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Synergic interaction between ritodrine and magnesium sulfate on the occurrence of critical neonatal hyperkalemia: A Japanese nationwide retrospective cohort study

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Our aim was to evaluate the association between ritodrine and magnesium sulfate (MgSO_4) and the occurrence of neonatal hyperkalemia or hypoglycemia among late preterm infants in a retrospective cohort study. We used a nationwide obstetrical database from 2014. A total of 4,622 live preterm infants born at 32–36 gestational weeks participated. Fourteen risk factors based on both clinical relevance and univariate analysis were adjusted in multivariable logistic regression analyses. Neonatal hyperkalemia and hypoglycemia occurred in 7.6% (284/3,732) and 32.4% (1,458/4,501), respectively. Occurrence of hyperkalemia was associated with concomitant usage of ritodrine and MgSO_4 compared with no usage (adjusted odds ratio [aOR] 1.53, 95% confidence interval [CI] 1.09–2.15). Occurrence of hypoglycemia was associated with ritodrine alone (aOR 2.58 [CI 2.21–3.01]) and with concomitant usage of ritodrine and MgSO_4 (aOR 2.59 [CI 2.13–3.15]), compared with no usage, and was associated with long-term usage (≥ 48 hours) of ritodrine and cessation directly before delivery. In conclusion, in late preterm infants, usage of ritodrine together with MgSO_4 was associated with occurrence of critical neonatal hyperkalemia, and long-term usage of ritodrine and cessation directly before delivery were associated with neonatal hypoglycemia.

The Cause Analysis Committee for Cerebral Palsy of the Japan Council for Quality Health Care (JCQHC) has suggested that of the nearly 1,000 cases of cerebral palsy, some may have occurred in neonates with hypoglycemia and/or hyperkalemia born to mothers receiving either ritodrine or magnesium sulfate (MgSO_4)¹. In addition, 14 cases of unexpected neonatal hyperkalemia from mothers using tocolytic agents^{2–14} – especially ritodrine and MgSO_4 concomitantly^{2,3} – have been independently reported by neonatologists in Japan. At JCQHC request, the Japan Society of Perinatal and Neonatal Medicine (JSPNM) is evaluating the association between these agents and neonatal hyperkalemia or hypoglycemia occurrence. However, to the best of our knowledge, there have been no

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cohort studies in English suggesting a relationship between ritodrine administration and neonatal hyperkalemia. Regarding MgSO_4 , there has only been one case reported of a very low birth weight infant with hyperkalemia accompanied by hypermagnesemia¹⁵.

In 2013 the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommended against long-term tocolysis ≥ 48 hours with ritodrine and MgSO_4 ^{16–18}. Following these restrictions, Kissei Pharmaceutical Co. Ltd. manufacturing ritodrine in Japan, published “A review of EU restrictions on short-acting beta-agonists, and guidelines regarding efficacy and safety of ritodrine hydrochloride (injection and tablet) in Japan” in Dec. 2014¹⁹. Accordingly, two leading societies for obstetrical decision-making in Japan, the Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG), have not prohibited long-term tocolysis using ritodrine^{20,21}. Therefore, long-term tocolysis using ritodrine has often been performed²².

Although MgSO_4 had been used for seizure prophylaxis in women with preeclampsia or eclampsia²³, its usage as a tocolytic agent became covered by insurance in Japan in 2006²⁴. Generally, maintenance therapy with MgSO_4 is not recommended in the USA²⁵; however, long-term MgSO_4 tocolysis is widely performed in Japan because the package insert does not prohibit usage at 22–36 gestational weeks²⁴. In addition, long-term tocolysis with both ritodrine and MgSO_4 has been used in Japan when uterine contractions could not be controlled using ritodrine or MgSO_4 alone^{26–29}.

Ritodrine and MgSO_4 have been used widely as tocolytic agents in Japan^{20,21}. Although hyperglycemia and hypokalemia are well-known adverse events of ritodrine in pregnant women³⁰, and hypoglycemia is a well-known adverse event in neonates born to mothers receiving ritodrine³⁰, whether ritodrine usage in preterm labor is associated with increased risk of neonatal hyperkalemia is unknown. Furthermore, although hyperkalemia has been reported as a rare adverse event of MgSO_4 in pregnant women²⁴, it is unknown whether MgSO_4 usage in women during preterm labor is also associated with increased neonatal hyperkalemia risk. To our best knowledge, association between ritodrine and/or MgSO_4 usage and neonatal hyperkalemia occurrence has not been documented in a large cohort study.

We hypothesized that long-term tocolysis with either ritodrine or MgSO_4 until 36 gestational weeks, or the combination of ritodrine and MgSO_4 may be associated with increased risks of neonatal hypoglycemia or hyperkalemia in Japan. Moreover, we also hypothesized neonatal hypoglycemia or hyperkalemia may be associated with increased risks of abnormal neurological findings including cerebral palsy. Therefore, our main aim was to investigate hyperkalemia and hypoglycemia incidence in neonates born to mothers receiving either ritodrine or MgSO_4 therapy for preterm labor. Our secondary aim was to investigate the association between neonatal hypoglycemia and hyperkalemia and later occurrence of abnormal neurological findings including cerebral palsy. Our study focused only on late preterm infants born after 32 gestational weeks. Such preterm infants are usually not severely ill at birth, and tend to be cared for in step down neonatal units or obstetrical wards without close examination, unlike neonatal intensive care units (NICUs).

Results

Maternal and infantile characteristics based on presence /absence of hypoglycemia.

