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Tocolysis and the risk of nonreassuring fetal status among pregnant women in labor

Findings from a population-based retrospective cohort study

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Abstract

The purpose of this study was to evaluate the association between tocolysis for preterm uterine contraction and the risk of nonreassuring fetal status.

This was a retrospective cohort study using data from the Taiwan National Health Insurance Research Database. Pregnant women were enrolled if they delivered a baby during January 1, 2003 to December 31, 2011. The occurrence of the nonreassuring fetal status was compared between pregnant women with and without tocolytic treatment for preterm uterine contraction. Multivariable logistic regression models with adjusted cofounders were used to evaluate the association between tocolysis and the risk of nonreassuring fetal status.

Of 24,133 pregnant women, 1115 (4.6%) received tocolytic treatment during pregnancy. After adjusting for covariates, pregnant women receiving tocolysis more than one time during pregnancy were found to have significantly higher risk of the nonreassuring fetal status when compared with pregnant women who did not receive tocolysis for uterine contraction (Odds Ratio = 2.70, 95% Confidence Interval: 1.13–6.49).

Pregnant women with more frequent tocolysis for preterm uterine contraction during pregnancy had an increased risk of nonreassuring fetal status. Close evaluation of dose and duration of tocolytic treatment is necessary for pregnant women with preterm uterine contraction.

Abbreviations: DRG = diagnosis related groups, EFM = electronic fetal monitoring, FHR = fetal heart rate, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification Codes, LHID = longitudinal health insurance database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NRFS = nonreassuring fetal status.

Keywords: National Health Insurance Research Database (NHIRD), nonreassuring fetal status, preterm uterine contraction, Taiwan, tocolysis

1. Introduction

Nonreassuring fetal status refers to abnormal fetal heart rate that occurs when a fetus does not receive enough oxygen. A fetus may experience temporary or permanent oxygen deprivation which results in fetal hypoxia.[1,2] It is a critical condition that may occur in the late stage of pregnancy or during labor. Nonreassuring fetal status often requires performance of emergency cesarean section and leads to preterm birth.[3–7] It is associated with approximately 10% of primary cesareans in the United States (US).[8]

Preterm birth, which is highly associated with an increased risk of neonatal morbidity and mortality, has become a global health issue in obstetrics.[9–11] One in 10 babies born in the US was a preterm delivery in 2015,[10,11] and an estimated half million preterm births occur in Europe each year.[12] In Taiwan, a recent report in 2014 showed the preterm birth rate was 8.6% and significantly increased from 2001 to 2009.[13] A systemic review reporting preterm birth estimates from 1990 to 2010 showed that preterm birth can cause severe physical and mental complications and was the major cause of child deaths among children younger than five years old.[9]

Tocolytic treatment is used to inhibit preterm uterine contraction, which is a sign of preterm birth. The treatment can prevent preterm birth and improve infant outcomes.[14] Previous studies have shown that pregnant women with tocolytic treatment could

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delay childbirth from 48 hours to 7 days compared to pregnant women without the treatment.[14–16] Furthermore, a network meta-analysis reviewing 95 randomized controlled trials concluded that neonatal and maternal outcomes were significantly improved among pregnant women with tocolysis when compared to pregnant women without tocolysis.[17]

Tocolytic treatment is important for the management of preterm labor because it prolongs gestation and reduces preterm birth. However, little is known about its association with nonreassuring fetal status. Given that nonreassuring fetal status in the late stage of pregnancy often leads to preterm birth,[3–7] it is important to further investigate whether tocolytic treatment for preterm uterine contraction is associated with an increased risk of nonreassuring fetal status. Therefore, the purpose of this study was to evaluate the association between tocolysis for preterm uterine contraction and the risk of nonreassuring fetal status. First, we compared the risk of nonreassuring fetal status between pregnant women with and without tocolysis for preterm uterine contraction. Then, we evaluated whether the number of tocolytic treatments for the preterm uterine contraction during pregnancy was associated with an increased risk of nonreassuring fetal status. We hypothesized that pregnant women receiving more frequent tocolytic treatments for the preterm uterine contraction were at a higher risk of nonreassuring fetal status when compared with women without tocolysis.

