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Association between total dose of ritodrine hydrochloride and pulmonary edema in twin pregnancy: a retrospective cohort study in Japan

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Abstract

Objective

Pulmonary edema is widely recognized as a severe side effect of ritodrine hydrochloride. Recently, the number of twin pregnancies has been increasing. Few studies have reported the association between total dose of ritodrine hydrochloride prior to delivery and pulmonary edema in twin pregnancy. This study aimed to examine this association and determine the optimal cutoff threshold of total ritodrine hydrochloride dose to predict the incidence of pulmonary edema in twin pregnancy, based on obstetric records.

Design

Retrospective cohort study.

Setting

Yamanashi Prefectural Central Hospital, Japan

Participants

Two hundred twenty-six women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital between September 2009 and November 2016

Methods

The obstetric records of the participants were analyzed. We defined one unit of ritodrine

hydrochloride as 72 mg per 24 h continuous transfusion at 50 μg/min to calculate the dose of ritodrine used for tocolysis.

Outcome measures

Multivariable logistic regression analysis was performed to examine the association between total dose of ritodrine hydrochloride used for threatened preterm labor and pulmonary edema, while controlling for potential confounding factors. Then, a receiver-operating characteristic curve was used to determine the optimal cutoff of total ritodrine dose to predict pulmonary edema incidence.

Results

Mean maternal age was 32 (range, 18-46) years; 143 participants were nulliparous (63.3%), 109 had (48.2%) term deliveries, and 194 (85.8%) had cesarean deliveries. The overall incidence of pulmonary edema was 13.7% (31/226). Multivariable analysis showed that the total dose of ritodrine was significantly associated with pulmonary edema (adjusted odds ratio, 1.02; 95% confidence interval, 1.004-1.03). The best cut-off point to predict the incidence of pulmonary edema was 26 units (sensitivity, 61.3%; specificity, 87.8%).

Conclusion

Our results suggest that consideration of the total dose of ritodrine hydrochloride is helpful in the management of patients with threatened preterm labor in twin pregnancy.

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Article summary

Strengths and limitations of this study

- We retrospectively analyzed medical records to determine the cut-off dosage of ritodrine hydrochloride associated with increased incidence of pulmonary edema in twin pregnancy.
- Limitations include the single center, retrospective design and lack of inclusion of all potential confounding factors.

Introduction

Twin pregnancy arising from assisted reproductive technologies (ART) has been steadily increasing in developed countries, including Japan. [1-3] Although the total incidence of preterm birth in twin pregnancy is approximately 50%, [4] there is no globally established standard treatment for threatened preterm labor. [5] β2-adrenergic agonists, such as ritodrine hydrochloride, are most commonly used for preventing preterm birth worldwide.[6] Ritodrine hydrochloride is the only agent approved by the US Food and Drug Administration (FDA) for reduction of preterm birth within 48 hours of initiation of treatment.[7] It is commonly used for threatened preterm labor as a first-line tocolytic agent in Japan,[6] although the frequency of its use has decreased in other developed countries due to its various side effects.[5,8] Of these, pulmonary edema is known to be the most severe side effect of this drug when continuous intravenous infusion is performed over one week.[9-11] Moreover, previous studies reported that multiple pregnancies are associated with an increased risk of pulmonary edema.[12-13] However, few studies have focused on the association between the use of ritodrine hydrochloride for threatened preterm labor in twin pregnancy and the incidence of pulmonary edema. The aim of the present study was to examine the association of the total dose of ritodrine hydrochloride and the incidence of pulmonary edema in twin pregnancy.

Methods

Study design

For this retrospective cohort study, we collected obstetric records and delivery information of 233 women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital between September 2009 and November 2016. Exclusion criteria were women with single or double fetal demise, major fetal malformations, and twin arterial perfusion sequence. This study was reviewed and approved by the Human Subjects Review Committee of Yamanashi Prefectural Central Hospital.

