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Original Article

A nomogram to predict preterm birth in twin pregnancies

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Abstract: Purpose: To investigate risk factors for preterm birth in twin pregnancies, and to establish a nomogram model for predicting preterm birth and verify its application value. Methods: Data from 266 twin pregnancies between January 2015 and December 2020 were analyzed in this retrospective study. According to the gestational weeks of delivery, the included subjects were divided into a preterm birth group (gestational age < 37 weeks) and a full-term group (gestational age ≥ 37 weeks). The general situation and pregnancy complications of the two groups were analyzed by univariate analysis, and the factors with statistical significance were entered into multivariate logistic regression analysis. Furthermore, the nomogram model for predicting the risk of preterm birth was established by using R. The predictive effect of the model was evaluated by the area under the ROC curve, C-index, and decision curve analysis. Results: Demographic characteristics and their associations with preterm birth and full-term birth in twin pregnancies were summarized and analyzed. After validation, we identified the following significant predictors of preterm birth: chorionic status, inconsistent development of twins, premature rupture of membranes, fetal distress, scar uterus, and preeclampsia. Overall, we constructed preterm risk nomogram model with C-index of 0.783. A nomogram using a 0-100 scale illustrated our final model for predicting preterm birth in twin pregnancies. Conclusions: We developed and validated a clinical nomogram to predict preterm birth in twin pregnancy. Chorionic status, inconsistent development of twins, premature rupture of membranes, fetal distress, scar uterus, and preeclampsia were independent risk predictors for preterm birth in twin pregnancy.

Keywords: Preterm birth, nomogram, risk predictors, twin pregnancy

Introduction

In recent years, with the application of assisted reproductive technology and ovulation inducing drugs, an iatrogenic increase in twin pregnancy has brought new challenges for obstetric diagnosis and treatment [1, 2]. The current incidence of twin pregnancy is up to 60% [3]. Most studies have shown that the incidence of preterm birth in twin pregnancy is significantly higher than that in singleton pregnancy [4-6]. With an increase of gestational weeks, the uterus expands more and the pressure in the amniotic cavity increases, which predisposes to preterm birth [7-9]. The incidence of preterm birth is 5%~10% in developed countries [10, 11].

Preterm birth is defined as delivery at 28-37 weeks of gestation, which is one of the main factors causing perinatal morbidity and death [12]. However, there is no unified method to predict the occurrence of preterm birth in twin pregnancy. Previous studies have shown that the cervical length (CL) by transvaginal ultrasound can predict preterm birth [13], but its accuracy needs to be further improved. In addition, relevant studies have pointed out that premature delivery and neonatal respiratory diseases are associated with intrauterine infection, which is also closely related to the thickness the of fetal membrane [14]. Among them, Fetal membrane inflammation causes premature rupture of membranes and the risk of premature delivery in twin pregnancy [15]. Therefore, effective prediction and early prevention of preterm delivery will greatly reduce the incidence of preterm birth of fetuses and improve the physical quality of perinatal infants.

Therefore, this study investigated risk factors of preterm birth in twin pregnancies, and a nomo-

gram model for predicting preterm birth in twin pregnancies was established and validated.

Materials and methods

Study design and ethics

In this retrospective study, 266 twin-pregnant women at Chongqing maternal and Child Health Hospital from January 2015 to December 2020 were enrolled. This study was approved and recognized by the ethics committee of Chongqing Maternal and Child Health Hospital.

Inclusion criteria

(1) Pregnant women with twin pregnancy indicated B ultrasound during the first trimester of gestation; (2) Pregnant women who had routine prenatal examination in our hospital; (3) Pregnant women with no abnormality in fetus and placenta during prenatal examination; (4) Pregnant women with complete clinical data.

Exclusion criteria

(1) Pregnant women with incomplete records or delivered at other medical centers; (2) Pregnant women with severe coagulation dysfunction or thrombocytopenia, liver malfunction or renal failure; (3) Pregnant women with a fetus showing genetic or structural abnormalities, stillbirth of one or two fetuses, twin birth weight < 500 g, monoamniotic or monochorionic twin pregnancy complicated by twin transfusion syndrome (TTTS), or twin anaemia-polycythaemia sequence (TAPS); (4) Pregnant women with placement of cervical cerclage, or use of vaginal progesterone.

