Neonatal rebound hyperkalemia associated with long-term administration of maternal betamimetic: a single-center retrospective cohort study

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Research Article

Keywords: betamimetics, neonatal hyperkalemia, late preterm infants, retrospective cohort study, ritodrine

Posted Date: February 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1313318/v1

Abstract

Background

We recently reported on a late preterm infant born at 36 gestational weeks with serious arrhythmia due to hyperkalemia associated with long term maternal ritodrine administration. In a previous nation-wide surveillance, maternal combined administration of ritodrine and magnesium sulphate administration increased the risk of neonatal hyperkalemia in intermediate and late preterm infants born at 32–36 gestational weeks. It is unknown whether ritodrine alone increases the risk of neonatal hyperkalemia in late preterm infants born at 34–36 gestational weeks.

Methods

This single center retrospective cohort study enrolled late preterm infants born at 34–36 gestational weeks between 2004 and 2018. The association between neonatal hyperkalemia (K^+> 6.0 mEq/l) during 72 hours of life and maternal ritodrine use were investigated. Cases with maternal magnesium sulphate were excluded.

Results

In all, 213 late preterm infants with maternal ritodrine and 402 infants without tocolysis were included in the study. The risk of neonatal hyperkalemia was significantly increased by maternal ritodrine administration, with a crude odds ratio (OR) of 2.94 (95% confidence interval [CI] 1.20–7.61; $p < 0.01$) and an adjusted OR of 3.79 (95% CI 1.43–10.02; $p < 0.01$) on multivariable analysis. Long-term ritodrine administration (≥ 28 days) increased the risk of neonatal hyperkalemia.

Conclusion

This research suggests that late preterm infants born after long-term ritodrine administration are at risk of neonatal hyperkalemia and require special attention.

Background

Selective β_2-adrenergic receptor (AR) agonists such as isoxsuprine, hexoprenaline, orciprenaline, ritodrine (often used in Japan and other countries [1–3]), terbutaline, and salbutamol have been used widely for tocolysis since the 1980s [3–7]. However, because of the risk of serious cardiovascular side effects to both the mothers and fetuses, the US Food and Drug Administration issued a warning in 2013 that selective β_2-AR agonists should not be used in pregnant women for the prevention of preterm delivery for longer than 48–72 h. European Medicine Agency then also recommended that the use of selective β_2-AR agonists for tocolysis should be limited to a maximum of 48 h. Thereafter, tocolytics have been used in other countries to extend pregnancy by up to 48 h. During this time, pregnant women can be transferred to other hospitals that offer high-grade perinatal care and can receive antenatal steroids to help fetal lungs mature [8]. However, Kissei Pharmaceutical Co.Ltd reported that ritodrine could be used at lower doses than in other countries (i.e. up to 200 vs. 350

μg/min), and that long-term ritodrine was effective in prolonging pregnancy [9]. Accordingly, the Japan Society of Obstetrics and Gynecology and the Japan Association of Obstetricians and Gynecologists have not prohibited long-term tocolysis using ritodrine [10]. Therefore, in Japan, threatened preterm labor is diagnosed earlier and gynecologist often continue tocolytics, including ritodrine, with hospitalization for longer periods than in other countries.

Neonatal hyperkalemia is a serious problem that can be life-threatening because of its effect on cardiac rhythm [11]. Neonatal hyperkalemia, the etiology of which is based on prematurity itself (immature Na^+/K^+-ATPase, relative hypoaldosteronism, and immaturity of the renal distal tubules), generally occurs in extremely low birth weight infants and is rare in late preterm infants born at 34–36 weeks gestation [11, 12]. Based on a nationwide cohort research in Japan, Yada et al. recently reported that combination of ritodrine and magnesium sulfate ($MgSO_4$) increases the risk of neonatal hyperkalemia in intermediate and late preterm infants born at 32–36 weeks gestation [13]. However, in most cases, the use of $MgSO_4$ for threatened preterm labor is discontinued before 34 weeks gestation. Recently, we reported the case of an infant born at 36 weeks gestation with sudden cardiac arrest and ventricular tachycardia due to neonatal rebound hyperkalemia caused by maternal ritodrine use; this infant died of neonatal acute respiratory distress syndrome following resuscitation [14]. Although previous reports have described rebound hyperkalemia associated with the cessation of ritodrine in parturients [15, 16], the effect of maternal ritodrine on the risk of neonatal hyperkalemia in late preterm infants has not been elucidated yet. The lack of adequate data might be partly explained by the fact that late preterm infants are usually cared for in step-down neonatal units or obstetric wards without the close monitoring, including electrolytes checks, provided in the neonatal intensive care units (NICU) and growth care units (GCU); thus, some ritodrine related cases of hyperkalemia might have been missed. The aim of the present study was to clarify the association between maternal ritodrine administration and neonatal hyperkalemia in late preterm infants.