Date collections

We collected the obstetric data from the medical and operative records. Selected data were maternal age, parity, occurrence of preterm delivery, delivery method (vaginal or cesarean delivery), chorionicity, and use of ART (in vitro fertilization or intracytoplasmic sperm injection). In addition, the presence of pregnancy-induced hypertension (PIH), pregestational weight status, administration of corticosteroids and magnesium sulfate, intraoperative transfusion, and postpartum hemorrhage (PPH) were assessed. These factors have been previously described as risk factors for pulmonary edema in

pregnancy.[12-14] PPH was defined as “active bleeding, including amniotic fluid, exceeding 1000 ml within 24 hours following delivery.”[15] PIH was defined as a blood pressure of ≥140/90 mmHg on at least two occasions.[16] We also evaluated prolonged bed rest and gestational age, which are reported to affect cardiovascular physiology.[17-18] Prolonged bed rest was defined as bed rest greater than 6 weeks.[17] Regarding the pregestational weight status, pregestational body mass index (BMI) was calculated according to the World Health Organization standards (bodyweight [kg]/height [m]^2), and patients were classified as obese (≥25.0 kg/m^2) or non-obese (<25.0 kg/m^2) according to the Japan Society of Obstetrics and Gynecology Guidelines for Obstetrical Practice 2014.[15] The dose of ritodrine hydrochloride for tocolysis was determined by each obstetrician. The dose of ritodrine hydrochloride administered intravenously ranged from 50 to 200 μg/min, and we defined one unit as 72 mg per 24 h continuous transfusion at 50 μg/min. Magnesium sulfate dose ranged from 1 to 2 g/h by drip infusion. Pulmonary edema was defined as the clinical syndrome of acute respiratory distress associated with pulmonary rales, radiographic evidence of alveolar pulmonary edema, and supplemental oxygen requirement to maintain oxygen saturation of the peripheral arteries above 95%.[19]

Statistical analyses

First, the Mann-Whitney U test and the chi-square test were used to determine potential confounding factors for pulmonary edema. Second, a multiple logistic regression model was used to identify variables significantly associated with pulmonary edema. Then, a receiver-operating characteristic (ROC) curve was used to determine the best cut-off value for the total dose of ritodrine hydrochloride to predict pulmonary edema. We used the Youden index,[20] which describes the maximum vertical distance between the ROC curve and the diagonal or chance line, to define the optimal cut-off value.

All analyses were performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and the significance level was set at $p < 0.05$.

Results

Due to missing data on ritodrine hydrochloride total dosage (n=4) and single fetal demise (n=3), 226 (96.9%) women were considered eligible for inclusion in this study. Mean maternal age was 32 (range, 18-46) years, with 143 (63.3%) women being nulliparous, 109 (48.2%) having term deliveries, and 194 (85.8%) having cesarean deliveries. The overall incidence of pulmonary edema was 13.7% (31/226). Table 1 described the clinical characteristics of the enrolled women.

Table 1. Baseline characteristics of the study population

Variables	Intravenous administration of ritodrine hydrochloride (+)	Intravenous administration of ritodrine hydrochloride (-)	p-value
Pulmonary edema	22（26.8）	9 (6.3)	< 0.001
Maternal age	32 (18-46)	32 (23-41)	0.06
Nulliparity	55（67.1）	88 (61.1)	0.37
Preterm birth	51（62.1）	65 (45.1)	0.01
Cesarean section	76 (92.3)	118 (82.0)	0.03
Pre-pregnancy BMI	20.6 (16.6-40.9)	19.5 (15.8-36.5)	0.003
Monochorionic	36（43.9）	56 (38.9)	0.46
ART	14 (17.1)	26 (18.1）	0.85

Values are presented as median (range) or number (%).

BMI: Body mass index, ART: Assisted reproductive technology

The characteristics of the group with intravenous administration of ritodrine versus the group with no intravenous administration of ritodrine were similar, except for a higher incidence of pulmonary edema, preterm birth, and cesarean section and higher pre-pregnancy BMI in the intravenous administration of ritodrine group. Table 2 reports the distribution of total dose of ritodrine hydrochloride and pulmonary edema among the entire study population.

