternal age (years)					
<20	4	0.30	17	1.45	6.63 (2.22,19.82)
20–24	303	23.01	252	21.56	1.29 (1.06,1.59)
25–29	711	53.99	456	39.01	1.00 (Reference)
30–34	238	18.07	269	23.01	1.76 (1.43,2.18)
≥35	61	4.63	175	14.97	4.47 (3.27,6.13)

History of previous pregnancies

As is shown in Table 3, about 62% of women in preterm group and 42% in control group had been pregnant previously, and about 39% of women in preterm group and 21% in control group had previous deliveries. The proportion of women with a previous pregnancy or previous delivery in the preterm group was significantly higher than in the control group (P = 0.000). Analysing the data of previous abortion revealed that the maternal history of abortions were significantly more common in the preterm group ($P = 0.000$).

Prenatal care

Prenatal care in preterm cases and term controls are presented in Table 4. Although the majority of women received regular prenatal care, some of these women have no prenatal care or irregular prenatal care. As expected, lack of prenatal care was associated with an increased risk of preterm birth. Women without prenatal care during the index pregnancy had a 5.19-fold increased risk of preterm birth (OR = 5.19, 95% CI: 3.77, 7.14) (Table 4). Moreover, pregnant women with irregular prenatal care had a 2.87-fold increased risk of preterm birth (OR = 2.87, 95% CI: 2.16, 3.80) (Table 4).

Assisted reproduction treatment (IVF)

Cases with assisted reproduction treatment (IVF) in the control and preterm groups are shown in Table 5. As we excluded all the multiple pregnancies from the study, there were not many cases left. As shown in Table 5, assisted reproduction treatment (IVF) were not significantly associated with preterm delivery ($P = 0.697$).

Complications of pregnancy

The incidence of maternal, fetal and other complications of pregnancy is shown in Table 6. When the incidence of complications of pregnancy is presented separately in control and preterm pregnancies, very different patterns were observed. Cases with scarred uterus, women who had cesarean section once or more or other previous uterine surgery, occurred in both control and preterm pregnancies, but were significantly increased in the latter ($P = 0.000$). Hypertension was also significantly increased in the preterm group ($P = 0.000$). Cases with intrahepatic cholestasis of pregnancy (ICP) were more common in preterm pregnancies ($P = 0.000$), but the incidence was low. Cases with gestational diabetes mellitus (GDM) were similar in both groups ($P = 0.216$).

Fetal complications especially abnormal presentation and fetal growth restriction (FGR) were more frequent in the preterm group (Table 6). However, fetal distress occurred in both control and preterm pregnancies, and was not significantly associated with preterm delivery ($P = 0.132$) (Table 6).

Premature rupture of the membranes (PROM) was the most common another complication in both control and preterm pregnancies, and it was significantly more common in the preterm group ($P = 0.000$) (Table 6). Women with placenta previa or abnormal S/D ratio were more likely to have preterm delivery ($P = 0.000$ and 0.000 respectively) (Table 6). Finally, cases with placental abruption, oligohydramnios or hydramnios occurred in both control and preterm pregnancies, and were similar in both groups ($P > 0.05$ for all) (Table 6).

Correlative clinical factors of preterm birth

Results from multivariable logistic regression models for preterm birth (after adjusted for all other covariates in the models) are summarized in Table 7. In multivariable adjusted analyses, seven factors emerged as being statistically significant risk factors for preterm birth. These factors include: prior history of previous pregnancy (Exp(B) = 1.263, 95% CI:1.059,1.508), hypertension (Exp(B) = 4.677, 95% CI: 2.110,10.369), ICP (Exp(B) = 5.580, 95% CI:

Table 3
History of previous pregnancy in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		*P* value
	n	%	n	%	
Gravida					
=0	764	58.01	448	38.32	0.000
>0	553	41.99	721	61.68	
Para					
=0	1042	79.12	717	61.33	0.000
>0	275	20.88	452	38.67	
Number of previous abortion					
=0	889	67.50	591	50.56	0.000
>0	428	32.50	578	49.44	

