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# BMJ Open

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

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

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2

3 Abstract

4 Objective

5 Pulmonary edema is widely recognized as a severe side effect of ritodrine hydrochloride.

6 Recently, the number of twin pregnancies has been increasing. Few studies have reported

7 the association between total dose of ritodrine hydrochloride prior to delivery and pulmonary

8 edema in twin pregnancy. This study aimed to examine this association and determine the

9 optimal cutoff threshold of total ritodrine hydrochloride dose to predict the incidence of

10 pulmonary edema in twin pregnancy, based on obstetric records.

11 Design

12 Retrospective cohort study.

13 Setting

14 Yamanashi Prefectural Central Hospital, Japan

15 Participants

16 Two hundred twenty-six women with twin pregnancy who delivered at Yamanashi

17 Prefectural Central Hospital between September 2009 and November 2016

18 Methods

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

3

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

### 3 Outcome measures

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

### 9 Results

10 Mean maternal age was 32 (range, 18-46) years; 143 participants were nulliparous (63.3%),  
11 109 had (48.2%) term deliveries, and 194 (85.8%) had cesarean deliveries. The overall  
12 incidence of pulmonary edema was 13.7% (31/226). Multivariable analysis showed that the  
13 total dose of ritodrine was significantly associated with pulmonary edema (adjusted odds  
14 ratio, 1.02; 95% confidence interval, 1.004-1.03). The best cut-off point to predict the  
15 incidence of pulmonary edema was 26 units (sensitivity, 61.3%; specificity, 87.8%).

### 16 Conclusion

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

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1 Article summary

2 Strengths and limitations of this study

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

6

## 1 Introduction

2 Twin pregnancy arising from assisted reproductive technologies (ART) has been steadily  
3 increasing in developed countries, including Japan. [1-3] Although the total incidence of  
4 preterm birth in twin pregnancy is approximately 50%, [4] there is no globally established  
5 standard treatment for threatened preterm labor. [5]  $\beta$ 2-adrenergic agonists, such as  
6 ritodrine hydrochloride, are most commonly used for preventing preterm birth worldwide.[6]  
7 Ritodrine hydrochloride is the only agent approved by the US Food and Drug Administration  
8 (FDA) for reduction of preterm birth within 48 hours of initiation of treatment.[7] It is  
9 commonly used for threatened preterm labor as a first-line tocolytic agent in Japan,[6]  
10 although the frequency of its use has decreased in other developed countries due to its  
11 various side effects.[5,8] Of these, pulmonary edema is known to be the most severe side  
12 effect of this drug when continuous intravenous infusion is performed over one week.[9-11]  
13 Moreover, previous studies reported that multiple pregnancies are associated with an  
14 increased risk of pulmonary edema.[12-13] However, few studies have focused on the  
15 association between the use of ritodrine hydrochloride for threatened preterm labor in twin  
16 pregnancy and the incidence of pulmonary edema. The aim of the present study was to  
17 examine the association of the total dose of ritodrine hydrochloride and the incidence of  
18 pulmonary edema in twin pregnancy.



7

1

## 2 **Methods**

### 3 **Study design**

4 For this retrospective cohort study, we collected obstetric records and delivery information of  
5 233 women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital  
6 between September 2009 and November 2016. Exclusion criteria were women with single  
7 or double fetal demise, major fetal malformations, and twin arterial perfusion sequence. This  
8 study was reviewed and approved by the Human Subjects Review Committee of Yamanashi  
9 Prefectural Central Hospital.

10

### 11 **Data collections**

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

8

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

17

## 18 **Statistical analyses**

9

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

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

## 12 Results

13 Due to missing data on ritodrine hydrochloride total dosage ( $n=4$ ) and single fetal demise  
14 ( $n=3$ ), 226 (96.9%) women were considered eligible for inclusion in this study. Mean  
15 maternal age was 32 (range, 18-46) years, with 143 (63.3%) women being nulliparous, 109  
16 (48.2%) having term deliveries, and 194 (85.8%) having cesarean deliveries. The overall  
17 incidence of pulmonary edema was 13.7% (31/226). Table 1 described the clinical  
18 characteristics of the enrolled women.