Methods

Enrollment

Preterm infants who were born at $34^{0/7}$-$36^{6/7}$ weeks gestation and were admitted to the NICU and GCU in Tokushima University Hospital between 2004 and 2018 were included in this study. Infants with chromosomal abnormalities, congenital major malformations, and early death within the first 48 h of life were excluded. The number of late preterm infants whose mothers were administered $MgSO_4$ use was not sufficient for statistical analysis, and so they were excluded from the study. Basic clinical information was obtained from the NICU database, with individual medical records reviewed by several authors (CK, MT, ST, KO, and MS).

Neonatal Hyperkalemia

The primary outcome of the study was the occurrence of neonatal hyperkalemia. Peak K^+ concentrations during the first 72 h were recorded, and neonatal hyperkalemia was defined as $K^+ > 6.0$ mEq/L [11]. Other blood examination data were obtained at the time of the peak K^+ concentration.

Risk factors for the occurrence of hyperkalemia were determined on the basis of clinical relevance, univariate analysis, and previous reports [13, 17], namely maternal age > 35 years, ritodrine use during pregnancy, gestational ages, and calendar year (grouped into 5-year intervals).

Tocolysis

The half-life of ritodrine ranges from 4.2 to 29.6 h, and ritodrine remains in the serum for up to 24–48 h after birth [18]. Therefore, if ritodrine was discontinued 4 days before delivery, its effect was considered negligible and was reclassified in this study. In addition, data on the duration of ritodrine administration was also obtained.

Statistical analysis.

Statistical analyses were performed using JMP ver.14.2 (SAS institute Inc, Cary, NC, USA). Continuous variables are presented as the median with interquartile range (IQR), whereas categorical variables are presented as percentages with numbers in parentheses. Categorical variables were compared using the Chi-squared test and Fisher's exact test, as appropriate. Continuous variables were compared using the Wilcoxon test because all were determined to be non-parametric by the Shapiro-Wilk normality test. Univariate logistic regression analyses were used to evaluate associations between ritodrine use and the confounding variables specified above. Multivariable regression analyses were performed to adjust the confounding variables specified above. In all cases, $p < 0.05$ was considered significant.

Results

Eligibility

In all, there were 857 preterm infants born at $34^{0/7}$-$36^{6/7}$ weeks gestation between 2004 and 2018 (Fig. 1). After excluding 27 patients with chromosomal abnormalities, 59 with congenital major malformations, eight who died within 48 h of life, 27 born to mothers treated with $MgSO_4$ alone, 36 born to mothers treated with both ritodrine and $MgSO_4$, and 85 with missing K^+ values, there were 615 infants included in this study: 213 infants whose mothers were administered ritodrine and 402 infants whose mothers did not receive tocolytics (control group; Fig. 1). Of the 615 infants in this study, 20 (3.3%) were diagnosed with neonatal hyperkalemia.

Maternal And Infant Characteristics According To Ritodrine Use

Mothers administered ritodrine were younger than those in the control group (median [IQR] age 31[28–34] vs. 33 [29–36] years, respectively; $p < 0.001$; Table 1). The percentage of women with hypertension disorder of pregnancy was lower in the ritodrine than control group (4.7% vs. 21.9%; $p < 0.001$; Table 1). In addition, the ritodrine group had a higher percentage of women administered antenatal steroids (5.6% vs. 1.0%; $p < 0.01$) and a lower percentage undergoing cesarean section (46.5% vs. 60.0%; $p < 0.01$; Table 1).