Hypoglycemia occurred in 32.4% at birth and at < 3 hours after delivery in 94.3% of cases. Frequencies of the following were significantly higher in infants with hypoglycemia: Mother with PL/shortened CL/CI (preterm labor/shortened cervical length/cervical incompetency), placenta previa/low-lying placenta, cesarean section, twins/triplets, small-for-gestational-age (SGA) infants, and women with ritodrine alone or the concomitant usage of both ritodrine and MgSO_4 . However, in infants with hypoglycemia, frequencies of women with preterm premature rupture of the membranes (pPROM), and GH/PE/eclampsia/HELLP/AFLP (gestational hypertension/preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelets/acute fatty liver of pregnancy) were significantly lower (Table 1).

Effects of various risk factors on hypoglycemia occurrence. In multivariable logistic regression analyses using the “Hypoglycemia set”, independent risk factors for hypoglycemia occurrence were cesarean section, SGA infants, and delivery to a mother with ritodrine alone or concomitant usage of ritodrine and MgSO_4 (Table 2). Interestingly, preterm premature rupture of the membranes (pPROM) was a negative independent risk factor for hypoglycemia occurrence.

Maternal and infantile characteristics based on presence/absence of hyperkalemia. Hyperkalemia occurred in 7.6% of cases at birth, and 24.0% at < 3 hours, 9.2% at 3–5 hours, 53.0% at 6–23 hours, and 13.8% at ≥ 24 hours. Frequencies of hyperkalemia were significantly higher in infants born at < 35 gestational weeks, with an Apgar score at 1 minute < 3 , and whose mother used ritodrine and MgSO_4 concomitantly (Table 3)

Effects of various risk factors on hyperkalemia occurrence. In multivariable logistic regression analyses using the “Hyperkalemia set”, independent risk factors for hyperkalemia occurrence were delivery at < 35 gestational weeks, an Apgar score at 1 minute < 3 , and delivery to a mother with concomitant usage of ritodrine and MgSO_4 (Table 4).

Maternal and infantile characteristics with the combination of MgSO_4 and ritodrine. Data from four usage groups – MgSO_4 alone, ritodrine alone, both MgSO_4 and ritodrine, and neither MgSO_4 nor ritodrine – are shown in Supplementary Table S1. MgSO_4 was the smallest group ($n = 243$, 5.3%), but frequency of GH/PE/eclampsia/HELLP/AFLP was highest (67.1%), suggesting MgSO_4 alone was mainly used eclampsia prevention during pregnancy (Supplementary Table S1). On the contrary, frequencies of PL/shortened CL/CI were significantly higher in the ritodrine alone group (79.6%) and the combined MgSO_4 and ritodrine group (85.0%)

Characteristics	Non-hypoglycemia	Hypoglycemia	Missing value	P-value
	(N = 3,043)	(N = 1,458)		
Maternal characteristics				
Age (yr)	32.5 (29.5–36.5)	33.5 (29.5–37.5)	1	0.079
Nulliparity	1,509 (49.6)	704 (48.3)	0	0.426
Possible maternal risk factors for hypoglycemia				
Obstetrical complications				
TPL/shortened CL/CI	1,612 (53.0)	965 (66.2)	0	<0.001
pPROM	884 (29.1)	290 (19.9)	0	<0.001
GH/PE/eclampsia/HELLP/AFLP	483 (15.9)	198 (13.6)	0	0.046
Placental abruption	93 (3.1)	37 (2.5)	0	0.392
Placenta previa/Low-lying placenta	175 (5.8)	114 (7.8)	0	0.009
DM	29 (1.0)	16 (1.1)	0	0.634
GDM	159 (5.2)	77 (5.3)	0	0.943
Cesarean section	1,755/3,018 (58.2)	1,071/1,432 (74.8)	51	<0.001
MgSO ₄ usage	606 (19.9)	362 (24.8)	0	<0.001
Ritodrine usage	1,371 (45.1)	988 (67.8)	0	<0.001
Combination of MgSO ₄ and ritodrine ^a				
Neither MgSO ₄ nor ritodrine	1,486 (48.8)	423 (29.0)	0	<0.001
MgSO ₄ alone	186 (6.1)	47 (3.2)		
Ritodrine alone	951 (31.3)	673 (46.2)		
Both MgSO ₄ and ritodrine	420 (13.8)	315 (21.6)		
Possible children's risk factors for hypoglycemia				
Gestational weeks at delivery	35.6 (34.2–36.4)	35.6 (34.2–36.4)	0	0.617
Delivery at <35 wk	1,169 (38.4)	563 (38.6)	0	0.922
Birthweight (g)	2,202 (1,916–2,464)	2,150 (1,820–2,432)	0	<0.001
Twins/Triplets	770 (25.3)	572 (39.2)	0	<0.001
Sex: male	1,732/3,042 (56.9)	788 (54.0)	1	0.072
SGA infants	342 (11.2)	196 (13.4)	0	0.035
Large-for-gestational-age infants	33 (1.1)	18 (1.2)	0	0.654
Apgar score at 1 min <3	93/3,040 (3.1)	43/1,456 (3.0)	5	0.926

Table 1. Maternal and infantile characteristics in 4,501 infants with data on hypoglycemia who were born at 32–36 gestational weeks. Abbreviations: yr, years old; TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetence; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using “Hypoglycemia set”. Continuous variables are shown as median (interquartile range), and discrete variables are shown as n (%). The statistical differences between infants with vs. without hypoglycemia were tested using the Mann-Whitney test, Fisher’s exact test, or χ^2 test. ^a The incidence of HG in women with “no usage of either MgSO₄ or ritodrine (Group 1: G1)”, “MgSO₄ alone (Group 2: G2)”, “ritodrine alone (Group 3: G3)”, and “both MgSO₄ and ritodrine (Group 4: G4)” was 22.2, 20.2, 41.4, and 42.9%, respectively. Significant pairs by Bonferroni test were G1 vs. G3, G1 vs. G4, G2 vs. G3, and G2 vs. G4.

compared to the MgSO₄ alone group (35.8%) and the control group using neither MgSO₄ nor ritodrine (30.4%). This suggests ritodrine alone or both ritodrine and MgSO₄ in combination was mainly selected for PL therapy. Frequencies of hypoglycemia were significantly higher in women using ritodrine alone (41.4%) and using both MgSO₄ and ritodrine (42.9%) than in controls (22.2%). Frequency of hyperkalemia was significantly higher in women using both MgSO₄ and ritodrine (10.9%) than in controls (6.5%).