Table 2. Prevalence of pulmonary edema according to total dose of ritodrine hydrochloride

Total dose of ritodrine hydrochloride (units)	Pulmonary edema, n (%)
0~10	10/157 (6.4%)
11~20	1/14 (7.1%)
21~30	5/17 (29.4%)
31~40	3/6 (50.0%)
41~50	3/5 (60.0%)
>51	9/27 (33.3%)

Smaller total dose of ritodrine hydrochloride was significantly associated with a lower rate of pulmonary edema. On multivariable analyses, the total dose of ritodrine hydrochloride (adjusted odds ratio (OR), 1.02; 95% confidence interval (CI), 1.004-1.03), PIH (adjusted OR, 6.56; 95% CI, 1.96-21.9), and PPH (adjusted OR, 4.18; 95% CI, 1.23-14.2) were associated with pulmonary edema (Table 3).

Table 3. Crude and adjusted odds ratios of risk factors for pulmonary edema

Variables	Pulmonary edema	No pulmonary edema	Crude		Adjusted	
			OR	95% CI	OR	95% CI
Ritodrine hydrochloride (unit:median (25^{th}-75^{th} percentile))	29 (0-77.3)	0 (0-10)			1.02	1.004-1.03
PIH						
No (n)	22	173	1.0	Reference	1.0	Reference
Yes (n)	9	22	3.21	1.32-7.86	5.51	1.84-16.5

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Obese						
No (n)	28	172	1.0	Reference	1.0	Reference
Yes (n)	3	23	0.80	0.23-2.84	0.63	0.15-2.68
PPH						
No (n)	4	71	1.0	Reference	1.0	Reference
Yes (n)	27	124	3.86	1.30-11.5	4.18	1.23-14.2
Administration of corticosteroids						
No (n)	25	163	1.0	Reference	1.0	Reference
Yes (n)	6	32	1.22	0.46-3.21	2.01	0.51-7.92
Administration of magnesium						
No (n)	21	158	1.0	Reference	1.0	Reference
Yes (n)	10	37	2.03	0.88-4.68	0.95	0.28-3.26
Intraoperative transfusion						
<2000 mL (n)	24	177	1.0	Reference	1.0	Reference
≥2000 mL (n)	7	18	2.87	1.09-7.58	1.56	0.49-4.89
Preterm						
No (n)	17	100	1.0	Reference	1.0	Reference
Yes (n)	14	95	0.86	0.41-1.86	1.81	0.67-4.90
Bed rest						
< 6 weeks (n)	13	135	1.0	Reference	1.0	Reference
≥ 6 weeks (n)	18	60	3.12	1.43-6.76	1.53	0.34-6.91

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2 Values are presented as mean ± standard deviation or number.

3

4 PIH: pregnancy-induced hypertension, PPH: postpartum hemorrhage

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ROC curve analysis suggested that the cut-off value of 26 units for the total dose of ritodrine hydrochloride would allow for the maximum number of patients to be correctly classified according to the presence or absence of pulmonary edema. A cutoff point of 26 units provided a sensitivity of 61.3%, specificity of 87.8%, positive predictive value of 44.2%, and negative predictive value of 93.4% (Fig. 1).

Discussion

Results of this study suggest that there is an association between total dose of ritodrine hydrochloride and pulmonary edema in twin pregnancy after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to observe this association and to suggest a threshold optimal cutoff of total ritodrine dose to predict the incidence of pulmonary edema in twin pregnancy.

First, although treatment for preterm labor with a beta-agonist, including ritodrine, significantly reduces the number of women giving birth within 48 hr and seven days.[21] these tocolytic agents can cause serious complications, including pulmonary edema. There are few studies focused on the association between the dose of ritodrine hydrochloride administered for threatened preterm labor in twin pregnancy and the incidence of pulmonary edema. Gabriel R. et al reported that multiple pregnancies dramatically increased the

incidence of pulmonary edema with prolonged intravenous ritodrine hydrochloride therapy.[22] However, that study was different from our analysis because that report was limited by a small sample size and did not examine the association between the total dose of ritodrine hydrochloride and pulmonary edema.

Several possible factors are assumed to play a role in the pathophysiology of ritodrine hydrochloride induced pulmonary edema. Ritodrine hydrochloride leads to maternal tachycardia and retention of sodium and water by inducing secretion of renin, angiotensin, and aldosterone due to its β2-adrenergic stimulatory effect.[11] The desensitization of β-adrenergic receptors caused by the prolonged exposure to β2 stimulants could disturb the normal response of the heart in physiological status.[23-24] In addition, in twin pregnancy, maternal cardiac output is increased by 20% compared with singleton pregnancy at term.[25-26] The resulting increase in maternal stroke volume and heart rate might lead to myocardial dysfunction and pulmonary edema. Therefore, the incidence of pulmonary edema might to be increased in proportion to total dose of ritodrine hydrochloride in twin pregnancy.