Data collection and measurement

Medical records were surveyed retrospectively, including clinical data of pregnant women and pregnancy complications. General data include age, body mass index (BMI), times of birth, mode of conception, adverse pregnancy and delivery history, and mode of delivery. Pregnancy complications include pregnancy induced hypertension, pregnancy induced diabetes, pregnancy induced anemia, fetal distress, premature rupture of membranes, placental abnormalities (placenta previa, placental abruption), abnormal amniotic fluid, scarred uterus, and membranous insertion. The primary indicators included the gestational age, chorionic status, history of previous preterm or late abortion (during 12-28 weeks), complications during pregnancy, use of assisted reproductive technology. The secondary indicators included general data such as body mass index (BMI) and times of birth.

Statistical analysis

SPSS 20.0 software was used to analyze the data. The measured data were expressed by X ± s or median. Independent sample t-test or rank sum test was used for intergroup comparison; The counted data were expressed as a percentage (%), and X^2 test was used for comparison. Multivariate logistic regression model was used to screen the factors influencing the risk of preterm delivery of twin pregnancy. $P < 0.05$ was statistically significant. The risk factors were introduced into R software (R3.6.3) to construct a nomogram model to predict the risk of preterm delivery of a twin pregnancy. The variables and their regression coefficients were determined using a regression model, and the ROC curve was drawn to verify the predictive value of risk factors.

Result

Participant recruitment

In this study, 266 twin-pregnant women were retrospectively enrolled and divided into two groups, preterm birth group (gestational age < 37 weeks) (n=88 cases) and full-term group (gestational age ≥ 37 weeks) (n=178 cases) based on gestational age.

Clinical characteristics

The included 266 twin-pregnant women which involved 88 pregnant women in the preterm birth group and 178 pregnant women in the full-term group. There were statistical differences in the factors such as delivery modes, inconsistent development of twins, and chorionic status between two groups (all $P < 0.05$); however, in terms of cervical cerclage, birth weight, conception mode, parity, BMI before pregnancy and age, there were no differences between the two groups (all $P>0.05$) (**Table 1**).

Comparison of pregnancy complications between groups

The pregnancy related complications were analyzed in this study. The results showed that the incidences of premature rupture of mem-

Table 1. Comparison of clinical data between the two groups

	Preterm birth group (n=88)	Full-term group (n=178)	t/x^2	*P*
Age	31.21±3.86	31.73±3.33	1.658	0.127
BMI before pregnancy	24.74±2.67	24.35±3.41	1.178	0.278
Parity			2.198	0.148
Primipara	70 (79.5%)	138 (77.5%)		
Parturient women	18 (20.5%)	40 (22.5%)		
Conception mode			0.925	0.351
Conceived by nature	61 (69.3%)	128 (71.9%)		
Assisted reproduction	27 (30.7%)	50 (28.1%)		
Birth weight (g)	2868.1±196.2	3173.2±136	2.39	0.108
Delivery modes			9.52	0.031*
Cesarean section	85 (96.6%)	43 (24.2%)		
Natural labor	3 (3.4%)	135 (75.8%)		
Inconsistent development of twins	18 (20.5%)	20 (11.2%)	3.165	0.023*
Cervical cerclage	7 (8%)	4 (2.2%)	8.21	0.052
Chorionic status			9.647	0.002*
Double chorionic	61 (69.3%)	138 (77.5%)		
Monochorionic	27 (30.7%)	40 (22.5%)		

Note: BMI, body mass index. *p < 0.05 compared with full-term group.

Table 2. Comparison of pregnancy related complications between the two groups (%)

	Preterm birth group (n=88)	Full-term group (n=178)	t/x^2	*P*
Postpartum hemorrhage	13 (14.8%)	18 (10.1%)	4.45	0.073
Premature rupture of membranes	22 (25%)	61 (34%)	6.02	0.011
Placenta previa	7 (8%)	4 (2.2%)	8.21	0.052
Placental abruption	8 (9.1%)	18 (10.1%)	0.791	0.062
Fetal distress	8 (9.1%)	11 (6.2%)	7.13	0.043
Fetal growth restriction	36 (40.9%)	57 (26.4%)	19.14	0.019
Pregnancy induced hypertension	24 (27.2%)	15 (8.4%)	16.18	0.003
Gestational diabetes mellitus	13 (14.8%)	3 (1.7%)	22.17	0.006
Scar uterus	7 (8%)	3 (1.7%)	11.4	0.044
Preeclampsia	18 (20.5%)	4 (2.2%)	12.38	0.004
Gestational anemia	16 (18.2%)	36 (20.2%)	10.64	0.318
Intrahepatic cholestasis	8 (9.1%)	3 (1.7%)	6.439	0.038
Chorioamnionitis	7 (8%)	2 (1.1%)	4.964	0.048
Abnormal amniotic fluid	10 (11.3%)	11 (6.2%)	5.553	0.037