Duration- and dose-dependent effects of ritodrine on hypoglycemia occurrence. Next, we evaluated the association of the duration, maximum rate of administration, final rate of administration just before cessation, and time from cessation to delivery for ritodrine with the occurrence of hypoglycemia using the “Hypoglycemia: Ritodrine-alone plus control set” (Supplementary Table S2). The risk of hypoglycemia was associated with long-term tocolysis (total administration periods ≥ 2 days [48 hours]). However, short-term tocolysis (<2 days [48 hours]) was not a risk factor for hypoglycemia. The maximum rate of injection or final rate of injection just before cessation of ritodrine did not show dose-dependence. The risk of hypoglycemia was related to cessation just before delivery; if ritodrine was stopped ≥ 4 hours before delivery, the aOR of hypoglycemia was almost two thirds of when stopped <4 hours before delivery.

Risk factors ^a	Univariate analysis			Multivariable analysis ^b		
	Crude odds ratio (95% CI)	P-value		Adjusted odds ratio (95% CI)	P-value	
Combination of MgSO ₄ and ritodrine						
MgSO ₄ alone vs. no usage	0.89 (0.63–1.24)	0.489		0.81 (0.56–1.16)	0.244	
Ritodrine alone vs. no usage	2.49 (2.15–2.88)	<0.001		2.58 (2.21–3.01)	<0.001	
Both MgSO₄ and ritodrine vs. no usage	2.64 (2.20–3.16)	<0.001		2.59 (2.13–3.15)	<0.001	
Obstetrical complications						
pPROM	0.61 (0.52–0.71)	<0.001		0.72 (0.61–0.85)	<0.001	
GH/PE/eclampsia/HELLP/AFLP	0.83 (0.70–0.996)	0.045		0.91 (0.74–1.12)	0.355	
Placental abruption	0.83 (0.56–1.22)	0.332		0.91 (0.60–1.38)	0.670	
Placenta previa/Low lying placenta	1.39 (1.09–1.78)	0.008		0.96 (0.74–1.26)	0.782	
DM	1.15 (0.62–2.13)	0.649		1.62 (0.85–3.08)	0.145	
GDM	1.01 (0.77–1.34)	0.937		1.14 (0.85–1.54)	0.372	
Cesarean section	2.14 (1.86–2.46)	<0.001		1.96 (1.67–2.31)	<0.001	
Delivery at <35 wk	1.01 (0.89–1.15)	0.898		0.95 (0.82–1.09)	0.646	
Twins/triplets	1.91 (1.67–2.18)	<0.001		1.23 (1.06–1.44)	0.009	
Sex: male	0.89 (0.79–1.01)	0.068		0.91 (0.80–1.04)	0.166	
SGA infants	1.23 (1.02–1.48)	0.033		1.35 (1.10–1.65)	0.004	
Large-for-gestational-age infants	1.14 (0.64–2.03)	0.656		1.58 (0.85–2.94)	0.146	
Apgar score at 1 min <3	0.96 (0.67–1.39)	0.846		0.98 (0.66–1.45)	0.917	

Table 2. Effects of various risk factors on hypoglycemia occurrence in 4,501 infants born at 32–36 gestational weeks. Abbreviations: CI, confidence interval; MgSO₄, magnesium sulfate; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using “Hypoglycemia set”. ^aRisk factors were determined based on both clinical relevance and univariate analysis as follows: combination of MgSO₄ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, and Apgar score at 1 min <3. ^bMultivariable analyses were performed using the same risk factors as in univariate analyses. However, birthweight was not used as a risk factor due to the close relationship with gestational weeks. In addition, the obstetric complication of TPL/shortened CL/CI was not used as a risk factor because either ritodrine or MgSO₄ was commonly used under these conditions. Excluding 57 patients with missing data for 14 variables, a total of 4,444 patients underwent multivariable analysis. Abbreviations: TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency.

Duration- and dose-dependent effects of ritodrine or MgSO₄ on hyperkalemia occurrence. Incidence rate of hyperkalemia in women with ritodrine alone was not different from that in women with MgSO₄ alone. We then evaluated the association of tocolytic agents’ duration, maximum rate of administration, final rate of administration just before cessation, and time from cessation to delivery with hyperkalemia occurrence, using the “Hyperkalemia: Both ritodrine and MgSO₄ plus control set” (Supplementary Table S3, S4). Hyperkalemia risk was associated with long-term tocolysis with ritodrine. In women in whom the maximum rate of injection or final rate of injection just before cessation of ritodrine was ≥ 170 $\mu\text{g}/\text{min}$, the risk was significantly higher than in those with no usage of ritodrine. Risk of hyperkalemia was related to the cessation of ritodrine just before delivery; if stopped ≥ 4 hours before delivery, hyperkalemia risk almost equaled no usage. As for MgSO₄, there was no relationship between duration of administration, maximum rate of injection, or final rate of injection before cessation. However, risk of hyperkalemia was related to MgSO₄ cessation just before delivery; hyperkalemia risk in women in whom MgSO₄ was stopped ≥ 4 hours before delivery was not significantly different from that in women with no usage of ritodrine.

Maternal and infantile characteristics based on presence/absence of cerebral palsy occurring 3 years after birth. Cerebral palsy occurred in 23 cases (0.5%) (Supplementary Table S5). Frequencies of placental abruption, delivery at <35 weeks of gestation, and Apgar score at 1 minute <3 were significantly higher in infants with cerebral palsy. Gestational weeks at delivery was earlier, and birth weight was also smaller. Due to this small sample size, we did not perform multivariable analysis.