The present study showed that the incidence of pulmonary edema could have been increased by the total dosage of ritodrine hydrochloride, irrespective of the therapeutic duration of this agent in twin pregnancy, and the validated cutoff value of total dosage of

ritodrine hydrochloride for predicting pulmonary edema is 26 units. The maximum dose of ritodrine hydrochloride intravenously injected is limited to 200 μg/min in Japan and 350 μg/min in the USA and Canada.[6] Even if we continue to use ritodrine at 350 μg/min for 48 hours, which is the maximum dose allowed in other countries, the total dose of ritodrine reaches only 14 units. In other words, it can be presumed that ritodrine hydrochloride might be safely used over 48 hours for management of threatened preterm labor in twin pregnancy. In contrast, our results also demonstrate the safety of ritodrine over one week within the cutoff value, because the observed negative predictive value of ritodrine total dosage was extremely high (93.4%). This result might be meaningful for all obstetricians, especially in Japan, where ritodrine hydrochloride is used as the first-line tocolytic agent for threatened preterm labor.

PIH was also significantly associated with pulmonary edema. Several studies have reported that twin pregnancy itself is one of the most important risk factors for PIH.[15, 27] Impaired endothelial permeability is thought to be a cause of pulmonary edema in PIH.[12] Therefore, more attention should be paid to the use of ritodrine hydrochloride in twin pregnancies with suspected PIH. In this study, long term tocolysis with total dose of ritodrine being more than 26 units in twin pregnancy with PIH caused pulmonary edema in 4 out of the 5 (80.0%) cases (data not shown).

Our study has several limitations. First, it might be difficult to extrapolate our results to the general population because our study was conducted at a single center. Therefore, a large-scale, multicenter, cohort study is needed to confirm these results in the general population. Second, data regarding sepsis, history of heart disease, endocrine disorders, amniotic fluid embolism, and pulmonary embolism were not included in our statistical model, although these are potential contributors to the incidence of pulmonary edema.[12] However, to the best of our knowledge, this study is the first to suggest an association between pulmonary edema and the total dose of ritodrine hydrochloride for tocolysis in twin pregnancies after controlling for some potential risk factors for pulmonary edema.

In conclusion, pulmonary edema was significantly associated with the total dose of ritodrine hydrochloride in twin pregnancy. Accurate risk stratification for pulmonary edema including consideration of the total dose of ritodrine hydrochloride might improve the management of patients with twin pregnancy and preterm labor.

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Hospital approved the study design.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

Contributorship statement

1. Conception or design of the work

Satoshi Shinohara, Rei Sunami

2. Data collection

Satoshi Shinohara

3. Data analysis and interpretation

Satoshi Shinohara, Rei Sunami, Kohta Suzuki

4. Drafting of the article

Satoshi Shinohara, Rei Sunami, Yuzo Uchida, Shuji Hirata, Kohta Suzuki

5. Critical revision of the article

Satoshi Shinohara, Rei Sunami, Kohta Suzuki

6. Final approval of the version to be published

Satoshi Shinohara, Rei Sunami, Yuzo Uchida, Shuji Hirata, Kohta Suzuki

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FIGURE LEGENDS

Fig. 1. Receiver operating curve analysis to determine the best cut-off value of total dose of ritodrine hydrochloride for predicting pulmonary edema

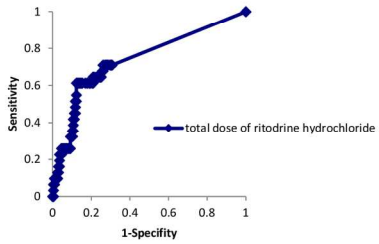

Fig1

215x279mm (200 x 200 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	All cases were followed-up.