2. Methods

Data for this study came from the Longitudinal Health Insurance Database 2010 (LHID 2010), which was a random sample of one million individuals in 2010 from the National Health Insurance Research Database (NHIRD) in Taiwan. In 1995, the Taiwanese government launched a single-payer National Health Insurance (NHI) program, which covered 99.9% of the 23.4 million Taiwanese residents by 2014.[18] The NHIRD was created by the National Health Insurance Administration and is maintained by the Taiwan National Health Research Institutes. The NHIRD is an administrative claims dataset which contains registration files, medical claims files, patient identification files, inpatient files, ambulatory care files, and inpatient and outpatient prescription files.[19] All patients' personal information are de-identified in the dataset. Diagnoses and medical procedures are identified based on the International Classification of Disease, Ninth Revision, Clinical Modification Codes (ICD-9-CM).[20]

This study was a retrospective cohort design using the LHID 2010 of the NHIRD. The overall study period was from January 1, 2000 to December 31, 2011. Patients were enrolled in this study if they delivered a baby between January 1, 2003 and December 31, 2011 (the enrollment period). We identified the subjects by using the Diagnosis Related Groups (DRG) code from the Inpatient Expenditures by Admissions file of the NHIRD. Patients were enrolled if they had a DRG code of 0373A and 0373C for the normal spontaneous, or 071A and 0373B for the cesarean section during the enrollment period. We only kept the first medical delivery record if patients had multiple delivery records.

In order to define the beginning of the pregnancy and gestational age, we used the estimated date of the last menstrual period to be 245 days before the date of delivery for preterm birth (ICD-9-CM codes: 644.0, 644.2, and 765.x), and 270 days before the date of delivery for regular pregnancies (ICD-9-CM codes: 645, 650–659, and 766).[21–23] The beginning of the pregnancy was defined as the index date of this study. The pre-index period was then defined as the two-year period before the index date. Figure 1 shows the design of the study.