Maternal and infantile characteristics based on presence/absence of any neurological impairments occurring 3 years after birth. Neurological impairments occurred in 193 cases (4.5%) (Supplementary Table S6). Cerebral palsy was only 12%. Other impairments included developmental language disorder alone, low score of developmental quotient, autism spectrum disorder (autism), attention-deficit/hyperactivity disorder (ADHD), auditory disorder, visual impairment, epilepsy, or developmental coordination disorder. Frequencies of nulliparous women, GH/PE/eclampsia/HELLP/AFLP, placenta abruption, delivery at <35 weeks of gestation, male infants, SGA infants, Apgar score at 1 minute <3, and hypoglycemia were higher in infants with neurological impairments. In addition, frequencies of PL/shortened CL/CI, or cervical

Characteristics	Non-hyperkalemia	Hyperkalemia	Missing value	P-value
	(N = 3,448)	(N = 284)		
Maternal characteristics				
Age (yr)	33.5 (29.5–36.5)	33.5 (29.8–37.5)	2	0.221
Nulliparity	1,766 (51.2)	161 (56.7)	0	0.084
Possible maternal risk factors for hyperkalemia				
Obstetrical complications				
TPL/shortened CL/CI	1,973 (57.2)	175 (61.6)	0	0.152
pPROM	953 (27.6)	65 (22.9)	0	0.096
GH/PE/eclampsia/HELLP/AFLP	561 (16.3)	54 (19.0)	0	0.244
Placental abruption	119 (3.5)	6 (2.1)	0	0.302
Placenta previa/Low-lying placenta	214 (6.2)	23 (8.1)	0	0.206
DM	38 (1.1)	2 (0.7)	0	0.766
GDM	163 (4.7)	20 (7.0)	0	0.086
Cesarean section	2,229/3,417 (65.2)	191/281 (68.0)	34	0.362
MgSO ₄ usage	770 (22.3)	82 (28.9)	0	0.015
Ritodrine usage	1,830 (53.1)	174 (61.3)	0	0.008
Combination of MgSO ₄ and ritodrine ^a				
neither MgSO ₄ nor ritodrine	1,418 (41.1)	98 (34.5)	0	0.003
MgSO ₄ alone	200 (5.8)	12 (4.2)		
Ritodrine alone	1,260 (36.5)	104 (36.6)		
Both MgSO₄ and ritodrine	570 (16.5)	70 (24.6)		
Possible children's risk factors for hyperkalemia				
Gestational weeks at delivery	35.2 (34.1–36.2)	34.8 (33.4–36.1)	0	<0.001
Delivery at <35 wk	1,549 (44.9)	154 (54.2)	0	0.003
Birthweight (g)	2,126 (1,832–2,388)	2,056 (1,814–2,363)	0	0.042
Twins/Triples	1,005 (29.1)	91 (32.0)	0	0.310
Sex: male	1,937/3,447 (56.2)	153 (53.9)	1	0.456
SGA infants	462 (13.4)	34 (12.0)	0	0.585
Large-for-gestational-age infants	33 (1.0)	1 (0.4)	0	0.513
Apgar score at 1 min < 3	112/3,443 (3.3)	18 (6.3)	5	0.011

Table 3. Maternal and infantile characteristics in 3,732 infants with data on hyperkalemia who were born at 32–36 gestational weeks. Abbreviations: yr, years old; GH, gestational hypertension; PE, preeclampsia; TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using “Hyperkalemia set”. Continuous variables are shown as median (interquartile range), and discrete variables are shown as n (%). The statistical differences between infants with hypoglycemia vs. those without were tested using the Mann-Whitney test, Fisher’s exact test, or χ^2 test. ^aThe incidence of HK in women with “no usage of either MgSO₄ or ritodrine (Group 1: G1)”, “MgSO₄ alone (Group 2: G2)”, “ritodrine alone (Group 3: G3)”, and “both MgSO₄ and ritodrine (Group 4: G4)” was 6.5, 5.7, 7.6, and 10.9%, respectively. Significant pair by Bonferroni test was G1 vs. G4.

incompetency, and twins/triplets were significantly lower in infants with neurological impairments. Median gestational weeks at delivery was earlier and birthweight was also smaller.

Effects of various risk factors on occurrence of any neurological impairments. Neurological impairments were evaluated in 4,279 infants (Supplementary Table S7). Excluding 989 patients with missing data for 16 variables, a total of 3,290 patients underwent multivariable analysis to assess effects on occurrence of any neurological impairments with the following 16 risk factors: combination of MgSO₄ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, Apgar score at 1 min <3, hypoglycemia at <48 h after birth, and hyperkalemia at <48 h after birth. Placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia were independent risk factors for the occurrence of any neurological impairments.

Discussion

Our current large cohort study yielded three novel findings. First, neonatal hyperkalemia within 48 hours after birth was associated with the concomitant usage of ritodrine and MgSO₄ among late preterm infants born at 32–36 gestational weeks. Second, neonatal hypoglycemia within 48 hours was associated with the usage of ritodrine alone or the concomitant usage of ritodrine and MgSO₄; incidence of hypoglycemia was markedly higher in