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	We did not use a flow diagram in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Since this is retrospective cohort study, there is no mention of follow-up time.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	8-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	15

		which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Abstract

Objective

Pulmonary edema is recognized as a severe side effect of ritodrine hydrochloride. Recently, the number of twin pregnancies has been increasing. Few studies have reported the association between total dose of ritodrine hydrochloride prior to delivery and pulmonary edema in twin pregnancy. We aimed to examine this association and determine the optimal cutoff threshold of total ritodrine hydrochloride dose to predict the incidence of pulmonary edema in twin pregnancy, based on obstetric records.

Design

Retrospective cohort study.

Setting

Yamanashi Prefectural Central Hospital, Japan

Participants

Two hundred twenty-six women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital between September 2009 and November 2016

Methods

The obstetric records of the participants were analyzed. We defined one unit of ritodrine

hydrochloride as 72 mg per 24 h continuous transfusion at 50 μg/min to calculate the dose of ritodrine used for tocolysis.

Outcome measures

Multivariable logistic regression analysis was performed to examine the association between total dose of ritodrine hydrochloride used for threatened preterm labor and pulmonary edema, while controlling for potential confounding factors. Then, a receiver-operating characteristic curve was used to determine the optimal cutoff of total ritodrine dose to predict pulmonary edema incidence.

Results

Mean maternal age was 32 (range, 18-46) years; 143 participants were nulliparous (63.3%), 109 had (48.2%) term deliveries, and 194 (85.8%) had cesarean deliveries. The overall incidence of pulmonary edema was 13.7% (31/226). Multivariable analysis showed that the total dose of ritodrine was significantly associated with pulmonary edema (adjusted odds ratio 1.02; 95% confidence interval, 1.004-1.03). The best cut-off point to predict the incidence of pulmonary edema was 26 units (1872 mg) (sensitivity, 61.3%; specificity, 87.8%).

Conclusion

Our results suggest that consideration of the total dose of ritodrine hydrochloride is helpful in

the management of patients with threatened preterm labor in twin pregnancy.

Article summary

Strengths and limitations of this study

- We retrospectively analyzed medical records to determine the cut-off dosage of ritodrine hydrochloride associated with increased incidence of pulmonary edema in twin pregnancy.
- Limitations include the single center, retrospective design and lack of inclusion of all potential confounding factors.

Introduction

Twin pregnancy arising from assisted reproductive technologies (ART) has been steadily increasing in developed countries, including Japan. [1-3] Although the total incidence of preterm birth in twin pregnancy is approximately 50%, [4] there is no globally established standard treatment for threatened preterm labor. [5] β2-adrenergic agonists, such as ritodrine hydrochloride, are most commonly used for preventing preterm birth worldwide.[6] Ritodrine hydrochloride is the only agent approved by the US Food and Drug Administration (FDA) for reduction of preterm birth within 48 hours of initiation of treatment.[7] It is commonly used for threatened preterm labor as a first-line tocolytic agent in Japan,[6] although the frequency of its use has decreased in other developed countries due to its various side effects.[5,8] Of these, pulmonary edema is known to be the most severe side effect of this drug when continuous intravenous infusion is performed over one week.[9-11] Moreover, previous studies reported that multiple pregnancies are associated with an increased risk of pulmonary edema.[12-13] However, few studies have focused on the association between the use of ritodrine hydrochloride for threatened preterm labor in twin pregnancy and the incidence of pulmonary edema. The aim of the present study was to examine the association of the total dose of ritodrine hydrochloride and the incidence of pulmonary edema in twin pregnancy.

Methods

Study design

For this retrospective cohort study, we collected obstetric records and delivery information of 233 women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital between September 2009 and November 2016. Exclusion criteria were women with single or double fetal demise, major fetal malformations, and twin arterial perfusion sequence. This study was reviewed and approved by the Human Subjects Review Committee of Yamanashi Prefectural Central Hospital.