10

1

2 Table 1. Baseline characteristics of the study population

3

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

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

5 BMI: Body mass index, ART: Assisted reproductive technology

6

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

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

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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%)

4

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

10

11 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 <sup>th</sup> -75 <sup>th</sup> 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

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.

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

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

## 7 Discussion

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

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

14

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

5 Several possible factors are assumed to play a role in the pathophysiology of ritodrine  
6 hydrochloride induced pulmonary edema. Ritodrine hydrochloride leads to maternal  
7 tachycardia and retention of sodium and water by inducing secretion of renin, angiotensin,  
8 and aldosterone due to its  $\beta$ 2-adrenergic stimulatory effect.[11] The desensitization of  
9  $\beta$ -adrenergic receptors caused by the prolonged exposure to  $\beta$ 2 stimulants could disturb the  
10 normal response of the heart in physiological status.[23-24] In addition, in twin pregnancy,  
11 maternal cardiac output is increased by 20% compared with singleton pregnancy at  
12 term.[25-26] The resulting increase in maternal stroke volume and heart rate might lead to  
13 myocardial dysfunction and pulmonary edema. Therefore, the incidence of pulmonary  
14 edema might to be increased in proportion to total dose of ritodrine hydrochloride in twin  
15 pregnancy.

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



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1 ritodrine hydrochloride for predicting pulmonary edema is 26 units. The maximum dose of  
2 ritodrine hydrochloride intravenously injected is limited to 200 µg/min in Japan and 350  
3 µg/min in the USA and Canada.[6] Even if we continue to use ritodrine at 350 µg/min for 48  
4 hours, which is the maximum dose allowed in other countries, the total dose of ritodrine  
5 reaches only 14 units. In other words, it can be presumed that ritodrine hydrochloride might  
6 be safely used over 48 hours for management of threatened preterm labor in twin pregnancy.  
7 In contrast, our results also demonstrate the safety of ritodrine over one week within the  
8 cutoff value, because the observed negative predictive value of ritodrine total dosage was  
9 extremely high (93.4%). This result might be meaningful for all obstetricians, especially in  
10 Japan, where ritodrine hydrochloride is used as the first-line tocolytic agent for threatened  
11 preterm labor.  
12 PIH was also significantly associated with pulmonary edema. Several studies have reported  
13 that twin pregnancy itself is one of the most important risk factors for PIH.[15, 27] Impaired  
14 endothelial permeability is thought to be a cause of pulmonary edema in PIH.[12] Therefore,  
15 more attention should be paid to the use of ritodrine hydrochloride in twin pregnancies with  
16 suspected PIH. In this study, long term tocolysis with total dose of ritodrine being more than  
17 26 units in twin pregnancy with PIH caused pulmonary edema in 4 out of the 5 (80.0%)  
18 cases (data not shown).

16

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

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

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17

1 Hospital approved the study design.

2

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

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5 Data sharing statement: No additional data are available.

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11 2. Data collection

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19 6. Final approval of the version to be published

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

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2

3 **Reference**

- 4 1. Wei J, Wu QJ, Zhang TN, et al. Complications in multiple gestation pregnancy: a  
5 cross-sectional study of ten maternal-fetal medicine centers in China. *Oncotarget*  
6 2016;24:30797–803.
- 7 2. Pison G, D'Addato AV. Frequency of twin births in developed countries. *Twin Res Hum*  
8 *Genet* 2006;9:250–9.
- 9 3. Geisler ME, O'Mahony A, Meaney S, et al. Obstetric and perinatal outcomes of twin  
10 pregnancies conceived following IVF/ICSI treatment compared with spontaneously  
11 conceived twin pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2014;181:78–83.
- 12 4. Elliott JP. Preterm labor in twins and high-order multiples. *Clin Perinatol* 2007;34:599–  
13 609.
- 14 5. Haas DM, Caldwell DM, Kirkpatrick P, et al. Tocolytic therapy for preterm delivery:  
15 systematic review and network meta-analysis. *BMJ* 2012;9:345:e6226.
- 16 6. Takagi K, Satoh T. Is long-term tocolysis effective for threatened premature labour? *J Int*  
17 *Med Res* 2009;37:227–39.
- 18 7. Kareli D, Pouliliou S, Liberis A, et al. Genotoxic effect of tocolytic drug ritodrine in