Risk factors ^a	Univariate analysis			Multivariable analysis ^b		
	Crude odds ratio (95% CI)	P-value		Adjusted odds ratio (95% CI)	P-value	
Combination of MgSO₄ and ritodrine						
MgSO ₄ alone vs. no usage	0.87	(0.47–1.61)	0.654	0.63	(0.33–1.20)	0.155
Ritodrine alone vs. no usage	1.19	(0.90–1.59)	0.224	1.20	(0.89–1.62)	0.231
Both MgSO₄ and ritodrine vs. no usage	1.78	(1.29–2.45)	<0.001	1.53	(1.09–2.15)	0.015
Obstetrical complications						
pPROM	0.78	(0.58–1.04)	0.085	0.78	(0.57–1.07)	0.118
GH/PE/eclampsia/HELLP/AFLP	1.21	(0.89–1.65)	0.232	1.37	(0.96–1.96)	0.085
Placental abruption	0.60	(0.26–1.38)	0.233	0.46	(0.19–1.09)	0.076
Placenta previa/Low lying placenta	1.33	(0.85–2.09)	0.210	1.24	(0.76–2.02)	0.389
DM	0.64	(0.15–2.65)	0.535	0.85	(0.20–3.56)	0.818
GDM	1.53	(0.94–2.47)	0.085	1.63	(0.998–2.67)	0.051
Cesarean section	1.13	(0.87–1.47)	0.354	0.96	(0.71–1.31)	0.798
Delivery at <35 wk	1.45	(1.14–1.85)	0.003	1.46	(1.13–1.88)	0.004
Twins/triplets	1.15	(0.88–1.49)	0.303	1.11	(0.82–1.50)	0.501
Sex: male	0.91	(0.71–1.16)	0.994	0.92	(0.72–1.18)	0.511
SGA infants	0.88	(0.61–1.27)	0.496	0.87	(0.59–1.28)	0.477
Large-for-gestational-age infants	0.37	(0.05–2.68)	0.323	0.35	(0.05–2.61)	0.306
Apgar score at 1 min < 3	2.01	(1.21–3.36)	0.008	2.21	(1.29–3.81)	0.004

Table 4. Effects of various risk factors on hyperkalemia occurrence in 3,732 infants who were born at 32–36 gestational weeks. Abbreviations: CI, confidence interval; MgSO₄, magnesium sulfate; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using “Hyperkalemia set”. ^aRisk factors were determined based on both clinical relevance and univariate analysis as follows: combination of MgSO₄ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, and Apgar score at 1 min < 3. ^bMultivariable analyses were performed using all the risk factors using the univariate analyses. However, birthweight was not used as a risk factor due to the close relationship with gestational weeks. In addition, the obstetric complication of TPL/shortened CL/CI was not used as a risk factor because either ritodrine or MgSO₄ was commonly used under these conditions. Excluding 40 patients with missing data for 14 variables, a total of 3,692 patients underwent multivariable analysis. abbreviations: TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency.

infants born to mothers with cessation of ritodrine just before delivery; in addition, incidence of hypoglycemia was higher in infants born to mothers with long-term tocolysis with ritodrine. Third, in infants born at 32–36 weeks of gestation, placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia within 48 hours after birth were independent risk factors for the occurrence of any neurological impairments.

In the current study, for the first time we have revealed concomitant usage of ritodrine and MgSO₄ is associated with incidence of neonatal hyperkalemia within 48 hours after birth in neonates born at 32–36 gestational weeks, although we could not show an association between neonatal hyperkalemia and cerebral palsy. Suzuki² analyzed data available in the Cause Analysis Report and demonstrated the relationship between delivery and cerebral palsy was unknown in 6.2% of nearly 800 cases of cerebral palsy. These infants showed marked characteristics: although considered normal, thereafter their condition changed suddenly and finally they developed severe cerebral palsy. Of these, 6 were cases of hypoglycemia and 3 of hyperkalemia, and in 2 cases of hyperkalemia with later occurrence of cerebral palsy, ritodrine and MgSO₄ were concomitantly used. In addition, in 11 of 14 cases of unexpected neonatal hyperkalemia soon after birth, ritodrine and MgSO₄ were also concomitantly used³. Our results further support the suggested association between concomitant usage of ritodrine and MgSO₄ and neonatal hyperkalemia. It is well known neonatal hyperkalemia can cause electrocardiographic abnormalities including ventricular tachycardia³¹. Therefore, our results serve as a warning about concomitant usage of ritodrine and MgSO₄ to prevent neonatal hyperkalemia. However, it is unknown why concomitant usage of ritodrine and MgSO₄, but not ritodrine alone or MgSO₄ alone, is associated with neonatal hyperkalemia. Hypermagnesemia might affect Na⁺/K⁺-ATPase^{15,32}, however, to the best of our knowledge, there have been no cohort studies suggesting a relationship between ritodrine administration and neonatal hyperkalemia. Therefore, our clinical observations may suggest presence of synergy between ritodrine and hypermagnesemia to modify the Na⁺/K⁺-ATPase function.

Although we could not reveal the association between neonatal hypoglycemia and the later occurrence of cerebral palsy in this study, it is well-known that neonatal hypoglycemia increases the incidence of cerebral palsy^{33,34}. Risk factors for cerebral palsy in infants with hypoglycemia are as follows: blood glucose levels <15 mg/dL, long duration of hypoglycemia, non-reassuring fetal status (NRFS), low Apgar score <5 at 1 min, neonatal seizure,

pathological jaundice, and hypertensive disorders of pregnancy for the mother³⁵. Ritodrine is well-known to induce hyperglycemia in mothers which can cause hypoglycemia in neonates^{36,37}. In the current study, incidence of hypoglycemia was markedly higher in infants born to mothers with either long-term tocolysis of ritodrine or cessation just before delivery. Therefore, ritodrine might be one of the risk factors for cerebral palsy. Hyperkalemia was not associated with the occurrence of cerebral palsy. In addition, we found placental abruption, delivery at <35 weeks of gestation, and Apgar score at 1 minute <3 were associated with later occurrence of cerebral palsy. Placental abruption and early delivery are well-known risk factors for cerebral palsy³⁸. Although the contribution of asphyxia to the overall incidence of cerebral palsy is relatively small³⁹, metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery with both pH <7.00 and base deficit ≥ 12 mmol/L would have been sufficient to cause cerebral palsy⁴⁰.

