

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

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## ABSTRACT

**Objective** Pulmonary oedema is recognised 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 oedema in twin pregnancy. We aimed to examine this association and determine the optimal cut-off threshold of total ritodrine hydrochloride dose to predict the incidence of pulmonary oedema in twin pregnancy based on obstetric records.

**Design** Retrospective cohort study.

**Setting** Yamanashi Prefectural Central Hospital, Japan.

**Participants** Two hundred and 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 analysed. We defined 1 unit of ritodrine hydrochloride as 72 mg per 24 hours 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 labour and pulmonary oedema, while controlling for potential confounding factors. Then, a receiver–operating characteristic curve was used to determine the optimal cut-off of total ritodrine dose to predict pulmonary oedema 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 caesarean deliveries. The overall incidence of pulmonary oedema was 13.7% (31/226). Multivariable analysis showed that the total dose of ritodrine was significantly associated with pulmonary oedema (adjusted OR 1.02; 95% CI 1.004 to 1.03). The best cut-off point to predict the incidence of pulmonary oedema 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 labour in twin pregnancy.

## INTRODUCTION

Twin pregnancy arising from assisted reproductive technologies (ART) has been steadily

## Strengths and limitations of this study

- To the best of our knowledge, this study is the first to suggest an association between pulmonary oedema and the total dose of ritodrine hydrochloride for tocolysis in twin pregnancies after controlling for some potential risk factors for pulmonary oedema.
- This study was conducted at a single centre. Therefore, a large-scale, multicentre, cohort study is needed to confirm these results in the general population.
- Data regarding sepsis, history of heart disease, endocrine disorders, amniotic fluid embolism, and pulmonary embolism were not considered in this study, although these are potential contributors for pulmonary oedema.

increasing in developed countries, including Japan.<sup>1–3</sup> Although the total incidence of preterm birth in twin pregnancy is approximately 50%,<sup>4</sup> there is no globally established standard treatment for threatened preterm labour.<sup>5</sup> β<sub>2</sub>-adrenergic agonists, such as ritodrine hydrochloride, are most commonly used for preventing preterm birth worldwide.<sup>6</sup> 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.<sup>7</sup> It is commonly used for threatened preterm labour as a first-line tocolytic agent in Japan,<sup>6</sup> although the frequency of its use has decreased in other developed countries due to its various side effects.<sup>5,8</sup> Of these, pulmonary oedema is known to be the most severe side effect of this drug when continuous intravenous infusion is performed over 1 week.<sup>9–11</sup> Moreover, previous studies reported that multiple pregnancies are associated with an increased risk of pulmonary oedema.<sup>12,13</sup> However, few studies have focused on the association between the use of ritodrine hydrochloride for threatened

preterm labour in twin pregnancy and the incidence of pulmonary oedema. The aim of the present study was to examine the association of the total dose of ritodrine hydrochloride and the incidence of pulmonary oedema 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 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 caesarean delivery), chorionicity and use of ART (in vitro fertilisation 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 haemorrhage (PPH) were assessed. These factors have been previously described as risk factors for pulmonary oedema in pregnancy.<sup>12–14</sup> PPH was defined as 'active bleeding, including amniotic fluid, exceeding 1000 mL within 24 hours following delivery'.<sup>15</sup> PIH was defined as a blood pressure of  $\geq 140/90$  mm Hg on at least two occasions.<sup>16</sup> We also evaluated prolonged bed rest and gestational age, which are reported to affect cardiovascular physiology.<sup>17, 18</sup> Prolonged bed rest was defined as bed rest  $>6$  weeks.<sup>17</sup> Regarding the pregestational weight status, pregestational body mass index (BMI) was calculated according to the WHO standards (bodyweight (kg)/height (m<sup>2</sup>)), and patients were classified as 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 Obstetrics and Gynecology Guidelines for Obstetrical Practice 2014.<sup>15</sup> The criteria for tocolytic therapy include regular or frequent contractions resulting in a demonstrated change of  $< 25$  mm in transvaginal cervical length or  $\geq 20$  mm in cervical dilation.<sup>15</sup> The dose of ritodrine hydrochloride for tocolysis was determined by each obstetrician. The dose of ritodrine hydrochloride administered intravenously ranged from 50 to 200  $\mu$ g/min, and we defined 1 unit as 72 mg per 24 hours continuous transfusion at 50  $\mu$ g/min. Magnesium sulfate dose ranged from 1 to 2 g/h by drip infusion. Pulmonary oedema was defined as the clinical syndrome of acute respiratory distress associated with pulmonary rales, radiographic evidence of alveolar pulmonary oedema and supplemental oxygen