- 1  
2  
3  
4  
5  
6 1 combination with smoking during pregnancy. *J Matern Fetal Neonatal Med*  
7  
8  
9 2 2016;21:3496–505.  
10  
11  
12 3 8. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. The Canadian  
13  
14 4 Preterm Labor Investigators Group. *N Engl J Med* 1992;30:308–12.  
15  
16  
17 5 9. Gezginç K, Gül M, Karatayli R, et al. Noncardiogenic pulmonary edema due to ritodrine  
18  
19 6 usage in preterm labor. *Taiwan J Obstet Gynecol* 2008;47:101–2.  
20  
21  
22  
23 7 10. Gabriel R, Harika G, Saniez D, et al. Prolonged intravenous ritodrine therapy: a  
24  
25 8 comparison between multiple and singleton pregnancies. *Eur J Obstet Gynecol Reprod*  
26  
27 9 *Biol* 1994;57:65–71.  
28  
29  
30  
31  
32 10 11. Karaman S, Ozcan O, Akercan F, et al. Pulmonary edema after ritodrine therapy during  
33  
34 11 pregnancy and subsequent cesarean section with epidural anesthesia. *Clin Exp Obstet*  
35  
36 12 *Gynecol* 2004;31:67–9.  
37  
38  
39  
40  
41 13 12. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. *Anaesthesia*  
42  
43 14 2012;67:646–59.  
44  
45  
46  
47 15 13. Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists.  
48  
49 16 *BJOG*. 2000;107:439–44.  
50  
51  
52  
53 17 14. Teofili L, Bianchi M, Zanfini BA, et al. Acute lung injury complicating blood transfusion in  
54  
55 18 post-partum hemorrhage: incidence and risk factors. *Mediterr J Hematol Infect Dis*  
56  
57  
58  
59  
60

20

- 1  
2  
3  
4  
5  
6 1 201422;6:e2014069.  
7  
8  
9 2 15. Minakami H, Maeda T, Fujii T, et al. Guidelines for obstetrical practice in Japan: Japan  
10  
11 3 Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians  
12  
13 4 and Gynecologists (JAOG) 2014 edition. *J Obstet Gynaecol Res* 2014;40:1469–99.  
14  
15  
16  
17 5 16. Magee LA, Abalos E, von Dadelszen P, et al. How to manage hypertension in pregnancy  
18  
19 6 effectively. *Br J Clin Pharmacol* 2011;72:394–401.  
20  
21  
22  
23 7 17. Perhonen MA, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. *J*  
24  
25 8 *Appl Physiol* 2001;91:645–53.  
26  
27  
28  
29 9 18. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation*  
30  
31 10 2014;130:1003–8.  
32  
33  
34  
35 11 19. Pulmonary edema: pathophysiology and diagnosis. Murray JF. *Int J Tuberc Lung Dis*  
36  
37 12 2011;15:155–60.  
38  
39  
40  
41 13 20. Perkins NJ, Schisterman EF. The inconsistency of “optimal” cutpoints obtained using  
42  
43 14 two criteria based on the receiver operating characteristic curve. *Am J Epidemiol*  
44  
45 15 2006;163:670–5.  
46  
47  
48  
49 16 21. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. *Cochrane*  
50  
51 17 *Database Syst Rev*. 2014;5:CD004352.  
52  
53  
54  
55 18 22. Gabriel R, Harika G, Saniez D, et al. Prolonged intravenous ritodrine therapy: a  
56  
57  
58  
59  
60