Table 1
Demographic data and possible risk factors for neonatal hyperkalemia between infants with maternal ritodrine use and without tocolysis.

	Ritodrine n = 213	Control n = 402	Missing value	*P* value
Maternal characteristics				
Maternal age (y.o)	**31 (28–34)**	**33 (29–36)**	**0**	**< 0.001**
Maternal age > 35	**16.4% (n = 35)**	**27.6% (n = 111)**	**0**	**< 0.01**
Primipara	52.6% (n = 112)	51.0% (n = 205)	0	0.71
Multiple pregnancy	33.8% (n = 72)	35.8% (n = 144)	0	0.66
DM/GDM	5.2% (n = 11)	3.0% (n = 12)	0	0.18
pPROM	6.1% (n = 13)	4.5% (n = 18)	0	0.38
HDP/HELLP/AFLP	**4.7% (n = 10)**	**21.9% (n = 88)**	**0**	**< 0.001**
Placental abruption	1.9% (n = 4)	3.3% (n = 13)	0	0.44
Antenatal steroid	**5.6% (n = 12)**	**1.0% (n = 4)**	**0**	**< 0.01**
Cesarean section	**46.5% (n = 99)**	**60.0% (n = 168)**	**0**	**< 0.01**
Neonatal characteristics				
Outborn	0.5% (n = 1)	1.0% (n = 4)	0	0.66
NRFS	15.5% (n = 33)	22.0% (n = 88)	0	0.07
GW at delivery	**35 (35–36)**	**36 (35–36)**	**0**	**< 0.01**
Birth weight (g)	**2236 (1965–2464)**	**2144 (1822–2368)**	**0**	**< 0.01**
SGA	**15.7% (n = 30)**	**23.6% (n = 92)**	**0**	**< 0.05**
LFD	4.2% (n = 9)	2.5% (n = 10)	0	0.32
Male	55.4% (n = 118)	50.5% (n = 203)	0	0.27
Apgar score at 1min < 3	2.8% (n = 6)	4.5% (n = 18)	0	0.39
Neonatal hyperkalemia	**5.6% (n = 12)**	**2.0% (n = 8)**	**0**	**< 0.05**

Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 213 infants with ritodrine use and the 402 infants without tocolysis were examined using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.

DM: diabetes mellitus, GDM: gestational diabetes mellitus, pPROM: preterm premature rupture of membranes, HDP: hypertension disorder of pregnancy, HELLP: hemolysis, elevated liver enzyme, low platelets syndrome, AFLP: acute fatty liver of pregnancy, NRFS: non-reassuring fetal status, GW: gestational week, SGA: small for gestational age, LFD: large for date.

	Ritodrine n = 213	Control n = 402	Missing value	*P* value
Urination at 0 day of life (ml/kg/h)	**2.3 (1.4–3.2)**	**2.5 (1.9–3.3)**	**54**	**< 0.05**
Na^+ (mEq/l)	139 (137–141)	139 (137–142)	1	0.62
K^+ (mEq/l)	**4.7 (4.3–5.1)**	**4.5 (4.1-5.0)**	**0**	**< 0.01**
Calendar year				
2004–2008	**34.7% (n = 69)**	**65.3% (n = 130)**	**0**	**< 0.01**
2009–2013	**26.2% (n = 53)**	**73.7% (n = 149)**	**0**	
2014–2018	**42.3% (n = 91)**	**57.7% (n = 124)**	**0**	
Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 213 infants with ritodrine use and the 402 infants without tocolysis were examined using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.				
DM: diabetes mellitus, GDM: gestational diabetes mellitus, pPROM: preterm premature rupture of membranes, HDP: hypertension disorder of pregnancy, HELLP: hemolysis, elevated liver enzyme, low platelets syndrome, AFLP: acute fatty liver of pregnancy, NRFS: non-reassuring fetal status, GW: gestational week, SGA: small for gestational age, LFD: large for date.				

