

Different impacts of various tocolytic agents on increased risk of postoperative hemorrhage in preterm labor women undergoing Cesarean delivery

A population-based cohort study

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Abstract

Tocolytic agents, commonly used for inhibiting preterm labor, pose the risk of uterine atony, leading to postpartum hemorrhage. This study elucidated the effects of different tocolytic agents on postoperative hemorrhage among women in preterm labor undergoing Cesarean delivery (CD). Data from Taiwan National Health Insurance Research Database were analyzed. The risk (adjusted hazard ratio [aHR] and 95% confidence intervals [CI]) of postoperative hemorrhage in CD women with preterm labor diagnosis using tocolytic agents (Tocolysis group) comparing to CD women not using tocolytic agents (Control group) were determined. Impacts of different tocolytic agents in this regard were also investigated. Our data revealed that the incidence (11.7% vs 2.6%, $P < .001$) and risk (aHR: 1.21, 95% CI: 1.12–1.31, $P < .001$) of postoperative hemorrhage were significantly higher in the Tocolysis group ($n = 15,317$) than in the Control group ($n = 244,096$). Ritodrine was the most frequently used tocolytic agent (80.5%), followed by combination therapy (using more than one tocolytic agents) (8.5%), magnesium sulfate (MgSO_4 , 4.6%), calcium channel blockers (3.8%), betamimetics other than ritodrine (1.9%), prostaglandin synthase inhibitors (0.5%), and nitrates (0.1%). Barring those using calcium channel blockers and combination therapy, the use of MgSO_4 (aHR: 1.43, $P = .001$), betamimetics other than ritodrine (aHR: 1.71, $P < .001$), prostaglandin synthase inhibitors (aHR: 2.67, $P < .001$) and nitrates (aHR: 3.30, $P = .001$) was associated with higher risks of postoperative hemorrhage compared with ritodrine. In conclusion, CD women with preterm labor diagnosis using tocolytic agents exhibit an increased risk of postoperative hemorrhage and that this risk varies with the use of different tocolytic agents.

Abbreviations: aHR = adjusted hazard ratio, ATC = Anatomical Therapeutic Chemical, CD = Cesarean delivery, CI = confidence intervals, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, MgSO_4 = magnesium sulfate, NHIRD = National Health Insurance Research Database, NNH = number needed to harm.

Keywords: cesarean, postpartum hemorrhage, preterm labor, ritodrine, tocolytic agents

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1. Introduction

Tocolytic agents are used to inhibit spontaneous labor prior to 34 weeks of gestation.^[1] Betamimetics (e.g., ritodrine, terbutaline, hexoprenaline, salbutamol), calcium channel blockers (e.g., nifedipine, nicardipine), magnesium sulfate (MgSO₄), oxytocin receptor blockers (e.g., atosiban), prostaglandin synthase inhibitors (e.g., indomethacin, sulindac, celecoxib) and nitrates (e.g., nitroglycerin, nitric oxide) are among the most commonly used tocolytic agents.^[2–7] These medications reportedly induce smooth muscle relaxation of the uterus, thus suppressing premature contractions.^[8]

However, clinical data indicated that tocolytic agents may cause uterine atony, resulting in postpartum hemorrhage.^[8,9] A study revealed that Cesarean delivery (CD) per se poses an increased risk of postpartum hemorrhage compared with vaginal delivery.^[10] In line with this notion, we conjectured that the use of tocolytic agents may increase the risk of postoperative hemorrhage among women in preterm labor undergoing CD. Moreover, if the use of tocolytic agents increases the risk of postoperative hemorrhage, it becomes crucial to elucidate which tocolytic agent(s) exerts the least impact.

Therefore, we conducted this population-based cohort study to investigate whether tocolytic agents increase the risk of postoperative hemorrhage. Our hypothesis was that CD women who used tocolytic agents were at a higher risk of postoperative hemorrhage compared with CD women not using tocolytic agents. The impacts of different tocolytic agents in this regard were also explored.