21

- 1  
2  
3  
4  
5  
6 1 comparison between multiple and singleton pregnancies. *Eur J Obstet Gynecol Reprod*  
7  
8  
9 2 *Biol* 1994;57:65–71.
- 10  
11  
12 3 23. Hawker F. Pulmonary oedema associated with beta 2-sympathomimetic treatment of  
13  
14 4 premature labour. *Anaesth Intensive Care* 1984;12:143–51.
- 15  
16  
17 5 24. Tatara T, Morisaki H, Shimada M, et al. Pulmonary edema after long-term  
18  
19 6 beta-adrenergic therapy and cesarean section. *Anesth Analg* 1995;81:417–8.
- 20  
21  
22 7 25. Kuleva M, Youssef A, Maroni E, et al. Maternal cardiac function in normal twin  
23  
24 8 pregnancy: a longitudinal study. *Ultrasound Obstet Gynecol* 2011;38:575–80.
- 25  
26  
27 9 26. Kametas NA, McAuliffe F, Krampf E, et al. Maternal cardiac function in twin pregnancy.  
28  
29 10 *Obstet Gynecol* 2003;102:806–15.
- 30  
31  
32 11 27. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic  
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34 12 review of controlled studies. *BMJ* 2005;12:330.
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## 17 **FIGURE LEGENDS**

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

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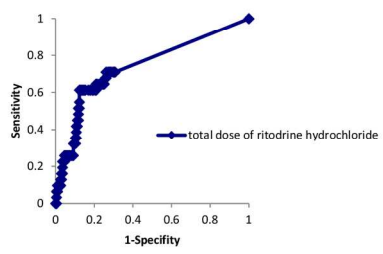


Fig1

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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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	All cases were followed-up.

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8
<b>Results</b>			
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) <i>Cohort study</i> —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*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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

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	which the present article is based	
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\*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](http://www.strobe-statement.org).

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# BMJ Open

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

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

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8 Satoshi Shinohara<sup>1</sup>, Rei sunami<sup>1</sup>, Yuzo Uchida<sup>1</sup>, Shuji Hirata<sup>2</sup>, Kohta Suzuki<sup>3</sup>

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28 Word Count: 2421

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3 Abstract

4 Objective

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

11 Design

12 Retrospective cohort study.

13 Setting

14 Yamanashi Prefectural Central Hospital, Japan

15 Participants

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

18 Methods

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

3

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

### 3 Outcome measures

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

### 9 Results

10 Mean maternal age was 32 (range, 18-46) years; 143 participants were nulliparous (63.3%),  
11 109 had (48.2%) term deliveries, and 194 (85.8%) had cesarean deliveries. The overall  
12 incidence of pulmonary edema was 13.7% (31/226). Multivariable analysis showed that the  
13 total dose of ritodrine was significantly associated with pulmonary edema (adjusted odds  
14 ratio 1.02; 95% confidence interval, 1.004-1.03). The best cut-off point to predict the  
15 incidence of pulmonary edema was 26 units (1872 mg) (sensitivity, 61.3%; specificity,  
16 87.8%).

### 17 Conclusion

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



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

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1 Article summary

2 Strengths and limitations of this study

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

6

## 1 Introduction

2 Twin pregnancy arising from assisted reproductive technologies (ART) has been steadily  
3 increasing in developed countries, including Japan. [1-3] Although the total incidence of  
4 preterm birth in twin pregnancy is approximately 50%, [4] there is no globally established  
5 standard treatment for threatened preterm labor. [5]  $\beta$ 2-adrenergic agonists, such as  
6 ritodrine hydrochloride, are most commonly used for preventing preterm birth worldwide.[6]  
7 Ritodrine hydrochloride is the only agent approved by the US Food and Drug Administration  
8 (FDA) for reduction of preterm birth within 48 hours of initiation of treatment.[7] It is  
9 commonly used for threatened preterm labor as a first-line tocolytic agent in Japan,[6]  
10 although the frequency of its use has decreased in other developed countries due to its  
11 various side effects.[5,8] Of these, pulmonary edema is known to be the most severe side  
12 effect of this drug when continuous intravenous infusion is performed over one week.[9-11]  
13 Moreover, previous studies reported that multiple pregnancies are associated with an  
14 increased risk of pulmonary edema.[12-13] However, few studies have focused on the  
15 association between the use of ritodrine hydrochloride for threatened preterm labor in twin  
16 pregnancy and the incidence of pulmonary edema. The aim of the present study was to  
17 examine the association of the total dose of ritodrine hydrochloride and the incidence of  
18 pulmonary edema in twin pregnancy.