Infants were delivered at an earlier gestational age in the ritodrine than control group (median [IQR] 35 [35–36] vs. 36 [35–36] weeks, respectively; $p < 0.01$), and the birth weight of newborns in the ritodrine group was greater than that in the control group (median [IQR] 2236 [1965–2464] vs. 2144 [1822–2368] g, respectively; $p < 0.01$; Table 1). In infants, serum K^+ concentrations were higher in the ritodrine than control group (median [IQR] 4.7 [4.3–5.1] vs. 4.5 [4.1–5.0] mEq/L, respectively; $p < 0.01$), and the ritodrine group had a higher frequency of infants with hyperkalemia (5.6% vs. 2.5%; $p < 0.05$; Table 1)

Ritodrine use was lowest (26.2%) in the period 2009–2013 and the highest (42.3%) in the period 2014–2018.

Risk Of Neonatal Rebound Hyperkalemia Following Maternal Ritodrine Use

As indicated in Table 2, the risk of neonatal hyperkalemia was higher for infants in the ritodrine group, with a crude odds ratio (OR) of 2.94 (95% confidence interval [CI] 1.20–7.61; $p < 0.01$); and an adjusted OR in multivariable analysis of 3.79 (95% CI 1.43–10.02; $p < 0.01$). Long-term tocolysis (≥ 28 days) with ritodrine increased the risk of neonatal hyperkalemia, with 8.8% (10/114) of infants developing hyperkalemia (adjusted OR 8.32; 95% CI 2.80–24.79; $p < 0.001$; Table 3).

Table 2
Effects of various risk factors for neonatal hyperkalemia.

Risk factors	Univariate analysis			Multivariable analysis		
	Crude odds ratio (95% CI)		*P*-value	Adjusted odds ratio (95% CI)		*P*-value
Maternal characteristics and management						
Maternal age > 35	2.20	(0.85–5.45)	0.10	**3.17**	**(1.15–8.69)**	**< 0.05**
Ritodrine	**2.94**	**(1.20–7.61)**	**< 0.01**	**3.79**	**(1.43–10.02)**	**< 0.01**
Neonatal characteristics						
Delivery at 36 w	1.00	-	-	1.00	-	-
35 w	1.95	(0.67–6.02)	0.21	1.58	(0.53–4.74)	0.41
34 w	2.26	(0.69–7.35)	0.17	2.00	(0.62–6.51)	0.25
Calendar year						
2004–2008	1.53	(0.48–5.24)	0.47	2.09	(0.60–7.28)	0.25
2009–2013	1.74	(0.57–5.85)	0.33	2.21	(0.69–7.14)	0.18
2014–2018	1	-	-	1	-	-

Those variables for which differences are significant are in bold font. Multivariate analysis was adjusted by the following variables: maternal aged > 35, ritodrine use, categorical gestational weeks, and calendar year with five years interval.

(CI: confidence interval)

Table 3
Effects of the duration of ritodrine administration for neonatal hyperkalemia

Duration of ritodrine administration	**Incidence of hyperkalemia**	**Crude odds ratio (95% CI)** **P-value**	**Adjusted odds ratio (95% CI)** **P-value**
no usage	2.0% (8/402)	1.00	1.00
< 48h	0.0% (0/17)	-	-
2 to 13 days	0.0% (0/40)	-	-
14 to 27 days	3.7% (1/26)	1.89 (0.23–15.8) P = 0.58	2.02 (0.22–18.57) P = 0.53
≧ 28 days	**8.8% (10/114)**	**4.73 (1.82–12.29)** **P < 0.01**	**8.32 (2.80-24.79)** **P < 0.001**

Multivariate analysis was adjusted by the following variables: maternal aged > 35, duration of ritodrine administration, categorical gestational weeks, i, and calendar year with five years interval. (CI: confidence interval)

One of the 20 neonates with neonatal hyperkalemia died of respiratory failure [14](Table 4). This infant developed neonatal acute respiratory distress syndrome after being resuscitated for severe arrhythmia and cardiac arrest caused by hyperkalemia associated with maternal ritodrine [14]. The characteristics of infants and their mothers according to the presence of neonatal hyperkalemia are summarized in Table 4.

Table 4
Demographic data of neonatal hyperkalemia between infants with and without neonatal hyperkalemia.