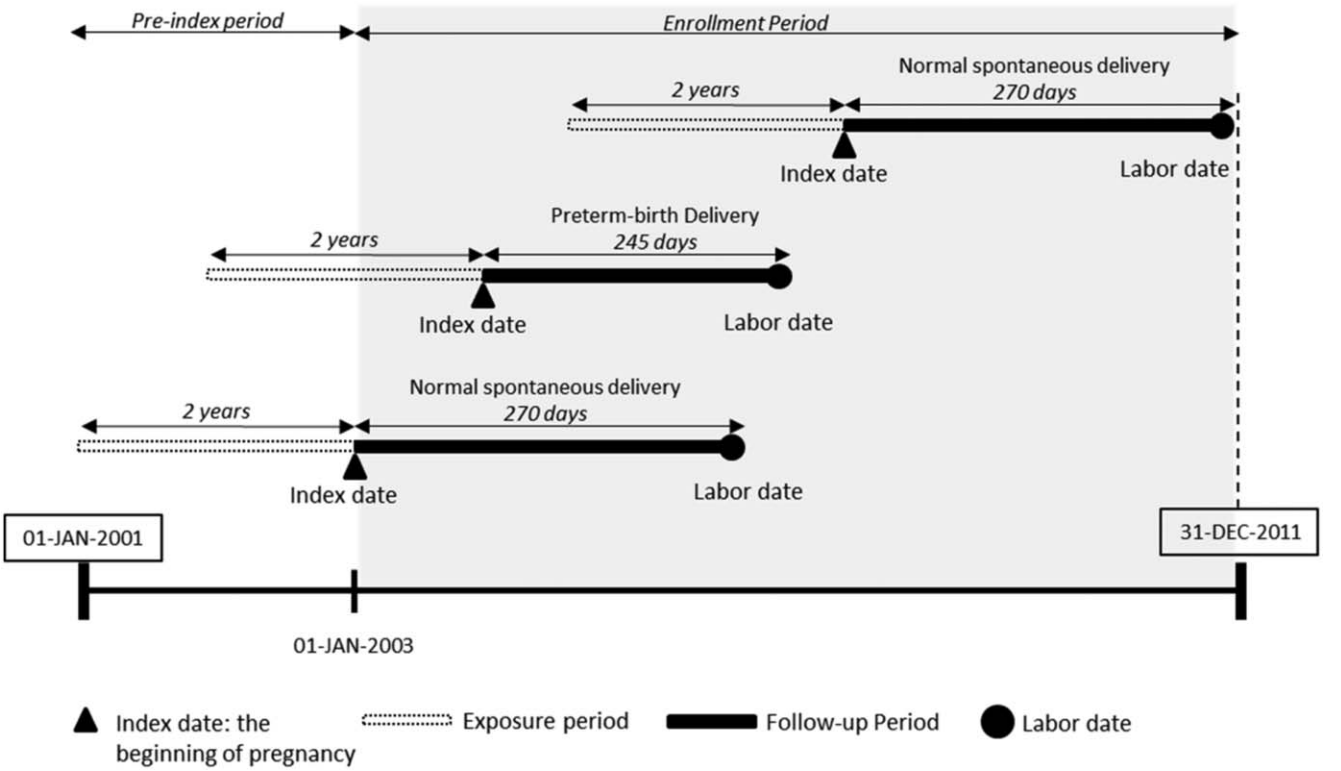

Figure 1. The design of the study.

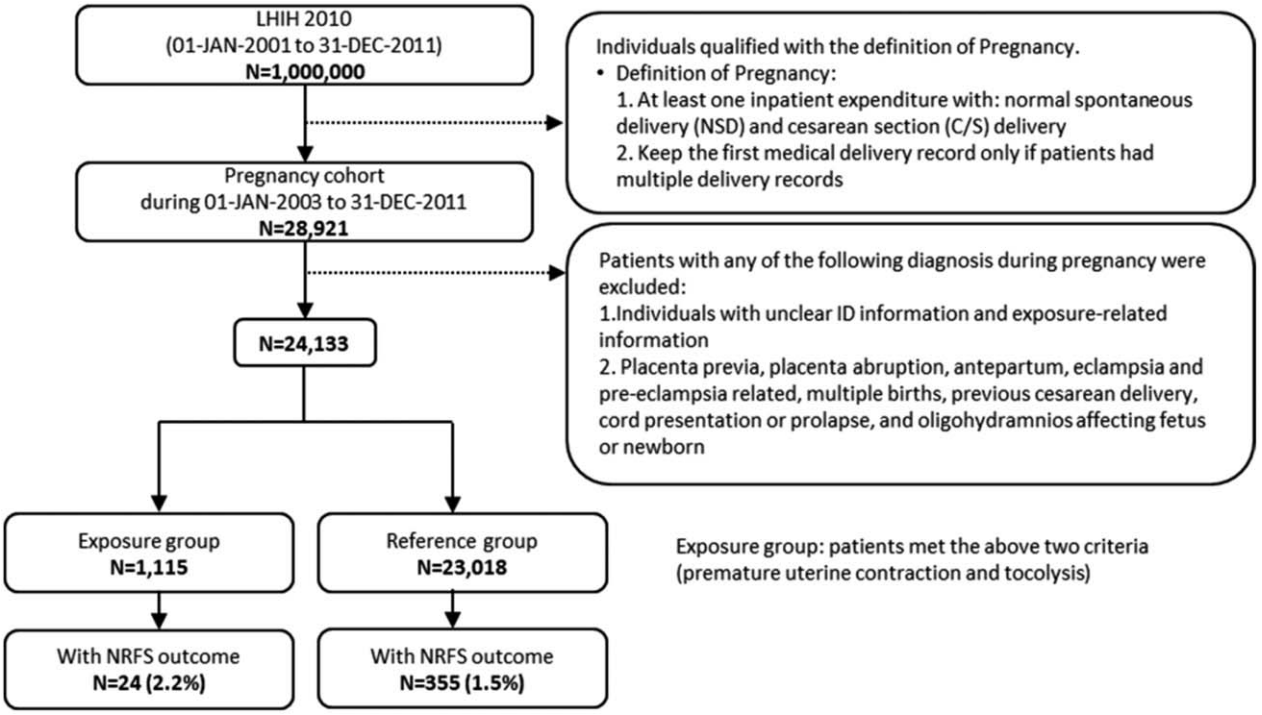

Figure 2. The flow chart of the study population enrolment.

Patients with any of the following diagnosis during pregnancy were excluded: placenta previa (ICD-9-CM codes: 641.0), placenta abruption (ICD-9-CM code: 641.2), antepartum hemorrhage (ICD-9-CM codes: 641.9), eclampsia and pre-eclampsia related diseases (ICD-9-CM codes:642.0–642.7), previous cesarean delivery (ICD-9-CM codes: 654.2), cord presentation or prolapse (ICD-9-CM code: 663.0), and oligohydramnios affecting fetus or newborn (ICD-9-CM code: 761.2). Figure 2 shows the flow chart of the enrollment process.