7

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## 2 **Methods**

### 3 **Study design**

4 For this retrospective cohort study, we collected obstetric records and delivery information of  
5 233 women with twin pregnancy who delivered at Yamanashi Prefectural Central Hospital  
6 between September 2009 and November 2016. Exclusion criteria were women with single  
7 or double fetal demise, major fetal malformations, and twin arterial perfusion sequence. This  
8 study was reviewed and approved by the Human Subjects Review Committee of Yamanashi  
9 Prefectural Central Hospital.

10

### 11 **Date collection**

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

8

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

9

1

## 2 **Statistical analyses**

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

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

12

13

## 14 **Results**

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

10

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

4 Table 1. Baseline characteristics of the study population

Variables	Intravenous administration of ritodrine hydrochloride (+)	Intravenous administration of ritodrine hydrochloride (-)	p-value
	n=82	n=144	
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

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

7 BMI: Body mass index, ART: Assisted reproductive technology

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

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

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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%)

6

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

12

13 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 <sup>th</sup> -75 <sup>th</sup> percentile))	29 (0-77.3)	0 (0-10)	1.02	1.004-1.03		



12

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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1 Values are presented as mean  $\pm$  standard deviation or number.

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

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

## 12 Discussion

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

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

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6 1 are few studies focused on the association between the dose of ritodrine hydrochloride  
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9 2 administered for threatened preterm labor in twin pregnancy and the incidence of pulmonary  
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12 3 edema. Gabriel R. et al reported that multiple pregnancies dramatically increased the  
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15 4 incidence of pulmonary edema with prolonged intravenous ritodrine hydrochloride  
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18 5 therapy.[22] However, that study was different from our analysis because that report was  
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21 6 limited by a small sample size and did not examine the association between the total dose of  
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24 7 ritodrine hydrochloride and pulmonary edema.  
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27 8 Several possible factors are assumed to play a role in the pathophysiology of ritodrine  
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30 9 hydrochloride induced pulmonary edema. Ritodrine hydrochloride leads to maternal  
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33 10 tachycardia and retention of sodium and water by inducing secretion of renin, angiotensin,  
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36 11 and aldosterone due to its  $\beta$ 2-adrenergic stimulatory effect.[11] The desensitization of  
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39 12  $\beta$ -adrenergic receptors caused by the prolonged exposure to  $\beta$ 2 stimulants could disturb the  
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42 13 normal response of the heart in physiological status.[23-24] In addition, in twin pregnancy,  
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45 14 maternal cardiac output is increased by 20% compared with singleton pregnancy at  
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48 15 term.[25-26] The resulting increase in maternal stroke volume and heart rate might lead to  
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51 16 myocardial dysfunction and pulmonary edema. Therefore, the incidence of pulmonary  
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6 1 The present study showed that the incidence of pulmonary edema could have been  
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9 2 increased by the total dosage of ritodrine hydrochloride, irrespective of the therapeutic  
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12 3 duration of this agent in twin pregnancy, and the validated cutoff value of total dosage of  
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15 4 ritodrine hydrochloride for predicting pulmonary edema is 26 units (1872 mg). The maximum  
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18 5 dose of ritodrine hydrochloride intravenously injected is limited to 200 µg/min in Japan and  
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21 6 350 µg/min in the USA and Canada.[6] Even if we continue to use ritodrine at 350 µg/min for  
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24 7 48 hours, which is the maximum dose allowed in other countries, the total dose of ritodrine  
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27 8 reaches only 14 units (1008 mg). In other words, it can be presumed that ritodrine  
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30 9 hydrochloride might be safely used over 48 hours for management of threatened preterm  
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33 10 labor in twin pregnancy. In contrast, our results also demonstrate the safety of ritodrine over  
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36 11 one week within the cutoff value, because the observed negative predictive value of ritodrine  
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39 12 total dosage was extremely high (93.4%). This result might be meaningful for all  
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42 13 obstetricians, especially in Japan, where ritodrine hydrochloride is used as the first-line  
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45 14 tocolytic agent for threatened preterm labor.