In infants born at 32–36 weeks of gestation, placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia were independent risk factors for occurrence of any neurological impairments. Hyperkalemia was not an independent risk factor. Male sex is at higher risk of autism^{41,42}, and may be at high risk of ADHD⁴³; however, the association between male sex and cerebral palsy is controversial⁴⁴. An SGA infant is a risk factor for cerebral palsy in moderate to late preterm infants⁴⁵, and may be also associated with autism or ADHD^{46,47}. Although our outcome of any neurological impairment was a composite outcome, and our data could be significantly biased due to a retrospective study design, our data support associations of male sex or an SGA infant on occurrence of neurological impairments including cerebral palsy, autism, or ADHD.

Our results warn about the concomitant usage of ritodrine and MgSO₄ to prevent neonatal hyperkalemia, and also warn about long-term usage of ritodrine and its cessation just before delivery to prevent neonatal hypoglycemia. Furthermore, because these adverse events occurring outside NICUs are not well-recognized among obstetricians and neonatologists, this study could have a marked impact on modifying current neonatal management for infants born to mothers with tocolytic agents. Accordingly, neonatal assessment of hyperkalemia can be suggested in women with concomitant usage of ritodrine and MgSO₄, and neonatal blood glucose monitoring can also be suggested in women with long-term tocolysis with ritodrine or cessation just before delivery.

The main strengths of our study include the following: (1) it is the first large cohort study evaluating associations between long-term tocolysis with both ritodrine and MgSO₄, and neonatal hypoglycemia and hyperkalemia; (2) it presents the first evidence of a synergic effect between ritodrine and MgSO₄ on occurrence of neonatal hyperkalemia; and (3) it is the first large cohort study investigating association of neonatal hyperkalemia and later occurrence of any neurodevelopmental impairments including cerebral palsy.

Our study has several limitations. First, it may be difficult to generalize results from this study with other countries. However, ritodrine hydrochloride and MgSO₄ have a long usage history in prenatal care, and MgSO₄ use is still widespread. The novel adverse events (neonatal hyperkalemia) due to concomitant use of ritodrine and magnesium sulfate should be added in the package insert of both MgSO₄ and ritodrine hydrochloride. Second, this was a retrospective cohort study possibly resulting in high risk of selection bias. Although we targeted infants born at 32–36 gestational weeks, 19% of infants did not have data for either hypoglycemia or hyperkalemia possibly leading to bias. In addition, we could not confirm presence/absence of neurodevelopmental impairments in almost 7% of infants, resulting in underestimation of the associations between hypoglycemia/hyperkalemia and subsequent occurrence of neurodevelopmental impairments. However, in this large retrospective cohort study, we attempted to decrease systematic bias through secondary investigation for ritodrine and magnesium sulfate usage, and attempted to adjust possible confounding factors using multivariable logistic regression analysis. In addition, before using the nationwide database, we checked for inappropriate values and transformed them to missing values. The main outcomes of hypoglycemia and hyperkalemia were newly investigated in the secondary inquiry, and diagnoses of hypoglycemia and hyperkalemia were validated by investigating levels of glucose and potassium within 48 hours after birth. Therefore, although this study is a retrospective study using a large database, we believe reducing selection bias risk is feasible as it adjusting for possible confounding factors in the relationship between ritodrine/magnesium sulfate usage and neonatal hypoglycemia/hyperkalemia occurrence. Third, we could not collect data on hypoglycemia/hyperkalemia from 277 hospitals (78%). However, the incidences of GH/PE/eclampsia/HELLP/AFLP, placenta previa/low-lying placenta, DM, GDM, and cesarean section in infants in the current study were almost the same as those in infants not involved in the current study (Supplementary Table S8), indicating current subjects may have been appropriately extracted from a nationwide obstetrical database. Fourth, inclusion criteria for pregnant women with only late preterm infants may limit generalizability of our results. However, since long-term tocolysis with ritodrine and MgSO₄ is often performed at 32–36 gestational weeks in Japan, and since tocolysis is not performed at ≥ 37 gestational weeks, we believe targeting at 32–36 gestational weeks may be appropriate for analyzing the relationship between tocolytic agents and occurrence of neonatal hypoglycemia and hyperkalemia.

Methods

Study design and participants. This was a retrospective cohort study of neonates born at 32–36 gestational weeks using a nationwide obstetrical database from 2014⁴⁸. Because we needed to collect information on the infantile prognosis until almost 3 years old, it was followed by a secondary survey conducted in Japan in 2017–2018. In previous case series of hyperkalemia neonates, 50% (7/14) were born at 32–36 gestational weeks^{3–14}. Neonates are usually managed on obstetrical wards in Japan if they have either $\geq 2,000$ g birthweight or are at ≥ 35 gestational weeks at delivery. Therefore, we speculated such neonates might have developed cerebral palsy due to possible delay of the detection of hyperkalemia, because in neonates on obstetrical wards electrolyte abnormalities are not checked routinely unless they show symptoms. In addition, hyperkalemia often occurs in neonates born at <32 gestational weeks; therefore, exclusion of such early preterm infants may facilitate analysis of the association between tocolytic agents and hyperkalemia occurrence. Thus, we decided to investigate neonates born in a relatively late preterm period (32–36 gestational weeks), to evaluate the possible relationship

between tocolytic agents and neonatal hyperkalemia. For hypoglycemia, Suzuki² analyzed data available in the Cause Analysis Report, and determined 5 of 6 neonates (83%) who had hypoglycemia suspected associated with development of cerebral palsy were born at ≥ 37 gestational weeks. However, we did not include neonates born at ≥ 37 gestational weeks in our analysis since assessment of hypoglycemia was not part of our routine examinations.