The outcome variable of this study was the occurrence of nonreassuring fetal status (ICD-9-CM: 659.7, 656.3). The diagnosis of nonreassuring fetal status was identified from the inpatient primary diagnosis. It is common that once nonreassuring fetal status is diagnosed, the women undergo cesarean section. Therefore, the occurrence of the study outcome was further constrained to women having the diagnosis associated with nonreassuring fetal status and cesarean section (DRG code: 0371A, 0373B).

The exposure of this study was receipt of tocolytic therapy for preterm uterine contraction during pregnancy. Preterm uterine contraction diagnosis was defined if pregnant women had an inpatient primary diagnosis of the preterm uterine contraction (ICD-9-CM: 644.0). Tocolysis was then defined as patients who received tocolytic treatment with an inpatient admission stay for preterm uterine contraction. Patients who met the above two criteria (preterm uterine contraction and tocolysis) were identified as the exposure group. Patients without any hospital admission for tocolysis or preterm uterine contraction diagnosis were defined as the reference group.

The secondary aim of our study was to evaluate the association between the number of tocolytic treatments for preterm uterine contraction and the risk of nonreassuring fetal status. The number of tocolytic treatments for the preterm uterine contraction were identified during pregnancy. Patients were placed in the exposure group if they had one or more tocolytic treatments while those without any tocolytic treatment for preterm uterine contraction during pregnancy were defined as the reference group.

Several covariates, which were identified during pregnancy, were included in our study. These covariates included age of patient on the index date, ever diagnosed with asthma, whether the new-born infant was underweight (light-for-date), ever diagnosed with gestational diabetes mellitus, ever diagnosed with polyhydramnios, ever diagnosed with hyperthyroidism, ever diagnosed with hypothyroidism, ever diagnosed with upper respiratory infection during pregnancy, whether the mother had a pre-term birth baby, drug and alcohol abuse, and diagnosed with psychologic disorders (including affective disorder, bipolar, schizophrenia, depression, and anxiety).

The initial step in the analysis was to determine the frequency of nonreassuring fetal status among pregnant women in the exposure and reference groups. Then, logistic regression models were used to determine the Odds Ratio (OR) and the corresponding 95% confidence intervals (95% CI) between two groups after controlling for covariates. We further conducted a sensitivity analysis to evaluate the association between tocolysis for uterine contraction during different gestational ages and the risk of the nonreassuring fetal status. All data management, analysis, and statistical procedures were performed by the SAS software version 9.3 (SAS Institute, Cary, NC). In this study, a two-tailed p value under 0.05 was considered statistically significant. The study was reviewed and granted an exempt status from the Taipei Medical University Joint Institutional Review Board.

3. Results

Table 1 describes the patient characteristics of the study population. A total 24,133 pregnant women with an average

Table 1

Patient characteristics: pregnant women with and without tocolytic treatment for preterm uterine contraction (N = 24,133).

Characteristics	Study population N = 24,133		Pregnant women with tocolytic treatment n = 1,115 (4.6%)		Pregnant women without tocolytic treatment n = 23,018 (95.4%)		
	Frequency	%	Frequency	%	Frequency	%	*P* value
Age $_{(mean, SD)}$	28	4.9	29	5.1	28	4.9	
Age							<.05
<20	953	3.9	46	4.1	907	3.9	
20–24	4543	18.8	178	16.0	4365	18.8	
25–29	9396	38.9	408	36.6	8988	38.7	
30–34	7116	29.5	350	31.4	6766	29.2	
35–39	2023	8.4	114	10.2	1909	8.2	
>=40	291	1.2	19	1.7	272	1.2	
Asthma during pregnancy	203	0.8	14	1.3	189	0.8	.19
Light-for-dates (birth weight)	848	3.5	62	5.6	786	3.4	<.01
Gestational diabetes mellitus	1140	4.7	86	7.7	1054	4.5	<.01
Polyhydramnios	82	0.3	13	1.2	69	0.3	<.05
Hyperthyroidism	178	0.7	14	1.3	164	0.7	.10
Hypothyroidism	30	0.1	2	0.2	28	0.1	.65
Upper respiratory related infection	14,867	61.6	671	60.2	14,196	61.2	.51
Pre-birth	528	2.2	108	9.7	420	1.8	<.01
Drug or alcohol abuse	19	0.1	4	0.4	15	0.1	.10
Psychologic disorders	318	1.3	31	2.8	287	1.2	<.01