2. Materials and methods

2.1. Ethics

This Institutional Review Board of Taipei Medical University, Taipei, Taiwan (protocol number: N201803088) approved our study. Because we used anonymous claim data of patients from the Taiwan National Health Insurance Research Database (NHIRD), no patient consent is required.

2.2. Cohort and outcomes

The study analyzed data retrieved from the NHIRD, which comprises monthly summaries for all claims with diagnoses coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and up to 4 secondary diagnoses being listed for each patient that is covered by the Taiwan National Health Insurance Program. This program provides a comprehensive benefit package covering preventive, dental, and medical services to all residents (approximately 24 million) in Taiwan.

The study cohort (Tocolysis group) comprised parturient women who underwent CD in hospitals or obstetric clinics between January 2002 and December 2006. Diagnosis-Related Group codes 0371A (CD) and 0373B (maternally requested CD) were used to identify CD women from the database.^[11] If any participant underwent multiple CDs during the observation period, only the first CD was counted. The exclusion criteria were CD women with hemorrhage, receiving blood transfusion, with coagulopathy, or using anticoagulants before surgery. We also excluded CD women younger than 16 years, older than 50 years, with more than 1000 days of hospital stay after CD, or with missing data. Only CD women who met the criteria of tocolysis

(i.e., with relevant diagnosis and using tocolytic agents) were included to precisely represent the study population. Therefore, CD women using tocolytic agents without relevant diagnosis (i.e., early or threatened labor, or preterm labor) were excluded. Moreover, only those with the diagnosis of postpartum hemorrhage as well as receiving blood transfusion were identified as having postoperative hemorrhage. The Anatomical Therapeutic Chemical codes were used to identify medication use (Table 1). Furthermore, medical comorbidities, pregnancy characteristics, and postoperative hemorrhage were identified using the ICD-9-CM and order codes (Table 1).^[12] We also had a control cohort (Control group) that included CD women not using tocolytic agents.

2.3. Statistical analysis

Data were analyzed using SPSS (version 16.0 for Windows; SPSS, Inc., Chicago, IL, USA). Continuous data were presented as mean \pm standard deviations. The between-group differences of patient characteristics were evaluated using the chi-square and Mann-Whitney *U* tests. Cox proportional-hazards regression analyses were performed to estimate the risk (i.e., hazard ratio [HR] and the 95% confidence intervals [CI]) of postoperative hemorrhage in the Tocolysis group compared with the Control group. Multivariate Cox models were used to adjust for the potential confounders affecting the risk of postoperative hemorrhage. Statistical significance was set at $P < .05$. The number needed to harm (NNH)^[13] was also calculated to further elucidate the clinical impacts of our results.

3. Results

3.1. Demographic data

Of 259,413 CD women included in total, 15,317 and 244,096 belonged to the Tocolysis and Control groups, respectively (Fig. 1). Significant differences were observed between the groups in terms of age, incidence of medical comorbidities (including diabetes mellitus, chronic hypertension, chronic heart failure, hyperlipidemia, anxiety, and depression), smoking, and medication use (including antidepressants, non-steroid anti-inflammatory drugs, opioids, cardiovascular drugs, and steroids; $P < .05$, Table 2). Moreover, pregnancy-related characteristics, including multiple gestation, gestational diabetes, pregnancy-induced hypertension, preeclampsia/eclampsia, intrauterine growth restriction, use of oxytocic drugs, and receipt of general anesthesia were also significantly different between the 2 groups ($P < .05$, Table 2).

3.2. A higher risk of postoperative hemorrhage in CD women with preterm labor diagnosis using tocolytic agents

The Tocolysis group showed a higher incidence of postoperative hemorrhage (11.7% vs 2.6%, $P < .001$) compared with the Control group (Table 3). Moreover, after adjustment for potential confounders that were significantly different between the 2 groups, the Tocolysis group showed a higher risk of postoperative hemorrhage (aHR: 1.21, 95% CI: 1.12–1.31, $P < .001$; NNH: 12) than the Control group (Table 4).