Table 4
Prenatal care in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		OR (95%CI)
	n	%	n	%	
Prenatal care					
regular	1184	89.90	821	70.23	1.00 (Reference)
irregular	81	6.15	161	13.77	2.87 (2.16,3.80)
no	52	3.95	187	16.00	5.19 (3.77,7.14)

Table 5
IVF in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		*P* value
	n	%	n	%	
Assisted reproduction treatment (IVF)					
yes	36	2.73	35	2.99	0.697
no	1281	97.27	1134	97.01	

Table 6
Complications of pregnancy in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		*P* value
	n	%	n	%	
Maternal complications					
Scarred uterus	145	11.01	200	17.11	0.000
Hypertension	36	2.73	161	13.77	0.000
Gestational diabetes mellitus	89	6.76	65	5.56	0.216
Intrahepatic cholestasis of pregnancy	16	1.21	48	4.11	0.000
Fetal complications					
Fetal growth restriction	16	1.21	70	5.99	0.000
Fetal distress	27	2.05	35	2.99	0.132
Abnormal presentation	48	3.64	174	14.88	0.000
Other complications					
Premature rupture of the membranes	174	13.21	413	35.33	0.000
Placenta previa	20	1.52	126	10.78	0.000
Placental abruption	12	0.91	17	1.45	0.208
Oligohydramnios	89	6.76	83	7.10	0.737
Hydramnios	8	0.61	13	1.11	0.170
Abnormal S/D ratio	4	0.30	35	2.99	0.000

Table 7
Correlative clinical factors of preterm birth.

	B	*S.E.*	*Wald*	*df*	*Sig.*	Exp(*B*) (95%CI)
Prenatal care	−0.403	0.038	113.085	1	0.000	0.669 (0.621,0.720)
Gravida	0.234	0.090	6.720	1	0.010	1.263 (1.059,1.508)
Hypertension	1.543	0.406	14.425	1	0.000	4.677 (2.110,10.369)
Scarred uterus	−0.516	0.296	3.034	1	0.082	0.597 (0.334,1.067)
Intrahepatic cholestasis of pregnancy	1.719	0.629	7.468	1	0.006	5.580 (1.626,19.149)
Fetal growth restriction	1.221	0.618	3.910	1	0.048	3.391 (1.011,11.376)
Premature rupture of the membranes	1.453	0.219	43.889	1	0.000	4.276 (2.782,6.572)
Placenta previa	1.362	0.525	6.732	1	0.009	3.906 (1.395,10.932)
Abnormal presentation	1.219	0.375	10.573	1	0.001	3.383 (1.623,7.054)

1.626,19.149), FGR (Exp(B) = 3.391, 95% CI: 1.011,11.376), PROM (Exp(B) = 4.276, 95% CI: 2.782,6.572), placenta previa (Exp(B) = 3.906, 95% CI: 1.395,10.932) and abnormal presentation (Exp(B) = 3.383, 95% CI: 1.623,7.054). The times of prenatal care was shown to be a protective factor for preterm birth (Exp(B) = 0.669, 95% CI: 0.621,0.720), which means regular prenatal care can reduce the risk of preterm birth. Abnormal S/D ratio during pregnancy and scarred uterus were not statistically significant risk factors for preterm birth risk overall.

Labor and delivery

50.80% of women in the control group went into spontaneous labor and 49.20% had an elective delivery (caesarean section or induction of labor) indicated for medical or obstetric reasons. In the preterm group 51.67% of women had spontaneous labor and 48.33% were delivered electively (Table 8). No significant difference of the delivery mode was found between the two groups ($P = 0.665$).

Neonatal outcome

There were 752 male babies and 417 female babies in the preterm group compared to 675 male babies and 642 female babies in the control group (Table 9). In agreement with previous reports [17], male babies are known to have a significantly higher risk of being preterm than female babies (OR = 1.72, 95% CI: 1.46, 2.02).

Table 10 displays neonatal weight and Apgar score of preterm cases and term controls. Cases in preterm birth group more frequently resulted in adverse perinatal outcomes, such as lower neonatal birth weight, lower Apgar score at 1 min and 5 min, compared with women in control group (Table 10) ($P < 0.05$).