branes, fetal distress, fetal growth restriction, pregnancy induced hypertension, gestational diabetes mellitus, scarred uterus, preeclampsia, intrahepatic cholestasis, chorioamnionitis, and abnormal amniotic fluid in the preterm group were significantly higher than those in the full-term group (all P < 0.05). However, there was no significant difference between the two groups in the incidence of postpartum hemorrhage, placenta previa, placental abruption and gestational anemia (all P>0.05) (**Table 2**).

Univariate and multivariate regression analysis

As shown in **Table 3**, the univariate analysis showed that chorionic status, delivery modes, inconsistent development of twins, premature rupture of membranes, fetal distress, fetal growth restriction, pregnancy induced hypertension, scar uterus, preeclampsia and intrahepatic cholestasis were statistically correlated with the preterm birth of twin pregnancies (all P < 0.05), while gestational diabetes melli-

Table 3. Univariate and multivariate risk analysis

Indexes	Univariate		Multivariate	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Chorionic status				
Double chorionic	Reference		Reference	
Monochorionic	1.68 [0.5989-0.973]	0.006	2.754 [1.251-2.749]	0.011
Delivery modes				
Cesarean section	Reference		Reference	
Natural labor	0.43 [0.133-0.636]	0.004	1.28 [0.77-1.38]	0.261
Inconsistent development of twins				
No	Reference		Reference	
Yes	2.52 [0.9206-0.982]	0.021	2.42 [0.85-0.95]	0.038
Premature rupture of membranes				
Yes	Reference		Reference	
No	1.36 [0.414-0.892]	0.023	3.59 [1.12-2.26]	0.013
Fetal distress				
Yes	Reference		Reference	
No	1.62 [0.639-0.928]	0.014	1.55 [1.014-1.09]	0.032
Fetal growth restriction				
Yes	Reference		Reference	
No	2.36 [0.414-0.892]	0.018	1.66 [1.29-4.30]	0.076
Pregnancy induced hypertension				
Yes	Reference		Reference	
No	1.95 [0.6390-0.6522]	0.022	1.58 [0.77-0.38]	0.056
Gestational diabetes mellitus				
Yes	Reference		Reference	
No	1.84 [0.69-1. 014]	0.98	5.58 [0.87-0.98]	0.066
Scarred uterus				
Yes	Reference		Reference	
No	5.95 [0.639-0.652]	0.012	2.58 [0.57-0.88]	0.006
Preeclampsia				
Yes	Reference		Reference	
No	5.35 [0.039-0.052]	0.032	4.58 [0.37-0.88]	0.016
Intrahepatic cholestasis				
Yes	Reference		Reference	
No	1.44 [0.69-1.114]	0.04	3.98 [0.47-0.58]	0.051
Chorioamnionitis				
Yes	Reference		Reference	
No	3.67 [0.69-1.114]	0.152	1.18 [1.09-2.23]	0.294
Abnormal amniotic fluid				
Yes	Reference		Reference	
No	3.24 [0.49-1.114]	0.08	3.18 [0.67-0.98]	0.073

tus, chorioamnionitis, and abnormal amniotic fluid had no correlation with the preterm birth of twin pregnancies (all P>0.05). The significant single factors (chorionic status, delivery modes, inconsistent development of twins, premature rupture of membranes, fetal distress, fetal growth restriction, pregnancy induced hypertension, scarred uterus, preeclampsia and intrahepatic cholestasis) were analyzed by Cox proportional hazards regression model, and the results showed that chorionic status, inconsistent development of twins, premature