3.3. Impacts of different tocolytic agents

Figure 1 shows the frequency of medications used, with ritodrine being the most commonly used tocolytic agent (80.5%), followed

Table 1**The Anatomical Therapeutic Chemical (ATC), the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and the order codes used in the study.**

Diagnosis/Order	ATC codes / ICD-9-CM codes / order codes
Tocolytic agents	
Ritodrine	G02CA01
Betamimetics other than ritodrine	R03CC02, R03CC03, R03CC05
Calcium channel blockers	C08CA04, C08CA05,
Magnesium sulfate	A12CC02
Oxytocin receptor blockers	G02CX01
Prostaglandin inhibitors	M01AB01, M01AB02, M01AH01, L01XX33
Nitrates	C01DA02, C05AE01, R07AX01
Systemic medications	
Antidepressants	N06AA, N06AB, N06AG, N06AX
Non-steroid anti-inflammatory drugs	M01A
Opioids	N02A
Cardiovascular drugs	C01DA, B01AC, C09A, C09B, C07A, C08, C03, C09C, C09D
Steroids	H02AB
Medical comorbidities	
Diabetes mellitus	250, 648.0
Chronic hypertension	401–405
Chronic heart disease	393–398, 424, 425, 426, 427, 428, 429, 648.61
Hyperlipidemia	272
Obesity	278, 278.0, 278.00, 278.01
†Chronic obstructive pulmonary diseases	490–496
Depression	296.2, 296.3, 311
Anxiety	300.0, 300.2, 300.3, 308.3, 309.81
Alcohol related illness	291, 303, 305.0, 571.0–571.3
Pregnancy characteristics	
Multiple gestation	651
Gestational diabetes	648.8
Pregnancy-induced hypertension	642.0–642.3, 642.9
Preeclampsia and eclampsia	642.4–642.7
Intrauterine growth restriction	656.50, 656.51, 656.53
Use of oxytocic drugs	G02A
General anesthesia	96020C, 96021C, 96022C
Complications	
Hemorrhage (including postoperative bleeding)	641, 640.9, 666, 667, 669.1, 998.0, 998.1 and 998.2
Postpartum blood transfusion	94001C, 94005C

† As a proxy of smoking.

by combination therapy (i.e., using more than 1 tocolytic agents) (8.5%), MgSO₄ (4.6%), calcium channel blockers (3.8%), betamimetics other than ritodrine (1.9%), prostaglandin synthase inhibitors (0.5%), and nitrates (0.1%). Notably, none used oxytocin receptor blockers.

Barring those using calcium channel blockers and combination therapy, the use of MgSO₄ (aHR: 1.43, 95% CI: 1.15–1.77, $P = .001$, NNH: 17), betamimetics other than ritodrine (aHR: 1.71, 95% CI: 1.32–2.22, $P < .001$, NNH: 10), prostaglandin synthase inhibitors (aHR: 2.67, 95% CI: 1.65–4.32, $P < .001$, NNH: 8), and nitrates (aHR: 3.30, 95% CI: 1.64–6.64, $P = .001$, NNH: 3) was associated with higher risks of postoperative hemorrhage compared with ritodrine (Table 5).

4. Discussion

Our study results confirmed that the use of tocolytic agents by CD women in preterm labor posed an increased risk of postoperative hemorrhage. Although these agents are reported to inhibit premature uterine contraction by inducing smooth muscle relaxation,^[8] this mechanism may result in uterine atony after delivery.^[9] Because studies have revealed that uterine atony is an

established risk factor for postpartum hemorrhage, resulting in requirement of blood transfusion,^[8,9] it is thus reasonable to observe our results. Similar results were observed in women who experienced vaginal delivery.^[9] Collectively, these data highlighted that tocolytic agents may exert adverse impacts on clinical outcomes in women undergoing vaginal delivery or CD. Clinical implications of these results are expected to be profound, as they were derived from 259,413 participants.