We received approval from the JSOG Clinical Research Ethics Committee to use a nationwide obstetrical database from 2014 (No. JSOG2017–51), and also received approval from the JSPNM Clinical Research Ethics Committee for execution of the current study in the survey group to study the effects of tocolytic agents on neonatal adverse events (No. JSPNM2017–1). Then, we requested the directors of Departments of Obstetrics and Gynecology in 355 hospitals that had registered in the nationwide obstetrical database from 2014 (total stillbirths and infants: $n = 220,052$; those born at 32–36 gestational weeks: $n = 24,943$) to cooperate with the current study. Finally, 78 directors consented to this study, and kindly secured the cooperation of neonatologists in each hospital. A research investigator and research team members in each hospital gained approval for this study from each Clinical Research Ethics Review Committee. All methods in this retrospective study were performed in accordance with the relevant guidelines (Ethical Guidelines for Medical and Health Research Involving Human Subjects). Because this study is a retrospective study, it was very difficult to gain appropriate informed consents from each subject. Therefore, we gained consents using opt-out, which is a way for investigators to give subjects an opportunity to refuse to participate in this study by announcing the detail of this study in each participating institute. The Survey Committee constructed input pages for survey data on the Web system. Data were collected within 1 year after the approval of the current study.

We excluded the following infants from our survey: (1) born to women with unknown data on the usage of ritodrine or $MgSO_4$, (2) whose mothers were administered $MgSO_4$ only after birth or at an unknown time, (3) with a birthweight of either < 500 or $> 4,000$ g, or unknown birth weight, (4) with stillbirth or major anomalies (chromosomal anomalies, neonatal abnormalities, conditions probably contributing to impaired neurodevelopment, conditions requiring emergency surgery soon after delivery, and lethal conditions), and (5) with unknown data on both hypoglycemia and hyperkalemia (Fig. 1). The remaining 4,622 infants with data on either hypoglycemia or hyperkalemia at < 48 hours after delivery were analyzed.

Collection of new variables by the secondary survey. The Survey Committee used a nationwide obstetrical database from 2014, which included 314 variables on maternal and neonatal information⁴⁸. The input data in all variables were initially automatically checked using internalized data check scripts, and data input staff were informed of possible incorrect data. However, since the database was built using data from 355 institutes, there were inappropriate data in the database. Then, one author (A.O.) attempted to validate the database. The initial number of cases in the database was 24,960, but we found that 17 cases were duplicated; after exclusion the remaining 24,943 cases were used. Next, we determined inappropriate values for maternal height, pre-pregnancy maternal body weight, maternal body weight at delivery, maternal age, bleeding amounts, gestational weeks at premature rupture of the membranes, disseminated intravascular coagulation (DIC) score, neonatal birth weight, neonatal birth height, neonatal head circumference, Apgar score at 1 minute (min), Apgar score at 5 min, pH of umbilical artery, placental weight, and umbilical cord length. We finally transformed the inappropriate values to missing values.

The Survey Committee extracted the following 6 variables: facility name, anonymization number, date of birth, gestational weeks and days at delivery, birth weight, and neonatal sex. The committee members collaboratively decided survey items for the secondary survey. In the survey for ritodrine they were: presence/absence of injections, medical product name, total administration days (6 codes), maximum infusion speed (8 codes), final infusion speed (8 codes), and interval (hours) from cessation of ritodrine to delivery (6 codes). In the $MgSO_4$ survey they were: presence/absence of injections, medical product name, total administration days (6 codes), maximum infusion speed (8 codes), final infusion speed (8 codes), interval hours from cessation of $MgSO_4$ to delivery (6 codes), and administration period (pre-delivery alone, post-delivery alone, both pre- and post-delivery, unknown). In the survey for neonatologists they were: presence/absence of admission to NICU, causes for admission to NICU, presence/absence of measurements of magnesium concentrations in umbilical cord, concentration of magnesium in umbilical cord, presence/absence of measurements of blood sugar within 48 hours after delivery, blood sugar level at the nadir (mg/dL), presence/absence of hypoglycemia defined as < 40 mg/dL⁴⁹, timing of the nadir blood sugar level (5 codes), presence/absence of measurements of potassium concentrations within 48 hours after delivery, potassium level at the maximum (mEq/L), presence/absence of hyperkalemia defined as > 6.5 mEq/L⁵⁰, timing of the maximum potassium level (5 codes), three consecutive potassium levels just after the occurrence of hyperkalemia, infantile prognosis at almost 3 years (4 codes: death, presence of abnormal neurological findings, absence of abnormal neurological findings, unknown), detailed information on the disease or condition leading to abnormal neurological findings, and date of judgment of infantile prognosis.

Primary/secondary outcomes and risk factors. Primary outcomes were the occurrence of hyperkalemia and hypoglycemia. Secondary outcomes were cerebral palsy, and any neurodevelopmental impairments including cerebral palsy occurring 3 years after birth. Cerebral palsy was judged by the senior pediatrician (S. K.) who was involved neither in data acquisition nor in database construction. Cerebral palsy was defined as a non-progressive, non-transient central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture⁵¹.

Based on both clinical relevance and univariate analysis, risk factors for occurrence of hypoglycemia or hyperkalemia were: obstetrical complications, cesarean section, $MgSO_4$ usage during pregnancy, ritodrine usage, gestational weeks at delivery, birth weight, multiple pregnancy, infantile sex, SGA and large-for-gestational-age defined as an infant with weight below the 10th percentile or \geq the 90th percentile of gestational age⁵², and Apgar score at 1 min < 3 . The above-mentioned 14 risk factors plus hypoglycemia and hyperkalemia were also determined risk factors for cerebral palsy or other neurological impairments.