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47 15 PIH was also significantly associated with pulmonary edema. Several studies have reported  
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50 16 that twin pregnancy itself is one of the most important risk factors for PIH.[15, 27] Impaired  
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53 17 endothelial permeability is thought to be a cause of pulmonary edema in PIH.[12] Therefore,  
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56 18 more attention should be paid to the use of ritodrine hydrochloride in twin pregnancies with  
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1 suspected PIH. In this study, long term tocolysis with total dose of ritodrine being more than  
2 26 units in twin pregnancy with PIH caused pulmonary edema in 4 out of the 5 (80.0%)  
3 cases (data not shown).

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

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

17  
18 Funding: This research received no specific grant from any funding agency in the public,  
19 commercial or not-for-profit sectors.

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2 Competing interests: None declared.

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4 Ethics approval: The Human Subjects Review Committee of Yamanashi Prefectural Central

5 Hospital approved the study design.

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

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9 Data sharing statement: No additional data are available.

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12 Contributorship statement

13 1. Conception or design of the work

14 Satoshi Shinohara, Rei Sunami

15 2. Data collection

16 Satoshi Shinohara

17 3. Data analysis and interpretation

18 Satoshi Shinohara, Rei Sunami, Kohta Suzuki

19 4. Drafting of the article

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

21 5. Critical revision of the article

22 Satoshi Shinohara, Rei Sunami, Kohta Suzuki

23 6. Final approval of the version to be published

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

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**Reference**

- 7 1. Wei J, Wu QJ, Zhang TN, et al. Complications in multiple gestation pregnancy: a  
8 cross-sectional study of ten maternal-fetal medicine centers in China. *Oncotarget*  
9 2016;24:30797–803.
- 10 2. Pison G, D'Addato AV. Frequency of twin births in developed countries. *Twin Res Hum*  
11 *Genet* 2006;9:250–9.
- 12 3. Geisler ME, O'Mahony A, Meaney S, et al. Obstetric and perinatal outcomes of twin  
13 pregnancies conceived following IVF/ICSI treatment compared with spontaneously  
14 conceived twin pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2014;181:78–83.
- 15 4. Elliott JP. Preterm labor in twins and high-order multiples. *Clin Perinatol* 2007;34:599–  
16 609.
- 17 5. Haas DM, Caldwell DM, Kirkpatrick P, et al. Tocolytic therapy for preterm delivery:  
18 systematic review and network meta-analysis. *BMJ* 2012;9:345:e6226.

- 1  
2  
3  
4  
5  
6 1 6. Takagi K, Satoh T. Is long-term tocolysis effective for threatened premature labour? *J Int*  
7  
8  
9 2 *Med Res* 2009;37:227–39.
- 10  
11  
12 3 7. Kareli D, Pouliliou S, Liberis A, et al. Genotoxic effect of tocolytic drug ritodrine in  
13  
14 4 combination with smoking during pregnancy. *J Matern Fetal Neonatal Med*  
15  
16 5 2016;21:3496–505.
- 17  
18  
19  
20  
21 6 8. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. The Canadian  
22  
23 7 Preterm Labor Investigators Group. *N Engl J Med* 1992;30:308–12.
- 24  
25  
26 8 9. Gezginç K, Gül M, Karatayli R, et al. Noncardiogenic pulmonary edema due to ritodrine  
27  
28 9 usage in preterm labor. *Taiwan J Obstet Gynecol* 2008;47:101–2.
- 29  
30  
31  
32 10 10. Gabriel R, Harika G, Saniez D, et al. Prolonged intravenous ritodrine therapy: a  
33  
34 11 comparison between multiple and singleton pregnancies. *Eur J Obstet Gynecol Reprod*  
35  
36 12 *Biol* 1994;57:65–71.
- 37  
38  
39  
40  
41 13 11. Karaman S, Ozcan O, Akercan F, et al. Pulmonary edema after ritodrine therapy during  
42  
43 14 pregnancy and subsequent cesarean section with epidural anesthesia. *Clin Exp Obstet*  
44  
45 15 *Gynecol* 2004;31:67–9.
- 46  
47  
48  
49 16 12. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. *Anaesthesia*  
50  
51 17 2012;67:646–59.
- 52  
53  
54  
55 18 13. Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists.  
56  
57  
58  
59  
60