Moreover, our study also showed that different tocolytic agents influence the risk of postoperative hemorrhage differently among CD women in preterm labor. As per our results, CD women using MgSO₄, betamimetics other than ritodrine, prostaglandin inhibitors, or nitrates may be associated with even higher risks of postoperative hemorrhage than those using ritodrine, calcium channels blockers, or combination therapy, with the NNH ranging between 3 and 17. Our study data highlighted the significantly adverse impacts that different tocolytic agents may have on postoperative hemorrhage in CD women in preterm labor. These data provide crucial information, which clinicians should consider before prescribing tocolytic agents. We recommend that if delivery is inevitable, clinicians should discontinue tocolytic agents as early as possible to avoid

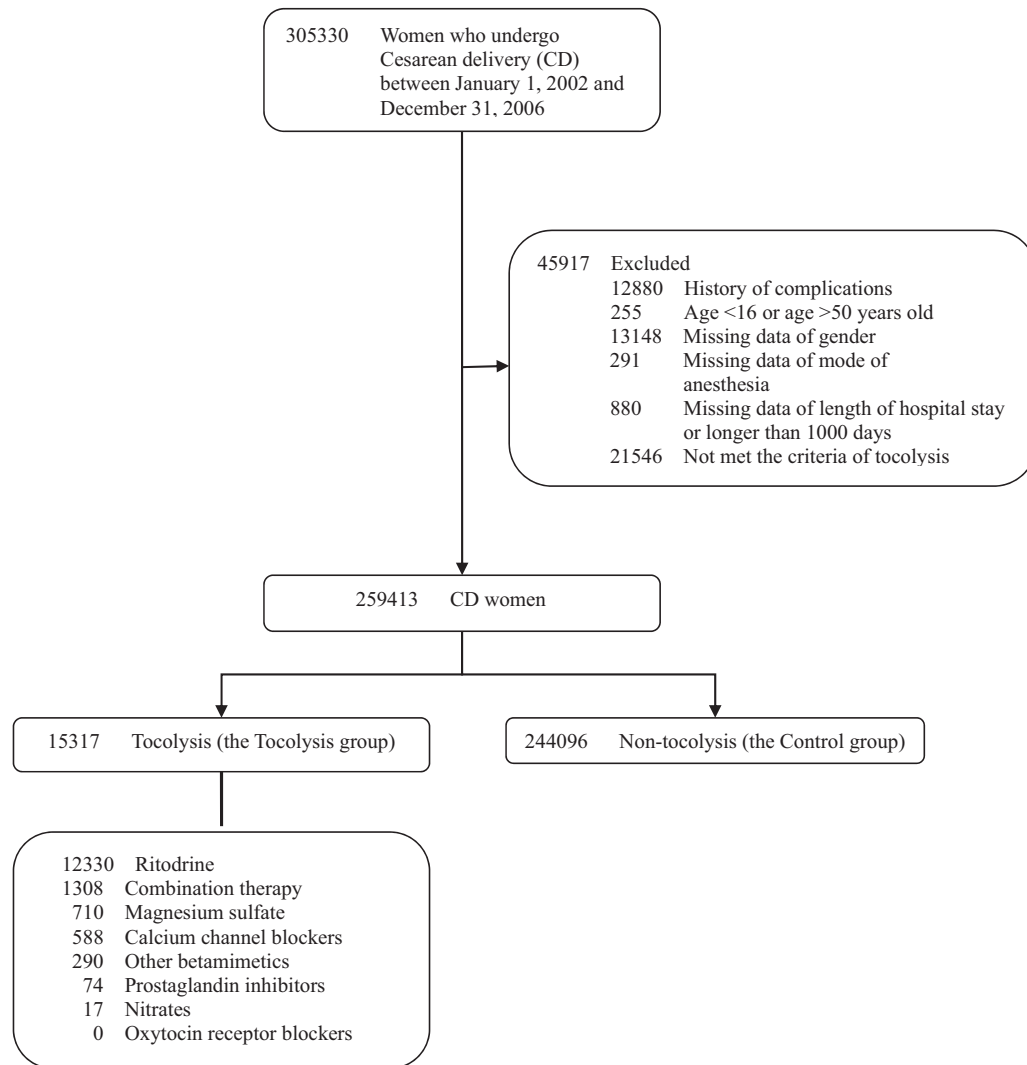


Figure 1. Flow of participants in this study. Tocolysis = CD women using tocolytic agents, Control: CD women not using tocolytic agents.