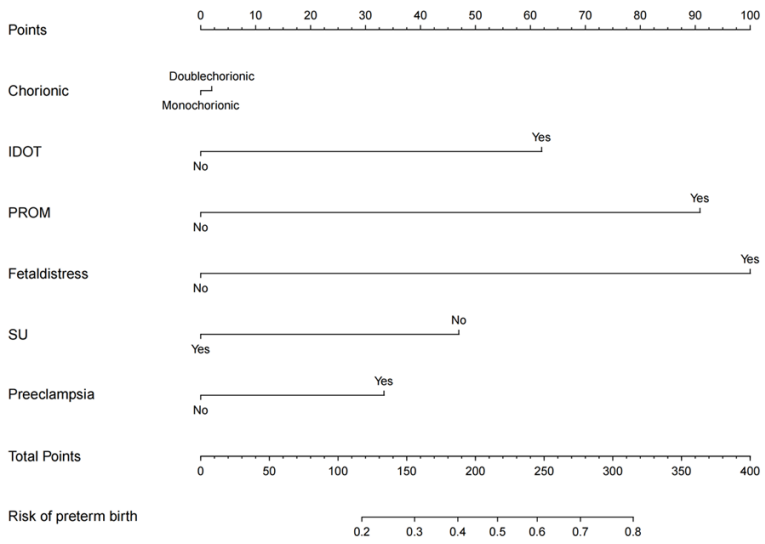

Figure 1. The nomogram for predicting preterm birth of twin pregnancies. Note: IDOT: Inconsistent development of twins; PROM: Premature rupture of membranes; SU: Scarred uterus.

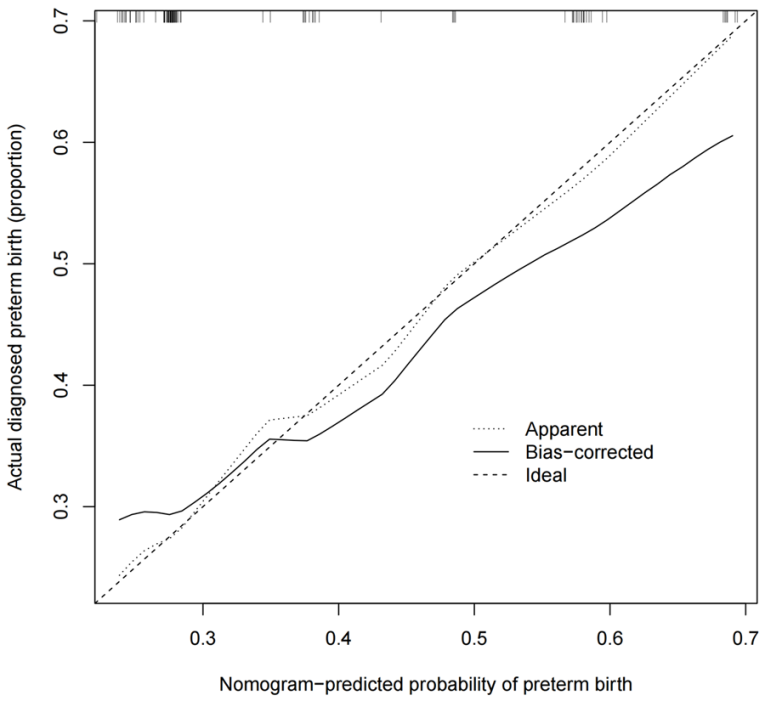

Figure 2. Calibration curves for predicting preterm birth in twin pregnancies.

rupture of membranes, fetal distress, scar uterus, and preeclampsia were independent predictors of preterm birth of twin pregnancies.

Development of nomogram model

The risk factors for preterm birth of twin pregnancies were included in the prediction model established by R software (R3.6.3). The prediction probability corresponding to the sum of the integral of each factor was the risk for preterm birth (**Figure 1**).

Validation of the nomogram model

The unadjusted concordance index (C-index) for the nomogram was 0.783 [95% confidence interval (CI), 0.815-0.994]. The calibration plot of the nomogram is shown in **Figure 2**. The AUC for the nomogram was 0.7746 (**Figure 3**), indicating that the nomogram model had a good discrimination and consistency in predicting the risk of preterm birth.

The decision curve analysis (DCA)

Decision curve analysis (DCA) of the model is shown in the **Figure 4**, and the results demonstrated that if the threshold probability of preterm birth of twin pregnancies was 20-60%, the validity of the model was increased. This predictive model was suitable for clinical use.