- 1  
2  
3  
4  
5  
6 1 BJOG. 2000;107:439–44.  
7  
8  
9 2 14. Teofili L, Bianchi M, Zanfini BA, et al. Acute lung injury complicating blood transfusion in  
10  
11  
12 3 post-partum hemorrhage: incidence and risk factors. *Mediterr J Hematol Infect Dis*  
13  
14 4 2014;22;6:e2014069.  
15  
16  
17 5 15. Minakami H, Maeda T, Fujii T, et al. Guidelines for obstetrical practice in Japan: Japan  
18  
19  
20 6 Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians  
21  
22 7 and Gynecologists (JAOG) 2014 edition. *J Obstet Gynaecol Res* 2014;40:1469–99.  
23  
24  
25 8 16. Magee LA, Abalos E, von Dadelszen P, et al. How to manage hypertension in pregnancy  
26  
27 9 effectively. *Br J Clin Pharmacol* 2011;72:394–401.  
28  
29  
30 10 17. Perhonen MA, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. *J*  
31  
32 11 *Appl Physiol* 2001;91:645–53.  
33  
34  
35 12 18. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation*  
36  
37 13 2014;130:1003–8.  
38  
39  
40 14 19. Pulmonary edema: pathophysiology and diagnosis. Murray JF. *Int J Tuberc Lung Dis*  
41  
42 15 2011;15:155–60.  
43  
44  
45 16 20. Perkins NJ, Schisterman EF. The inconsistency of “optimal” cutpoints obtained using  
46  
47 17 two criteria based on the receiver operating characteristic curve. *Am J Epidemiol*  
48  
49 18 2006;163:670–5.  
50  
51  
52  
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56  
57  
58  
59  
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2  
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6 1 21. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. *Cochrane*  
7  
8  
9 2 *Database Syst Rev.* 2014;5:CD004352.
- 10  
11  
12 3 22. Gabriel R, Harika G, Saniez D, et al. Prolonged intravenous ritodrine therapy: a  
13  
14 4 comparison between multiple and singleton pregnancies. *Eur J Obstet Gynecol Reprod*  
15  
16 5 *Biol* 1994;57:65–71.
- 17  
18  
19  
20  
21 6 23. Hawker F. Pulmonary oedema associated with beta 2-sympathomimetic treatment of  
22  
23 7 premature labour. *Anaesth Intensive Care* 1984;12:143–51.
- 24  
25  
26 8 24. Tatara T, Morisaki H, Shimada M, et al. Pulmonary edema after long-term  
27  
28 9 beta-adrenergic therapy and cesarean section. *Anesth Analg* 1995;81:417–8.
- 29  
30  
31  
32 10 25. Kuleva M, Youssef A, Maroni E, et al. Maternal cardiac function in normal twin  
33  
34 11 pregnancy: a longitudinal study. *Ultrasound Obstet Gynecol* 2011;38:575–80.
- 35  
36  
37  
38 12 26. Kametas NA, McAuliffe F, Krampfl E, et al. Maternal cardiac function in twin pregnancy.  
39  
40 13 *Obstet Gynecol* 2003;102:806–15.
- 41  
42  
43  
44 14 27. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic  
45  
46 15 review of controlled studies. *BMJ* 2005;12:330.
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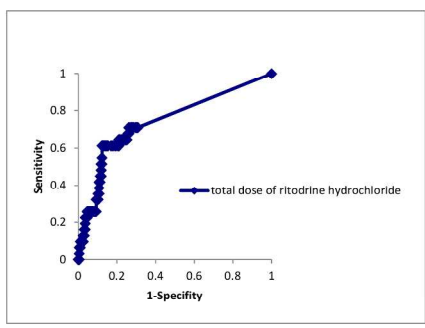
**FIGURE LEGENDS**

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

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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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	All cases were followed-up.

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8
<b>Results</b>			
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) <i>Cohort study</i> —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*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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

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	which the present article is based	
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\*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](http://www.strobe-statement.org).

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