or minimize the adverse effects. Moreover, they should prepare themselves beforehand for further management (such as transcatheter arterial embolism) of uncontrolled postoperative hemorrhage.

According to our data, ritodrine was the most frequently used tocolytic agent in Taiwan among CD women in preterm labor. Its therapeutic efficacy and adverse effects were investigated extensively.^[2] Abundant data have highlighted that ritodrine may cause arrhythmia, hypotension, fluid retention, hypokalemia/hyperkalemia, hyperglycemia, and pulmonary edema.^[2,14,15] Although its mechanism of inducing myometrial relaxation remains uncertain, the adverse effects of ritodrine are generally believed to be caused by the activation of beta-adrenergic receptors.^[16] Several other betamimetics similar to ritodrine (e.g., terbutaline, hexoprenaline and salbutamol) have been used clinically for treating preterm labor.^[2] These betamimetics also have been demonstrated to cause adverse effects similar to those caused by ritodrine.^[2,14,16] Therefore, ritodrine and other betamimetics were expected to exert similar effects on the risk of postoperative hemorrhage among CD women in preterm labor. However, to our surprise, those using

betamimetics other than ritodrine showed an approximately 70% higher risk of developing postoperative hemorrhage compared with those using ritodrine. Similar results have been previously reported, as those receiving terbutaline were noted to have a higher risk of hyperglycemia compared with those receiving ritodrine.^[17,18] Therefore, our results were consistent with those. Collectively, these data highlighted the variable impacts of the different betamimetics in this regard although the underlying mechanisms remain to be elucidated.

Because of ritodrine's several significant adverse effects, substitute tocolytic agents have been developed that can not only provide comparable therapeutic efficacy but also cause fewer unfavorable effects. One possible substitute is MgSO₄.^[19,20] Studies have demonstrated that MgSO₄ shows therapeutic efficacy and safety comparable with that of ritodrine.^[19,20] Another study further indicated that the adverse effects caused by MgSO₄ tended to be less serious than ritodrine.^[21] However, our data demonstrated an approximately 40% higher risk of postoperative hemorrhage in those using MgSO₄ compared with those using ritodrine, which contradicted the previous data.^[19–21] Although the mechanisms are as yet

Table 2
Distribution of Cesarean delivery (CD) women characteristics.

	Tocolysis (n = 15317)	Control (n = 244096)	P value ^a
Demographic data			
Age (years), mean ± standard deviations	30.40 ± 5.05	29.85 ± 4.89	<.001
Medical comorbidities			
Diabetes mellitus, n (%)	124 (0.8)	295 (0.1)	<.001
Chronic hypertension, n (%)	36 (0.2)	55 (0)	<.001
Chronic heart disease, n (%)	56 (0.4)	156 (0.1)	<.001
Hyperlipidemia, n (%)	10 (0.1)	33 (0)	<.001
Obesity, n (%)	2 (0)	24 (0)	.665
†Chronic obstructive pulmonary disease, n (%)	43 (0.3)	139 (0.1)	<.001
Depression, n (%)	12 (0.1)	54 (0)	<.001
Anxiety, n (%)	14 (0.1)	71 (0)	<.001
Alcohol related illness, n (%)	0 (0)	5 (0)	1.000
Medications			
Use of antidepressants, n (%)	46 (0.3)	94 (0)	<.001
Use of non-steroid anti-inflammatory drugs, n (%)	11574 (75.6)	177182 (72.6)	<.001
Use of opioids, n (%)	6508 (42.5)	65354 (26.8)	<.001
Use of ‡cardiovascular drugs, n (%)	7486 (48.9)	11285 (4.6)	<.001
Use of steroids, n (%)	6900 (45)	9437 (3.9)	<.001
Pregnancy characteristics			
Multiple gestation, n (%)	2595 (16.9)	5006 (2.1)	<.001
Gestational diabetes, n (%)	200 (1.3)	624 (0.3)	<.001
Pregnancy-induced hypertension, n (%)	683 (4.5)	1372 (0.6)	<.001
Preeclampsia and eclampsia, n (%)	2273 (14.8)	2602 (1.1)	<.001
Intrauterine growth restriction, n (%)	758 (4.9)	1125 (0.5)	<.001
Use of oxytocic drugs, n (%)	11067 (72.3)	195215 (80)	<.001
General anesthesia, n (%)	1832 (12)	7435 (3)	<.001

