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 threshold 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 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 labour.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 labour 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.8 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.9–11 Moreover, previous studies reported that multiple pregnancies are associated with an increased risk of pulmonary oedema.12 13 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), chorioicity 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.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 mm Hg 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 >6 weeks.17 Regarding the pregestational weight status, pregestational body mass index (BMI) was calculated according to the WHO 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 Gynaecology 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 1 unit as 72 mg per 24 hours continuous transfusion at 50 µg/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 requirement to maintain oxygen saturation of the peripheral arteries >95%.19

Statistical analyses

First, the Mann-Whitney U test and the $\chi^2$ 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,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, 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 1 | Baseline characteristics of the study population |
|-----------------------|-----------------------------------------------|
| Variables                          | Intravenous administration of ritodrine hydrochloride (n=226) | Intravenous administration of ritodrine hydrochloride (n=194) | P value |
| Pulmonary oedema                      | 22 (26.8)                                           | 9 (6.3)                                             | <0.001 |
| Maternal age (years)                   | 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  |
| BMI (kg/m$^2$)                        |                                              |                                                   |        |
| 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.
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 (1872mg) 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 (1872mg) 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...
of pulmonary oedema might be increased in proportion and pulmonary oedema. Therefore, the incidence of pulmonary oedema including consideration of 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.
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Ethics approval The Human Subjects Review Committee of Yamanashi Prefectural Central Hospital approved the study design.

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