	Neonatal hyperkalemia **n = 20**	***Non-hyperkalemia*** **n = 595**	**Missing value**	***P* value**
Maternal characteristics				
Maternal age (y.o)	33 (30–37)	32 (29–35)	0	0.29
Maternal age > 35	40.0% (n = 8)	23.2% (n = 138)	0	0.10
Primipara	50.0% (n = 10)	51.6% (n = 307)	0	0.89
Multiple pregnancy	45% (n = 9)	34.8% (n = 207)	0	0.35
DM/GDM	10.0% (n = 2)	3.5% (n = 21)	0	0.17
pPROM	0.0% (n = 0)	5.2% (n = 31)	0	0.62
HDP/HELLP/AFLP	10.0% (n = 2)	16.1% (n = 96)	0	0.75
Placental abruption	0.0% (n = 0)	2.9% (n = 17)	0	1.00
Ritodrine	**60.0% (n = 12)**	**33.8% (n = 201)**	**0**	**< 0.05**
Antenatal steroid	0.0% (n = 0)	2.7% (n = 16)	0	1.00
Cesarean section	65.0% (n = 13)	55.0% (n = 327)	0	0.37
Neonatal characteristics				
Outborn	5.0% (n = 1)	0.7% (n = 4)	0	0.16
NRFS	**0.0% (n = 0)**	**20.4% (n = 121)**	**0**	**< 0.05**
GW at delivery	35 (34–36)	36 (35–36)	0	0.13
Birth weight (g)	2170 (1908–2519)	2178 (1902–2394)	0	0.58
SGA	10.0% (n = 2)	20.2% (n = 120)	0	0.39
LFD	0.0% (n = 0)	3.2% (n = 19)	0	1.00
Male	50.0% (n = 10)	52.3% (n = 311)	0	0.84
Apgar score at 1min < 3	5.0% (n = 1)	3.9% (n = 23)	0	0.55

Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 20 infants with neonatal hyperkalemia and the 595 infants without hyperkalemia were examined using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.

DM: diabetes mellitus, GDM: gestational diabetes mellitus, pPROM: preterm premature rupture of membranes, HDP: hypertension disorder of pregnancy, HELLP: hemolysis, elevated liver enzyme, low platelets syndrome, AFLP: acute fatty liver of pregnancy, NRFS: non-reassuring fetal status, GW: gestational week, SGA: small for gestational age, LFD: large for date.

	Neonatal hyperkalemia n = 20	*Non-hyperkalemia* n = 595	Missing value	*P* value
Urination at 0 day of life (ml/kg/h)	**1.1 (0.7–2.6)**	**2.5 (1.8–3.3)**	**57**	**< 0.01**
Na^+ (mEq/l)	**135 (131–137)**	**139 (137–141)**	**0**	**< 0.0001**
K^+ (mEq/l)	**6.4 (6.3–6.8)**	**4.5 (4.2-5.0)**	**0**	**< 0.0001**
Mortality	5.0% (n = 1)	0.5% (n = 3)	0	0.12
Calendar year				
2004–2008	3.5% (n = 7)	96.5% (n = 192)	0	0.62
2009–2013	4.0% (n = 8)	96.0% (n = 194)	0	
2014–2018	2.3% (n = 5)	97.7% (n = 210)	0	

Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 20 infants with neonatal hyperkalemia and the 595 infants without hyperkalemia were examined using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.

DM: diabetes mellitus, GDM: gestational diabetes mellitus, pPROM: preterm premature rupture of membranes, HDP: hypertension disorder of pregnancy, HELLP: hemolysis, elevated liver enzyme, low platelets syndrome, AFLP: acute fatty liver of pregnancy, NRFS: non-reassuring fetal status, GW: gestational week, SGA: small for gestational age, LFD: large for date.

Discussion

This study shows, for the first time, that long-term tocolysis with betamimetic increases the risk of neonatal hyperkalemia in late preterm infants. Late preterm infants are known to have increased risks of apnea, hypoglycemia, transient tachypnea of the newborn, insufficient feeding, longer hospitalization and neurological impairment [19]. As a result, tocolysis is often continued to near term, and there are no recommendations in the clinical guidelines issued by the Japan Society of Obstetrics and Gynecology as to the optimal gestational age at which tocolysis should be discontinued [10, 20]. The Cause Analysis Committee for Cerebral Palsy of the Japan Council for Quality Health Care has also suggested that hyperkalemia in neonates born to mothers receiving ritodrine and/or $MgSO_4$ may cause cerebral palsy [21]. Therefore, the association between neonatal hyperkalemia and maternal ritodrine demonstrated in this study is very important for clinical practice in Japan.