^a Tested by the Chi-square test and the Mann-Whitney U test.

† As a proxy of smoking.

‡ Nitrates, anti-platelet agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers and diuretics.

Tocolysis group = CD women using tocolytic agents, Control group = CD women not using tocolytic agents.

unclear, our data indicated that MgSO₄ may cause more serious adverse effects than ritodrine. Previous experimental data also showed similar results when MgSO₄, but not ritodrine, was

Table 3
Incidences of postoperative hemorrhage within 30 days after Cesarean delivery (CD).

	Tocolysis (n = 15317)	Control (n = 244096)	P value ^a
Hemorrhage, n (%)	1785 (11.7)	6360 (2.6)	<.001

^a Tested by the Chi-Squared test.

Tocolysis group = CD women using tocolytic agents, Control group = CD women not using tocolytic agents.

Table 4
Relative risk of having postoperative hemorrhage within 30 days after Cesarean delivery (CD) in tocolytic users comparing to non-tocolytic users.

	Group	aHR	95% CI	P value ^{a,†}	NNH
Hemorrhage	Tocolysis	1.21	1.12–1.31	<.001	12
	Control	1.00			

^a Tested by Cox proportional hazard regression.

† Adjusted for age, diabetes mellitus, chronic hypertension, chronic heart disease, hyperlipidemia, obesity, chronic obstructive pulmonary disease, depression, anxiety, alcohol related illness, use of antidepressants, use of non-steroid anti-inflammatory drugs, use of opioids, use of cardiovascular drugs, use of steroids, multiple gestation, gestational diabetes, pregnancy-induced hypertension, preeclampsia and eclampsia, intrauterine growth restriction, use of oxytocic drugs and mode of anesthesia.

Tocolysis group = CD women using tocolytic agents, Control group = CD women not using tocolytic agents, aHR = adjusted hazard ratio, CI = confidence intervals, NNH = number needed to harm.

observed to worsen maternal hypotension in gravid ewes complicated with hemorrhage.^[22] More studies are required before further conclusions can be drawn.

Prostaglandin synthase inhibitors are also commonly used as tocolytic agents.^[6] Previous research demonstrated superior benefits of prostaglandin synthase inhibitors in both therapeutic efficacy and maternal adverse effects over ritodrine among women in preterm labor.^[6,23] Moreover, prostaglandin synthase inhibitors also show potent platelet inhibiting properties.^[24] Nevertheless, their platelet-inhibiting effects are of limited clinical significance in patients without underlying bleeding disorders.^[25] However, our study results contradicted those previous data^[6,23,25] with our observation of prostaglandin synthase inhibitors significantly increasing the risk of postoperative hemorrhage (more than two-fold increases) compared with ritodrine among CD women in preterm labor. Based on these data, we speculate that the effects of prostaglandin synthase inhibitors on inhibiting platelet functions may contribute, at least in part, to the development of postoperative hemorrhage among CD women in preterm labor.