Discussion

In this study, we developed a predictive nomogram model of preterm birth in twin pregnancies to provide an accurate and comprehensive risk estimation, which can serve as an assessment tool to help physicians make decisions about further management of twin pregnancy. Our results show an independent association between chorionic status, inconsistent development of twins, premature rupture of membranes, fetal distress, scar uterus, preeclampsia and preterm birth of twin pregnancies.

The results of this study showed that premature rupture of membranes was a risk factor for preterm birth in twin pregnancies. In twin preg-

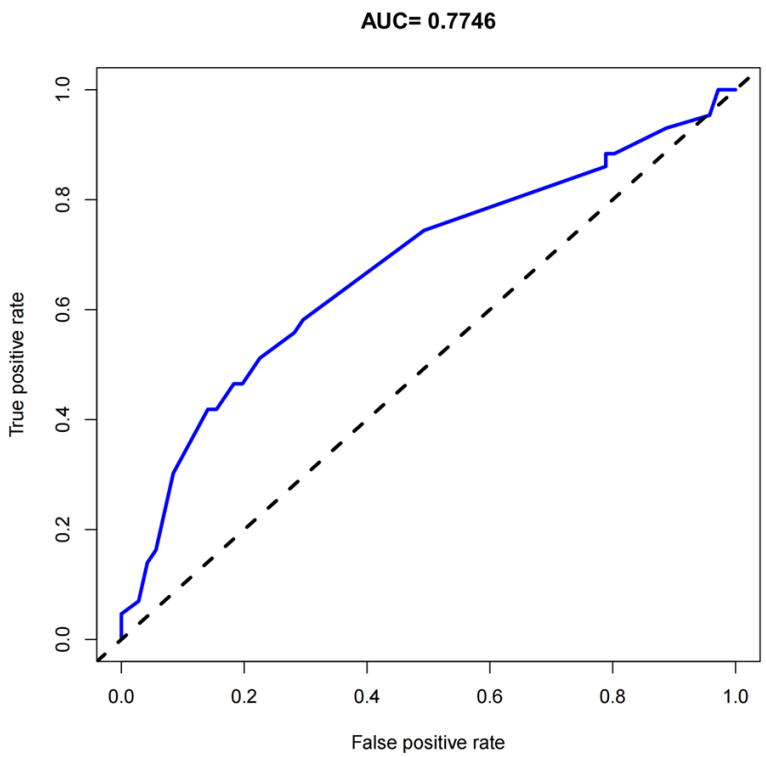

Figure 3. ROC curves for predicting preterm birth in twin pregnancies.

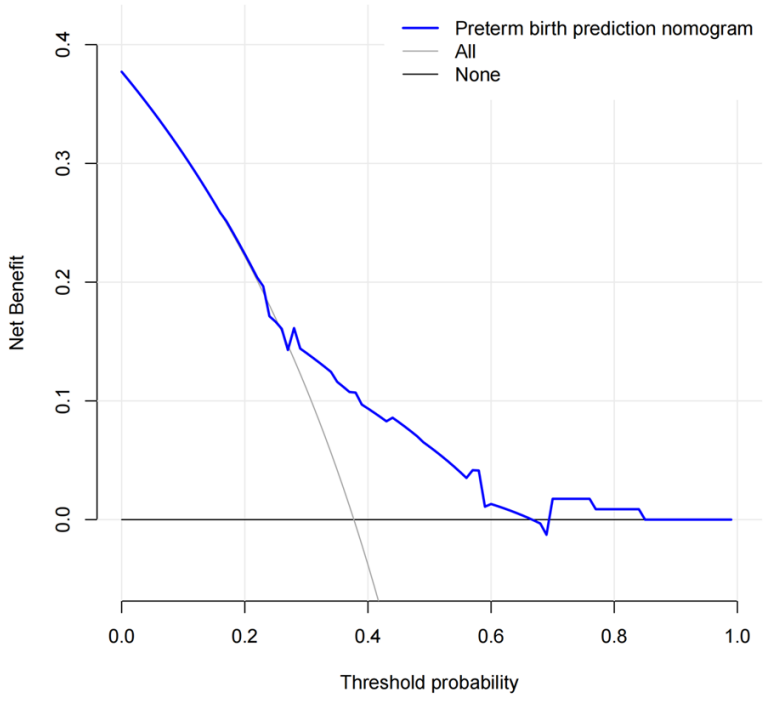

Figure 4. Decision curve analysis for the nomogram.