Discussion

This manuscript provides information on risk factors and neonatal outcomes associated with preterm birth in a tertiary referral hospital in China. Our findings are consistent with the hypothesized complex multifactorial etiology of preterm birth, and are also consistent with other studies that provide some evidence suggestive of heterogeneity of risk factors for preterm birth. The study highlights the main risk factors and neonatal outcomes of preterm birth, and emphasizes the need to promote research in developing effective management for preterm birth.

In agreement with other previous reports, our data confirm that young and advanced maternal age, respectively, were associated with preterm birth risk overall [18–20]. Furthermore, we observed evidence of a U-shaped relationship of preterm birth risk in relation to maternal age. This pattern in risk is consistent with observations made by previous investigators.

We noted that women with a prior history of pregnancy or delivery, as compared with those parous women who had no such history, had an increased risk of preterm birth in the current pregnancy. Additionally, we observed evidence that suggesting association of prior history of abortion with risk of preterm birth. This observation of high relative risk given prior history of abortion has been consistently reported by other investigators [21,22]. Similar to our findings, Shingairai A Feresu et al. reported that parous women with a prior history of abortion had a 1.21-fold increased risk of preterm birth (95% CI: 0.93, 1.56) when compared with parous women who did not have a history of abortion [21].

Previous investigators indicated that, lack of prenatal care was associated with preterm birth as women who deliver prematurely often deliver before their intended date of initiating care [21,23]. As would be expected, we found that the risk of preterm birth was greatly elevated among women who had no prenatal care or only had irregular prenatal care. This result shows that effective interventions are likely to necessitate women entering into prenatal programs.

Obstetric complications of pregnancy, although relatively infrequent, remain important risk factors for preterm birth. In our study, several factors emerged as being statistically significant risk factors for preterm birth, such as prior history of previous pregnancy, hypertension, ICP, FGR, PROM, placenta previa and abnormal presentation. The times of prenatal care was shown to be a

Table 8
Labor and delivery in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		*P* value
	n	%	n	%	
Spontaneous labor	669	50.80	604	51.67	0.665
Elective delivery	648	49.20	565	48.33	

Table 9
Neonatal gender in singleton pregnancies.

	Controls (n = 1317)		Preterm cases (n = 1169)		OR (95%CI)
	n	%	n	%	
Male	675	51.25	752	64.33	1.72 (1.46,2.02)
Female	642	48.75	417	35.67	1.00 (Reference)

Table 10
Neonatal weight and Apgar score in singleton pregnancies.

	Controls (n = 1317)	Preterm cases (n = 1169)	*P* value
Weight (g)	3456.53 ± 455.34	2335.76 ± 604.28	0.000
Apgar score			
1min	9.99 ± 0.17	9.58 ± 1.48	0.000
5min	10.00 ± 0.00	9.86 ± 0.82	0.005

protective factor for preterm birth. Unlike other previous report [18], oligohydramnios and fetal distress was found to be occurred in both control and preterm pregnancies, and were similar in both groups in our study.

In agreement with previous reports [17], we found that male babies are known to have a significantly higher risk of being preterm than female babies. And as would be expected, our data confirm that the neonatal birth weight and Apgar score at 1 min and 5 min were lower in preterm birth group compared with women in control group. These results instruct that women with preterm birth will more frequently result in adverse perinatal outcomes.

Preterm birth, a devastating obstetrical outcome with far-reaching implications for infants, parents, and communities at large, continues to be one of the most significant unsolved problems of public health and perinatology [23,24]. Premature infants, as compared with those infants born at term, are at greater risk for mortality and a wide range of medical and developmental complications [2,3,8,25–27]. Findings from our present study are consistent with increasing evidence that preterm birth is a complex cluster of problems with a set of overlapping factors and influences. This study has limitations as it has surveyed only a population of several hundred women in a single tertiary hospital. Further studies, preferably large geographical prospective cohort studies are needed to identify and characterize the underlying causes of preterm birth. The factors associated with preterm birth would be better addressed through such studies. Preterm birth is a global obstetric challenge that requires more attention. However, we believe that over the next several decades, epidemiological data will be supplemented by advanced in uterine physiology and maternofetal endocrinology which will improve our understanding of human parturition and help devise successful strategies to prevent preterm birth.

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Conflicts of interest

The authors declare that we have no conflict of interest regarding the publication of this paper.

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