Date collection

We collected the obstetric data from the medical and operative records. Selected data were maternal age, parity, occurrence of preterm delivery, delivery method (vaginal or cesarean delivery), chorionicity, and use of ART (in vitro fertilization or intracytoplasmic sperm injection). In addition, the presence of pregnancy-induced hypertension (PIH), pregestational weight status, administration of corticosteroids and magnesium sulfate, intraoperative transfusion, and postpartum hemorrhage (PPH) were assessed. These factors have been previously described as risk factors for pulmonary edema in

pregnancy.[12-14] PPH was defined as “active bleeding, including amniotic fluid, exceeding 1000 ml within 24 hours following delivery.”[15] PIH was defined as a blood pressure of ≥140/90 mmHg on at least two occasions.[16] We also evaluated prolonged bed rest and gestational age, which are reported to affect cardiovascular physiology.[17-18] Prolonged bed rest was defined as bed rest greater than 6 weeks.[17] Regarding the pregestational weight status, pregestational body mass index (BMI) was calculated according to the World Health Organization standards (bodyweight [kg]/height [m]^2), and patients were classified as obese (≥25.0 kg/m^2) or non-obese (<25.0 kg/m^2) according to the Japan Society of Obstetrics and Gynecology Guidelines for Obstetrical Practice 2014.[15] The criteria for tocolytic therapy include regular or frequent contractions resulting in a demonstrated change of <25 mm in transvaginal cervical length or ≥20 mm in cervical dilation. [15] The dose of ritodrine hydrochloride for tocolysis was determined by each obstetrician. The dose of ritodrine hydrochloride administered intravenously ranged from 50 to 200 μg/min, and we defined one unit as 72 mg per 24 h continuous transfusion at 50 μg/min. Magnesium sulfate dose ranged from 1 to 2 g/h by drip infusion. Pulmonary edema was defined as the clinical syndrome of acute respiratory distress associated with pulmonary rales, radiographic evidence of alveolar pulmonary edema, and supplemental oxygen requirement to maintain oxygen saturation of the peripheral arteries above 95%.[19]

Statistical analyses

First, the Mann-Whitney U test and the chi-square test were used to determine potential confounding factors for pulmonary edema. Second, a multiple logistic regression model was used to identify variables significantly associated with pulmonary edema. Then, a receiver-operating characteristic (ROC) curve was used to determine the best cut-off value for the total dose of ritodrine hydrochloride to predict pulmonary edema. We used the Youden index,[20] which describes the maximum vertical distance between the ROC curve and the diagonal or chance line, to define the optimal cut-off value.

All analyses were performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and the significance level was set at $p < 0.05$.

Results

Due to missing data on ritodrine hydrochloride total dosage (n=4) and single fetal demise (n=3), 226 (96.9%) women were considered eligible for inclusion in this study. Mean maternal age was 32 (range, 18-46) years, with 143 (63.3%) women being nulliparous, 109 (48.2%) having term deliveries, and 194 (85.8%) having cesarean deliveries. The overall

incidence of pulmonary edema was 13.7% (31/226). Table 1 described the clinical characteristics of the enrolled women.

Table 1. Baseline characteristics of the study population

Variables	Intravenous administration of ritodrine hydrochloride (+) n=82	Intravenous administration of ritodrine hydrochloride (-) n=144	p-value
Pulmonary edema	22（26.8）	9 (6.3)	< 0.001
Maternal age	32 (18-46)	32 (23-41)	0.06
Nulliparity	55（67.1）	88 (61.1)	0.37
Preterm birth	51（62.1）	66 (45.1)	0.01
Cesarean section	76 (92.3)	118 (82.0)	0.03
Pre-pregnancy BMI	20.6 (16.6-40.9)	19.5 (15.8-36.5)	0.003
Monochorionic	36（43.9）	56 (38.9)	0.46
ART	14 (17.1)	26 (18.1）	0.85

Values are presented as median (range) or number (%).
BMI: Body mass index, ART: Assisted reproductive technology

The characteristics of the group with intravenous administration of ritodrine versus the group with no intravenous administration of ritodrine were similar, except for a higher incidence of pulmonary edema, preterm birth, and cesarean section and higher pre-pregnancy BMI in the intravenous administration of ritodrine group. Table 2 reports the distribution of total dose of ritodrine hydrochloride and pulmonary edema among the entire study population.

Table 2. Prevalence of pulmonary edema according to total dose of ritodrine hydrochloride

Total dose of ritodrine hydrochloride (units)	Pulmonary edema, n (%)
0-10	10/157 (6.4%)
11-20	1/14 (7.1%)
21-30	5/17 (29.4%)
31-40	3/6 (50.0%)
41-50	3/5 (60.0%)
>51	9/27 (33.3%)

Smaller total dose of ritodrine hydrochloride was significantly associated with a lower rate of pulmonary edema. On multivariable analyses, the total dose of ritodrine hydrochloride (adjusted odds ratio (OR), 1.02; 95% confidence interval (CI), 1.004-1.03), PIH (adjusted OR, 5.51; 95% CI, 1.84-16.5), and PPH (adjusted OR, 4.18; 95% CI, 1.14-12.4) were associated with pulmonary edema (Table 3).