nancy, the uterus is large, the pressure in the uterine cavity is high, and the fetal membrane near the inner mouth of the cervix is easily ruptured, resulting in premature rupture of membranes. In addition, increased uterine pressure leads to pelvic vascular compression which can easily cause uterine contraction and premature rupture of membranes. At the same time, it is reported that the risk of premature delivery within 72 hours of premature rupture of membranes in twin pregnancy is greater than that of singleton pregnancy [16, 17]. The results showed that the incidence of premature rupture of membranes in the preterm twin pregnancy group was much higher than that in of the full-term twin pregnancy group.

Intrauterine infection is often one of the important factors causing premature delivery in both singleton and twin pregnancy. Studies have shown that reproductive tract infection is an independent risk factor for premature rupture of membranes [18]. Therefore, preventing premature rupture of membranes and prolonging gestational weeks as far as possible are important measures to reduce the incidence of premature delivery in twin pregnancy.

Preeclampsia is another independent risk factor for iatrogenic preterm birth [19]. Due to placental hypoxia, patients are prone to serious complications such as liver function damage and high edema [20]. The results showed that the incidence of preeclampsia in the preterm birth group was much higher than that of the full term group, and multivariate regression analysis showed that preeclampsia was an independent risk factor for prema-

ture delivery of twin pregnancy, which is consistent with the study by Ye et al. [21].

The occurrence of inconsistent development of twins increased the risk for perinatal preterm birth. Studies have shown that inconsistent development of twins combined with growth restriction of one fetus, can result in abnormal umbilical blood flow of one fetus [22-24]. Therefore, a healthy lifestyle and supplementing high-quality protein, with appropriate carbohydrate diet and exercise in the early stage of pregnancy can prevent the inconsistent development of twins and avoid premature delivery.

Women with a scarred uterus are predisposed to develop placenta previa in the next pregnancy. At the same time, the incidence of postpartum hemorrhage increases [25]. This study showed that a scarred uterus was an independent risk factor for premature delivery in twin pregnancy. The reason may be that the patients lack certain medical knowledge and think that cesarean section is a safe and painless way of delivery. In addition, an unfavorable doctor-patient relationship makes medical staff often consider self-protection first when making clinical decisions. Therefore, it is preferable to promote spontaneous labor and avoid scarred uterus.

Fetal distress refers to a series of syndromes such as acidosis caused by ischemia and hypoxia in the uterus [26, 27]. This study showed that fetal distress was an independent risk factor for preterm delivery of twin pregnancy. The fetus is affected by umbilical cord abnormalities and resulting in obstacles in blood oxygen transport and iatrogenic preterm birth [28].

The results of this study showed that chorionic status (monochorionic) was another risk factor for preterm birth of twin pregnancies. Twin pregnancies should be strictly monitored and rechecked regularly to prevent various complications [29]. Furthermore, pregnant women carrying twins should pay attention to rest, reduce uterine tension, avoid premature delivery, and reduce the incidence of perinatal and neonatal death [30].

The better identification of high-risk preterm birth of twin pregnancies by using a predictive tool could limit medical costs. Our predictive monogram was created based on a retrospective study performed with a cohort of twin pregnancies. It could therefore be reproducible in a high-risk population. Our model proposes to personalize the calculation of preterm birth risk with additional risk factors in twin pregnancies.

Unfortunately, this study has several limitations. First, the predictive value of the monogram was not verified in external cases. Second, although this was a representative sample of twin pregnancies females, sampling errors may exist due to the relatively small sample size. Third, the study was conducted in only one hospital, meaning that certain categories of patients may have been missed. Although efforts were made to minimize the possibility of observer bias, further studies with larger sample size are warranted.

In summary, this study developed and validated a clinical nomogram to predict preterm birth of twin pregnancies. Chorionic status, inconsistent development of twins, premature rupture of membranes, fetal distress, scar uterus, and preeclampsia are independent risk predictors for preterm birth of twin pregnancies.

Disclosure of conflict of interest

None.

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