**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 oedema	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
Caesarean section	76 (92.3)	118 (82.0)	0.03
Prepregnancy 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 (%). ART, assisted reproductive technology; BMI, body mass index.

requirement to maintain oxygen saturation of the peripheral arteries  $>95\%$ .<sup>19</sup>

### Statistical analyses

First, the Mann-Whitney U test and the  $X^2$  test were used to determine potential confounding factors for pulmonary oedema. Second, a multiple logistic regression model was used to identify variables significantly associated with pulmonary oedema. 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 oedema. We used the Youden index,<sup>20</sup> 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, 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 caesarean deliveries. The overall incidence of pulmonary oedema was 13.7% (31/226). Table 1 describes the clinical characteristics of the enrolled women.

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 oedema, preterm birth and caesarean section and higher prepregnancy BMI in the intravenous administration of ritodrine group. Table 2 reports the distribution of total dose of

**Table 2** Prevalence of pulmonary oedema according to total dose of ritodrine hydrochloride

Total dose of ritodrine hydrochloride (units)	Pulmonary oedema, 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%)

ritodrine hydrochloride and pulmonary oedema among the entire study population.

Smaller total dose of ritodrine hydrochloride was significantly associated with a lower rate of pulmonary oedema. On multivariable analyses, the total dose of ritodrine

hydrochloride (adjusted OR, 1.02; 95% CI 1.004 to 1.03), PIH (adjusted OR, 5.51; 95% CI 1.84 to 16.5) and PPH (adjusted OR, 4.18; 95% CI 1.14 to 12.4) were associated with pulmonary oedema (table 3).

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 oedema. A cut-off 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% (figure 1).

### DISCUSSION

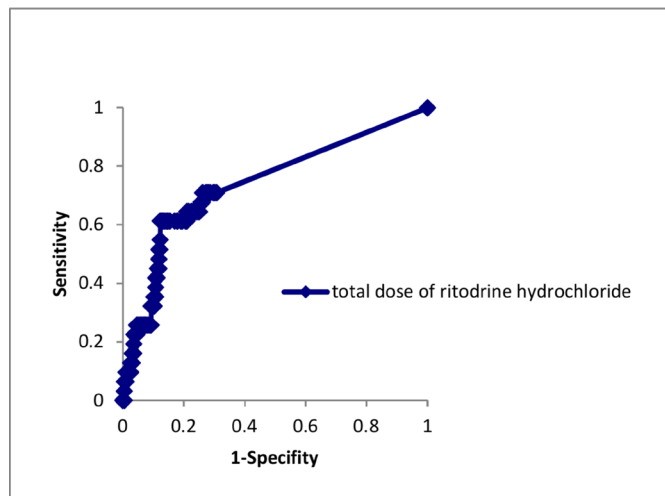
Results of this study suggest that there is an association between total dose of ritodrine hydrochloride and pulmonary oedema in twin pregnancy after adjusting for

**Table 3** Crude and adjusted ORs of risk factors for pulmonary oedema

Variables	Pulmonary oedema	No pulmonary oedema	Crude		Adjusted	
			OR	95% CI	OR	95% CI
Ritodrine hydrochloride (unit: median (25th–75th percentile))	29 (0–77.3)	0 (0–10)			1.02	1.004 to 1.03
PIH						
No (n)	22	173	1.0	Reference	1.0	Reference
Yes (n)	9	22	3.21	1.32 to 7.86	5.51	1.84 to 16.5
Obese						
No (n)	28	172	1.0	Reference	1.0	Reference
Yes (n)	3	23	0.80	0.23 to 2.84	0.63	0.15 to 2.68
PPH						
No (n)	4	71	1.0	Reference	1.0	Reference
Yes (n)	27	124	3.86	1.30 to 11.5	4.18	1.23 to 14.2
Administration of corticosteroids						
No (n)	25	163	1.0	Reference	1.0	Reference
Yes (n)	6	32	1.22	0.46 to 3.21	2.01	0.51 to 7.92
Administration of magnesium						
No (n)	21	158	1.0	Reference	1.0	Reference
Yes (n)	10	37	2.03	0.88 to 4.68	0.95	0.28 to 3.26
Intraoperative transfusion						
<2000 mL (n)	24	177	1.0	Reference	1.0	Reference
≥2000 mL (n)	7	18	2.87	1.09 to 7.58	1.56	0.49 to 4.89
Term						
No (n)	17	100	1.0	Reference	1.0	Reference
Yes (n)	14	95	0.86	0.41 to 1.86	1.81	0.67 to 4.90
Bed rest						
<6 weeks (n)	13	135	1.0	Reference	1.0	Reference
≥6 weeks (n)	18	60	3.12	1.43 to 6.76	1.53	0.34 to 6.91