Table 3. Crude and adjusted odds ratios of risk factors for pulmonary edema

Variables	Pulmonary edema	No pulmonary edema	Crude		Adjusted	
			OR	95% CI	OR	95% CI
Ritodrine hydrochloride (unit: median (25^{th}-75^{th} percentile))	29 (0-77.3)	0 (0-10)			1.02	1.004-1.03

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PIH						
No (n)	22	173	1.0	Reference	1.0	Reference
Yes (n)	9	22	3.21	1.32-7.86	5.51	1.84-16.5
Obese						
No (n)	28	172	1.0	Reference	1.0	Reference
Yes (n)	3	23	0.80	0.23-2.84	0.63	0.15-2.68
PPH						
No (n)	4	71	1.0	Reference	1.0	Reference
Yes (n)	27	124	3.86	1.30-11.5	4.18	1.23-14.2
Administration of corticosteroids						
No (n)	25	163	1.0	Reference	1.0	Reference
Yes (n)	6	32	1.22	0.46-3.21	2.01	0.51-7.92
Administration of magnesium						
No (n)	21	158	1.0	Reference	1.0	Reference
Yes (n)	10	37	2.03	0.88-4.68	0.95	0.28-3.26
Intraoperative transfusion						
<2000 mL (n)	24	177	1.0	Reference	1.0	Reference
≥2000 mL (n)	7	18	2.87	1.09-7.58	1.56	0.49-4.89
Term						
No (n)	17	100	1.0	Reference	1.0	Reference
Yes (n)	14	95	0.86	0.41-1.86	1.81	0.67-4.90
Bed rest						
< 6 weeks (n)	13	135	1.0	Reference	1.0	Reference
≥ 6 weeks (n)	18	60	3.12	1.43-6.76	1.53	0.34-6.91

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Values are presented as mean ± standard deviation or number.

PIH: pregnancy-induced hypertension, PPH: postpartum hemorrhage

ROC curve analysis suggested that the cut-off value of 26 units (1872 mg) for the total dose of ritodrine hydrochloride would allow for the maximum number of patients to be correctly classified according to the presence or absence of pulmonary edema. A cutoff point of 26 units (1872 mg) provided a sensitivity of 61.3%, specificity of 87.8%, positive predictive value of 44.2%, and negative predictive value of 93.4% (Fig. 1).

Discussion

Results of this study suggest that there is an association between total dose of ritodrine hydrochloride and pulmonary edema in twin pregnancy after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to observe this association and to suggest a threshold optimal cutoff of total ritodrine dose to predict the incidence of pulmonary edema in twin pregnancy.

First, although treatment for preterm labor with a beta-agonist, including ritodrine, significantly reduces the number of women giving birth within 48 hr and seven days.[21] these tocolytic agents can cause serious complications, including pulmonary edema. There

are few studies focused on the association between the dose of ritodrine hydrochloride administered for threatened preterm labor in twin pregnancy and the incidence of pulmonary edema. Gabriel R. et al reported that multiple pregnancies dramatically increased the incidence of pulmonary edema with prolonged intravenous ritodrine hydrochloride therapy.[22] However, that study was different from our analysis because that report was limited by a small sample size and did not examine the association between the total dose of ritodrine hydrochloride and pulmonary edema.

Several possible factors are assumed to play a role in the pathophysiology of ritodrine hydrochloride induced pulmonary edema. Ritodrine hydrochloride leads to maternal tachycardia and retention of sodium and water by inducing secretion of renin, angiotensin, and aldosterone due to its β2-adrenergic stimulatory effect.[11] The desensitization of β-adrenergic receptors caused by the prolonged exposure to β2 stimulants could disturb the normal response of the heart in physiological status.[23-24] In addition, in twin pregnancy, maternal cardiac output is increased by 20% compared with singleton pregnancy at term.[25-26] The resulting increase in maternal stroke volume and heart rate might lead to myocardial dysfunction and pulmonary edema. Therefore, the incidence of pulmonary edema might to be increased in proportion to total dose of ritodrine hydrochloride in twin pregnancy.