Our study demonstrated that nitrates also increased the risk of postoperative hemorrhage (more than three-fold increases) compared with ritodrine among CD women in preterm labor, which is similar to the results of prostaglandin synthase inhibitors. Nitrates are also reported to cause significant adverse effects, including hypotension and tachycardia, among women in preterm labor.^[7] Moreover, clinical data indicated that nitrates did not show superior effects in delaying delivery compared with placebos among women in preterm labor.^[7] These data highlight-

Table 5
Relative risk of having postoperative hemorrhage within 30 days after surgery in Cesarean women using tocolytic agents other than ritodrine comparing to those using ritodrine.

Hemorrhage	Tocolytic agents	aHR	95% CI	P value ^{a,†}	NNH
	Combination therapy	1.09	0.9–1.32	.363	16
	Magnesium sulfate	1.43	1.15–1.77	.001	17
	Calcium channel blocker	1.07	0.85–1.35	.557	29
	Other betamimetics	1.71	1.32–2.22	<.001	10
	Prostaglandin inhibitors	2.67	1.65–4.32	<.001	8
	Nitrates and others	3.30	1.64–6.64	.001	3
	Ritodrine	1.00			

^a Tested by Cox proportional hazard regression.

aHR = adjusted hazard ratio, CI = confidence intervals, NNH = number need to harm.

[†] Adjusted for age, diabetes mellitus, chronic hypertension, chronic heart disease, hyperlipidemia, obesity, chronic obstructive pulmonary disease, depression, anxiety, alcohol related illness, use of antidepressants, use of non-steroid anti-inflammatory drugs, use of opioids, use of cardiovascular drugs, use of steroids, multiple gestation, gestational diabetes, pregnancy-induced hypertension, preeclampsia and eclampsia, intrauterine growth restriction, use of oxytocic drugs and mode of anesthesia.

ed that nitrates are not effective tocolytic agents. Therefore, the appropriateness of using nitrates for tocolysis therapy among CD women in preterm labor is challenged with our study data.

Calcium channel blockers have also been used as tocolytic agents for more than 3 decades.^[2,6] Comparable tocolytic efficacy of calcium channel blockers and ritodrine has been confirmed by several studies.^[3,27,28] Moreover, they indicated that calcium channel blockers may cause less adverse maternal effects than ritodrine.^[3,27,28] Our data showed comparable impacts of calcium channel blockers and ritodrine on the risk of postoperative hemorrhage among CD women in preterm labor. Collectively, these data support the concept that calcium channel blockers can be substitute tocolytic agents for ritodrine.

None of the participants in this study used oxytocin receptor blockers. One main reason is that oxytocin receptor blockers are not covered by the Taiwan National Health Insurance program. As a result, their impact on the risk of postoperative hemorrhage among CD women in preterm labor remained uninvestigated in this study. Notably, we observed that combination therapy (i.e., the use of more than one tocolytic agents) and ritodrine may exert comparable impacts on the risk of postoperative hemorrhage among CD women in preterm labor. However, the mechanisms remain unclear. Nevertheless, one possible explanation may be that combination of different tocolytic agents may significantly reduce the individual dosage of tocolytic agents and thus minimize the adverse effects that tocolytic agents may have individually on postoperative hemorrhage. More studies are required before further conclusions can be drawn.

Our study comes with certain limitations. First, data from this study provide a correlation but not a cause–result relationship between tocolytic agents and risk of postoperative hemorrhage. Second, our sample sizes showed huge between-group differences. Therefore, the potential for bias is likely. Third, significant between-group differences in several potential confounders were noted. Although the potential impacts of these confounders were adjusted, the data should be interpreted cautiously.

In conclusion, CD women with preterm labor diagnosis using tocolytic agents exhibit an increased risk of postoperative hemorrhage and that this risk varies with the use of different tocolytic agents.

Author contributions

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Supervision: Pei-Shan Tsai, Chun-Jen Huang.

Writing – original draft: Hua-Lin Lee, Kuo-Ching Lu, Pei-Shan Tsai, Chun-Jen Huang.

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