Values are presented as mean ±SD deviation or number.

PIH, pregnancy-induced hypertension; PPH, postpartum haemorrhage.



**Figure 1** Receiver–operating curve analysis to determine the best cut-off value of total dose of ritodrine hydrochloride for predicting pulmonary oedema.

potential confounding factors. To the best of our knowledge, this is the first study to observe this association and to suggest a threshold optimal cut-off of total ritodrine dose to predict the incidence of pulmonary oedema in twin pregnancy.

First, although treatment for preterm labour with a beta-agonist, including ritodrine, significantly reduces the number of women giving birth within 48 hours and 7 days,<sup>21</sup> these tocolytic agents can cause serious complications, including pulmonary oedema. There are few studies focused on the association between the dose of ritodrine hydrochloride administered for threatened preterm labour in twin pregnancy and the incidence of pulmonary oedema. Gabriel *et al* reported that multiple pregnancies dramatically increased the incidence of pulmonary oedema with prolonged intravenous ritodrine hydrochloride therapy.<sup>10</sup> 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 oedema.

Several possible factors are assumed to play a role in the pathophysiology of ritodrine hydrochloride-induced pulmonary oedema. Ritodrine hydrochloride leads to maternal tachycardia and retention of sodium and water by inducing secretion of renin, angiotensin and aldosterone due to its  $\beta_2$ -adrenergic stimulatory effect.<sup>11</sup> The desensitisation of  $\beta$ -adrenergic receptors caused by the prolonged exposure to  $\beta_2$  stimulants could disturb the normal response of the heart in physiological status.<sup>22–23</sup> In addition, in twin pregnancy, maternal cardiac output is increased by 20% compared with singleton pregnancy at term.<sup>24–25</sup> The resulting increase in maternal stroke volume and heart rate might lead to myocardial dysfunction and pulmonary oedema. Therefore, the incidence of pulmonary oedema might be increased in proportion to the total dose of ritodrine hydrochloride in twin pregnancy.

The present study showed that the incidence of pulmonary oedema 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 cut-off value of total dosage of ritodrine hydrochloride for predicting pulmonary oedema is 26 units (1872 mg). The maximum dose of ritodrine hydrochloride intravenously injected is limited to 200  $\mu\text{g}/\text{min}$  in Japan and 350  $\mu\text{g}/\text{min}$  in the USA and Canada.<sup>6</sup> Even if we continue to use ritodrine at 350  $\mu\text{g}/\text{min}$  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 labour in twin pregnancy. In contrast, our results also demonstrate the safety of ritodrine over 1 week within the cut-off 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 labour.

PIH was also significantly associated with pulmonary oedema. Several studies have reported that twin pregnancy itself is one of the most important risk factors for PIH.<sup>15–26</sup> Impaired endothelial permeability is thought to be a cause of pulmonary oedema in PIH.<sup>12</sup> 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  $>26$  units in twin pregnancy with PIH caused pulmonary oedema in four out of the five (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 centre. Therefore, a large-scale, multicentre, 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 oedema.<sup>12</sup> However, to the best of our knowledge, this study is the first to suggest an association between pulmonary oedema and the total dose of ritodrine hydrochloride for tocolysis in twin pregnancies after controlling for some potential risk factors for pulmonary oedema.

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

**Contributors** SS: data collection. SS and RS: conception or design of the work. SS, RS and KS: data analysis and interpretation; critical revision of the article. SS, RS, YU, SH and KS: drafting of the article and final approval of the version to be published.

**Competing interests** None declared.

**Ethics approval** The Human Subjects Review Committee of Yamanashi Prefectural Central Hospital approved the study design.

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

**Data sharing statement** Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi: 10.5061/dryad.1v8v6.

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