The present study showed that the incidence of pulmonary edema could have been increased by the total dosage of ritodrine hydrochloride, irrespective of the therapeutic duration of this agent in twin pregnancy, and the validated cutoff value of total dosage of ritodrine hydrochloride for predicting pulmonary edema is 26 units (1872 mg). The maximum dose of ritodrine hydrochloride intravenously injected is limited to 200 μg/min in Japan and 350 μg/min in the USA and Canada.[6] Even if we continue to use ritodrine at 350 μg/min for 48 hours, which is the maximum dose allowed in other countries, the total dose of ritodrine reaches only 14 units (1008 mg). In other words, it can be presumed that ritodrine hydrochloride might be safely used over 48 hours for management of threatened preterm labor in twin pregnancy. In contrast, our results also demonstrate the safety of ritodrine over one week within the cutoff value, because the observed negative predictive value of ritodrine total dosage was extremely high (93.4%). This result might be meaningful for all obstetricians, especially in Japan, where ritodrine hydrochloride is used as the first-line tocolytic agent for threatened preterm labor.

PIH was also significantly associated with pulmonary edema. Several studies have reported that twin pregnancy itself is one of the most important risk factors for PIH.[15, 27] Impaired endothelial permeability is thought to be a cause of pulmonary edema in PIH.[12] Therefore, more attention should be paid to the use of ritodrine hydrochloride in twin pregnancies with

suspected PIH. In this study, long term tocolysis with total dose of ritodrine being more than 26 units in twin pregnancy with PIH caused pulmonary edema in 4 out of the 5 (80.0%) cases (data not shown).

Our study has several limitations. First, it might be difficult to extrapolate our results to the general population because our study was conducted at a single center. Therefore, a large-scale, multicenter, cohort study is needed to confirm these results in the general population. Second, data regarding sepsis, history of heart disease, endocrine disorders, amniotic fluid embolism, and pulmonary embolism were not included in our statistical model, although these are potential contributors to the incidence of pulmonary edema.[12] However, to the best of our knowledge, this study is the first to suggest an association between pulmonary edema and the total dose of ritodrine hydrochloride for tocolysis in twin pregnancies after controlling for some potential risk factors for pulmonary edema.

In conclusion, pulmonary edema was significantly associated with the total dose of ritodrine hydrochloride in twin pregnancy. Accurate risk stratification for pulmonary edema including consideration of the total dose of ritodrine hydrochloride might improve the management of patients with twin pregnancy and preterm labor.

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Competing interests: None declared.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

Contributorship statement

1. Conception or design of the work

Satoshi Shinohara, Rei Sunami

2. Data collection

Satoshi Shinohara

3. Data analysis and interpretation

Satoshi Shinohara, Rei Sunami, Kohta Suzuki

4. Drafting of the article

Satoshi Shinohara, Rei Sunami, Yuzo Uchida, Shuji Hirata, Kohta Suzuki

5. Critical revision of the article

Satoshi Shinohara, Rei Sunami, Kohta Suzuki

6. Final approval of the version to be published

Satoshi Shinohara, Rei Sunami, Yuzo Uchida, Shuji Hirata, Kohta Suzuki

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3 **FIGURE LEGENDS**

4 Fig. 1. Receiver operating curve analysis to determine the best cut-off value of total dose of
5 ritodrine hydrochloride for predicting pulmonary edema

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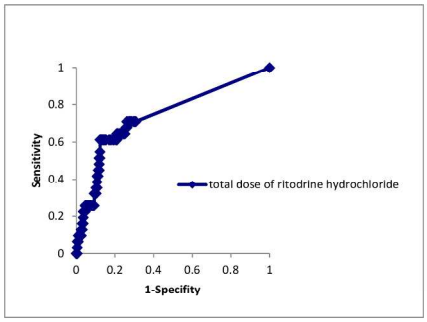

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	All cases were followed-up.

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	We did not use a flow diagram in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Since this is retrospective cohort study, there is no mention of follow-up time.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	8-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	15

		which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.