age of 28 years were identified. Among them, 4.6% received tocolysis for preterm uterine contraction. The average age of pregnant women with and without tocolysis was 29 years and 28 years, respectively. Several characteristics were found to be significantly different between pregnant women with and without tocolysis. Pregnant women with tocolysis were significantly more likely to be diagnosed with gestational diabetes (7.7% vs 4.5%, $P < .01$), polyhydramnios (1.2% vs 0.3%, $P < .05$) and psychologic disorders (2.8% vs 1.2%, $P < .01$) when compared with pregnant women without tocolysis. In addition, pregnant women with tocolysis were more likely to experience a shorter gestational age (9.7% vs 1.8%, $P < .01$) and to deliver an underweight infant (5.6% vs 3.4%, $P < .01$).

Table 2 shows the results of multivariable logistic regression models to evaluate the association between tocolysis for uterine contraction and the nonreassuring fetal status. The prevalence of nonreassuring fetal status among pregnant women with and without tocolytic treatment was 2.2% and 1.5%. The risk of developing nonreassuring fetal status was not found to be statistically significant between pregnant women with and without tocolysis (OR = 1.18, 95% CI: 0.77–1.83]. However, a significant association was found between the number of tocolytic treatments and the risk of the nonreassuring fetal status. Pregnant women who received more than one tocolytic treatments during pregnancy were found to have a 2.7 times higher risk of the nonreassuring fetal status when compared with pregnant women who did not receive any tocolytic treatment during pregnancy after adjusting for all covariates (OR = 2.70, 95% CI: 1.13–6.49).

Table 3 shows the results of the sensitivity analysis which evaluated the association between tocolysis for uterine contraction during different gestational ages and the risk of the nonreassuring fetal status. After adjustment for covariates, tocolysis for uterine contraction in different gestational ages was not found to be significantly associated with higher risk of the nonreassuring fetal status (the first trimester: OR = 2.75, 95% CI: 0.26–29.54; the second trimester: OR = 0.23, 95% CI: 0.01–3.79; the third trimester: OR = 1.24, 95% CI: 0.78–1.95).

Table 2

The association between tocolytic treatment and the risk of the nonreassuring fetal status (NRFS): results from multivariable logistic regression models.

Exposure	Number of NRFS events		Adjusted models*	
	N	%	Odds ratio	95% CI
Without vs with receiving tocolytic treatment				
Pregnant women without any tocolytic treatment during pregnancy (N = 23,018)	355	1.5	Reference	Reference
Pregnant women with tocolysis (N = 1,115)	24	2.2	1.18	(0.77–1.83)
Without vs with receiving more than one tocolytic treatment				
Pregnant women without any tocolysis during pregnancy (N = 23,018)	355	1.5	Reference	Reference
Pregnant women with tocolysis for one time during pregnancy (N = 1,006)	18	1.8	1.00	(0.61–1.64)
Pregnant women with tocolysis for more than one time during pregnancy (N = 109)	6	5.5	2.70	(1.13–6.49)

* Adjusted covariates included asthma diagnosis during pregnancy, light-for-dates, gestational diabetes mellitus, polyhydramnios, hyperthyroidism, hyperthyroidism, upper respiratory related infection, per-birth, drug or alcohol abuse, and psychologic disorders.

Table 3

The association between patients with tocolytic treatment and the nonreassuring fetal status (NRFS): results from multivariable logistic regression models by gestational age [*].

	Gestational age					
	First trimester		Second trimester		Third trimester	
Exposure	Adjusted odds ratio	95% CI[†]	Adjusted odds ratio	95% CI	Adjusted odds ratio	95% CI
Pregnant women with tocolytic treatment	2.75	(0.26–29.54)	0.23	(0.01–3.79)	1.24	(0.78–1.95)
Pregnant women without tocolytic treatment	Reference	Reference	Reference	Reference	Reference	Reference

[*] Adjusted covariates included asthma diagnosis during pregnancy, light-for-dates, gestational diabetes mellitus, polyhydramnios, hyperthyroidism, hyperthyroidism, upper respiratory related infection, per-birth, drug or alcohol abuse, and psychologic disorders.

[†] A broad confidence interval was observed here because among all pregnant women who received tocolytic treatment, only 1.7% of them had the treatment in the first trimester.