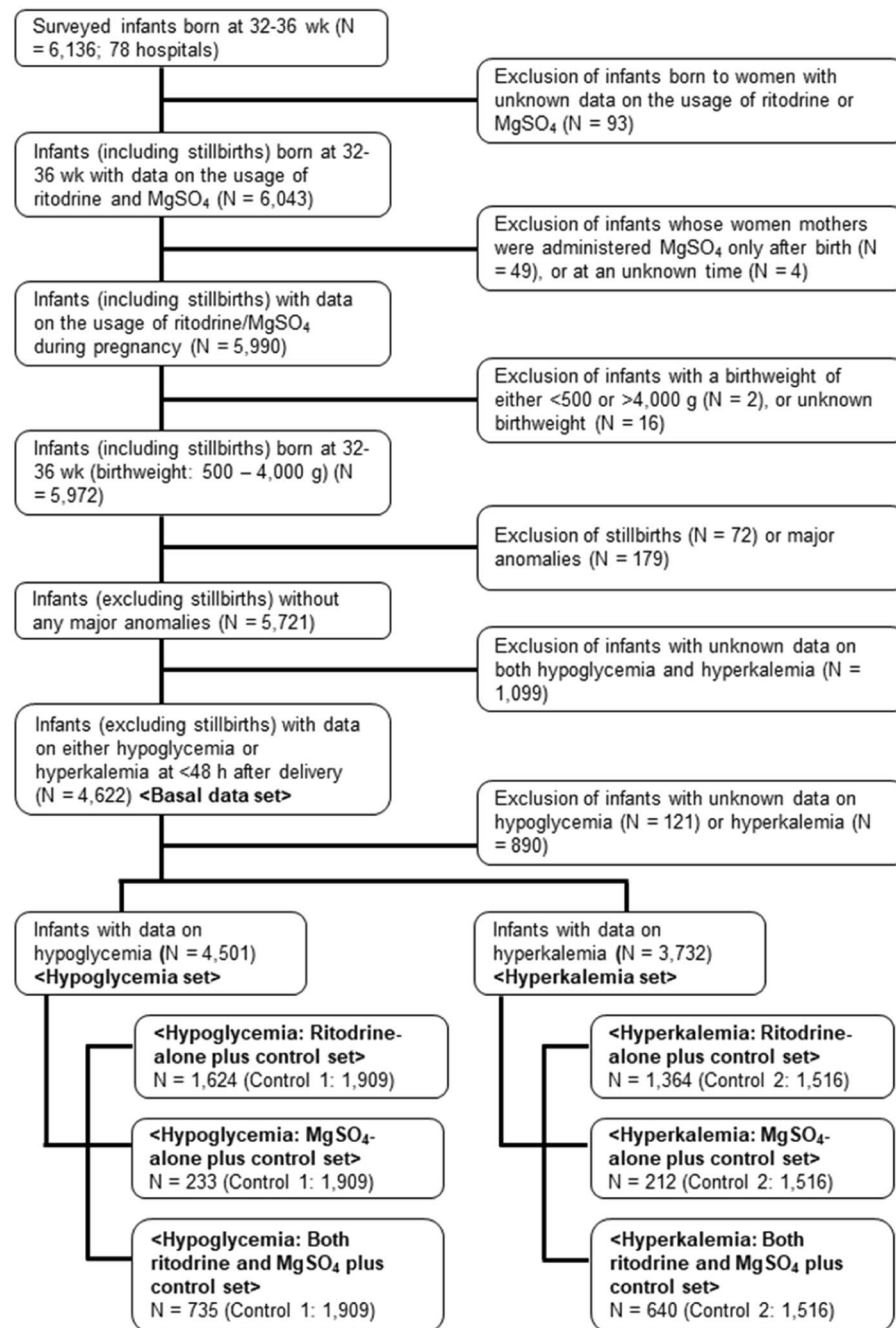


Figure 1. Patient Flowchart. “Basal data set” (N = 4,622) was created from 6,136 surveyed infants born at 32–36 gestational weeks. “Hypoglycemia set” (N = 4,501) was created from “Basal data set” after excluding 121 infants with unknown data on hypoglycemia; and “Hyperkalemia set” (N = 3,732) was created from “Basal data set” after excluding 890 infants with unknown data on hyperkalemia. “Hypoglycemia set” was divided into “Hypoglycemia: Ritodrine-alone plus control set” (Ritodrine-alone [N = 1,624] and control 1 without either ritodrine or MgSO₄ [N = 1,909]), “Hypoglycemia: MgSO₄-alone plus control set” (MgSO₄-alone [N = 233] and control 1), and “Hypoglycemia: Both ritodrine and MgSO₄ plus control set” (Both ritodrine and MgSO₄ [N = 735] and control 1). “Hyperkalemia set” was also divided into “Hyperkalemia: Ritodrine-alone plus control set” (Ritodrine-alone [N = 1,364] and control 2 without either ritodrine or MgSO₄ [N = 1,516]), “Hyperkalemia: MgSO₄-alone plus control set”, (MgSO₄-alone [N = 212] and control 2), and “Hyperkalemia: Both ritodrine and MgSO₄ plus control set” (Both ritodrine and MgSO₄ [N = 640] and control 2).

Statistical analysis. Continuous variables are shown as the median (interquartile range) because of non-normal distributions of gestational weeks and birth weight at 32–36 gestational weeks, and binary and categorical variables are shown as n (%). The associations of ritodrine/MgSO₄ usage during pregnancy and the occurrence of infantile hypoglycemia/hyperkalemia within 48 hours after delivery were analyzed using Fisher’s exact

test or the χ^2 test, followed by univariate logistic regression analyses. Then, multivariable regression analyses were performed while adjusting for confounding variables. Because the primary outcomes of hyperkalemia and hypoglycemia occurred in >200 cases, we judged we could use a maximum of 20 risk and/or confounding factors in the multivariable models. All analyses were performed using IBM SPSS Statistics (version 25 for Windows) and R (EZR ver. 1.37)⁵³. Level of $p < 0.05$ was considered significant.

Data availability

Data and materials used in this study are available upon reasonable request to the corresponding author and under a collaboration agreement.

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Competing interests

The authors declare no competing interests.

Additional information

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The Survey Group Studying the Effects of Tocolytic Agents on Neonatal Adverse Events in Japan Society of Perinatal and Neonatal Medicine

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