4. Discussion

To our knowledge, this is the first observational study using an administrative claims database to evaluate the association between tocolysis for uterine contraction and nonreassuring fetal status. Pregnant women who had tocolytic treatment more than one time during pregnancy were found to be at higher risk of the nonreassuring fetal status when compared to pregnant women without any tocolytic treatment.

In this study, a significant association was found between an increased risk of nonreassuring fetal status and a more frequent tocolytic treatment received by pregnant women. Two possible reasons could explain this significant finding. First, complete bedrest is included in the overall medical management for pregnant women admitted for preterm uterine contraction and tocolysis. A longer time of lying in a supine position increases the risk of thrombosis among pregnant women.[24] Furthermore, pregnancy itself is a risk factor for thrombosis. Studies have shown that the risk of venous thromboembolism among pregnant women was five times higher than non-pregnant women.[25,26] The hypercoagulability in pregnancy is thought to be a protective mechanism to prevent a massive bleeding in the postpartum.[27] However, the hypercoagulability also increases the risk of thrombosis during pregnancy.[27] Therefore, pregnancy coupled with forced bedrest increases the risk of developing thrombosis in placenta which leads to the nonreassuring fetal status.

Second, the use of tocolytic treatment not only reduces uterine smooth muscle contraction, but can also relax venous smooth muscle which leads to vasodilation, venous pooling, and thrombosis. Previous studies have showed that a change in blood flow in the placenta was a major risk factor for pregnancy complications including preterm labor, abruption placenta, intrauterine growth restriction, and eclampsia.[28–30] Pregnant women who receive repeated tocolytic treatments are exposed to higher doses and longer duration of therapy. This may lead to placental thrombosis which further exaggerates placental insufficiency and increases the risk of nonreassuring fetal status.

Our study used administrative claims data, which has several advantages, including obtaining a sufficient sample size, contributing evidence-based findings from real-world data, and avoiding an ethical dilemma often seen in randomized control trials among pregnant women.[31,32] Furthermore, we have adjusted several measurable confounders during pregnancy in our study design, which provided valid estimates of the effectiveness of tocolysis on the risk of nonreassuring fetal status.

From a clinical perspective, health care providers need to know that the risk of nonreassuring fetal status could be associated with multiple tocolytic treatments for uterine contraction. Blood circulation in the placenta needs to be carefully monitored when pregnant women receive tocolytic treatment. A limited amount of exercise instead of a complete bedrest may be beneficial to avoid thrombosis among those undergoing tocolytic treatment. In addition, physicians also need to be mindful when prescribing tocolytics to pregnant women for uterine contraction. A routine evaluation of dose and duration of tocolytic treatment is necessary. The treatment with high dose and long duration should be avoided if possible, to reduce the risk of nonreassuring fetal status. Effects of clinical intervention to reduce the frequency and duration of tocolysis could be considered to increase the overall efficacy and safety of tocolytic treatment.

This study has several potential limitations. First, the lack of clinical measures of obstetrical outcomes, including birth examination and weight, could result in residual confounding effects. Second, bias from unmeasurable confounders including smoking status, exercise habits, dietary habits, education, family income, and prenatal care could lower the precision of estimation. Therefore, only association but not causality can be inferred from our study. Third, identifying patients with only using ICD-9 CM codes may not be precise. There may be misclassification of disease diagnoses and under-coding of pregnancy outcomes. Fourth, the analyses were limited to pregnant women in Taiwan. Results from this study may not be extended to populations other than Taiwanese. Fifth, bias from the interobserver variability can still exist because the fetal heart rate (FHR) was traced by electronic fetal monitoring (EFM). Previous studies have shown that the high interobserver variability could lead to the inconsistent agreement among physicians to decide whether the FHR was classified as reassuring or nonreassuring.[33–35] Standardization and simplification of FHR definitions as well as interpretation with causation may lower the interobserver variability.[35] Finally, a lack of information of the baby birth date made it difficult to measure the exact gestational age for each pregnant woman. To overcome this difficulty, we adopted a method in previous studies that has proven valid in measuring gestational age using administrative claims data.[21–23]

In conclusion, pregnant women who had more frequent tocolytic treatments for uterine contraction during pregnancy were found to be at an increased risk of nonreassuring fetal status. Careful monitoring of the circulation in the placenta and close evaluation of the tocolytic treatment regarding the dose and duration are necessary. Physicians need to understand the risk and benefits of tocolysis for preterm uterine contraction to make an informed decision about whether to continue or discontinue tocolytic treatment.

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