Because most infants with neonatal hyperkalemia in the present study were born at Tokushima University Hospital, were admitted to the NICU or GCU with early examination, and were treated with gluconate calcium or a glucose–insulin infusion, they did not develop arrhythmia. However, one infant born at another hospital developed serious arrhythmia, suggesting that neonatal hyperkalemia may cause sudden unexpected neonatal death [22]. This infant was born at a local obstetric hospital and was transferred to the NICU of Tokushima

University Hospital with bag valve mask ventilation and chest compression performed by an obstetrician because of sudden cardiac arrest and ventricular fibrillation to ventricular tachycardia [14].

The etiology of neonatal hyperkalemia is assumed to be as follows. First, ritodrine passes through the placenta and stimulates fetal pancreatic β-cells, promoting insulin secretion and thereby increasing the uptake of extracellular potassium into the cells [2]. Then, when the transplacental passage of ritodrine is interrupted at birth, insulin secretion decreases and potassium starts to flow out of the cells. This proposed etiology is supported by the results of a single-center retrospective study in which serum potassium concentrations 12–24 h after birth were significantly higher in a group of neonates whose mothers had been administered ritodrine than in a non-tocolytic group [23]. However, rebound inhibition of insulin has not been directly proven in previous human and animal studies, so this point requires the further investigation.

The present study has several limitations. First, because this was a retrospective study, the results may have been affected by selection bias. In all, 85 cases were excluded because of missing data, and the peak in serum potassium concentrations may have been missed because the timing of blood examinations was at the discretion of individual clinicians. Second, this study did not examine the effects of maternal $MgSO_4$ use at 34–36 weeks gestation on the risk of neonatal hyperkalemia. Third, because this was a single-center cohort study, further larger studies are required to determine the risk of neonatal hyperkalemia due to ritodrine in late preterm infants. Finally, although a previous nation-wide study in Japan showed that the combined use of ritodrine and $MgSO_4$ increased the risk of neonatal hyperkalemia in infants born at 32–36 weeks gestation [13], the concomitant use of ritodrine and $MgSO_4$ is more common for infants born at 32–33 weeks of gestation. However, these infants are generally admitted to the NICU and undergo careful electrolytes monitoring. A secondary investigation limited to infants born at 34–36 weeks gestation may be useful.

In conclusion, late preterm infants born to mothers administered long-term ritodrine are at risk of neonatal hyperkalemia. Therefore, we recommend serum potassium measurements and electrocardiogram monitoring of newborns whose mothers have been administered ritodrine over a long period of time.

Declarations

Ethics approval and consent to participate

The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Tokushima University Hospital (IRB number. 3755). In order to access the medical record used in the study, the administrative permission is required, and the authority is granted by the institutional review board of Tokushima University Hospital, Tokushima, Japan (IRB number. 3755). The authors notified information concerning the research, including the purpose of utilization of information utilized in the research, and opportunities to refuse that the research is implemented shall be ensured for the research subjects to participants and their guardians on Tokushima University website ((http://www.tokushima-hosp.jp/about/disclosure_document.html) in accordance with the " Ethical Guidelines for Medical and Biological Research Involving Human Subjects". The Review Board of the Ethics committee of Tokushima University Hospital approved the opt-out consent option for this retrospective study.

Consent for publication

Not applicable.

Availability of data and materials

Data are available upon reasonable request. The authors are not authorized to share unauthorized data with a third party. However, data for statistical analysis are available from the corresponding author on reasonable request.

Competing interests

Th authors have no conflicts of interest relevant to this article to disclose.

Funding

This study did not receive any specific funding.

Authors' contributions

Writing the first draft and manuscript revision: KS; statistical advice and methodology: YW, MU; data collection and analysis: CK, MT, ST, KO, SM; research supervision: RN, SK. All authors revised the manuscript and agreed to its submission.

Acknowledgements

The authors are indebted to the clinicians at Tokushima University Hospital who care for the infants and their families. The authors thank ELSS (https://www.elss.co.jp/) for English language editing of this manuscript.

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Figures

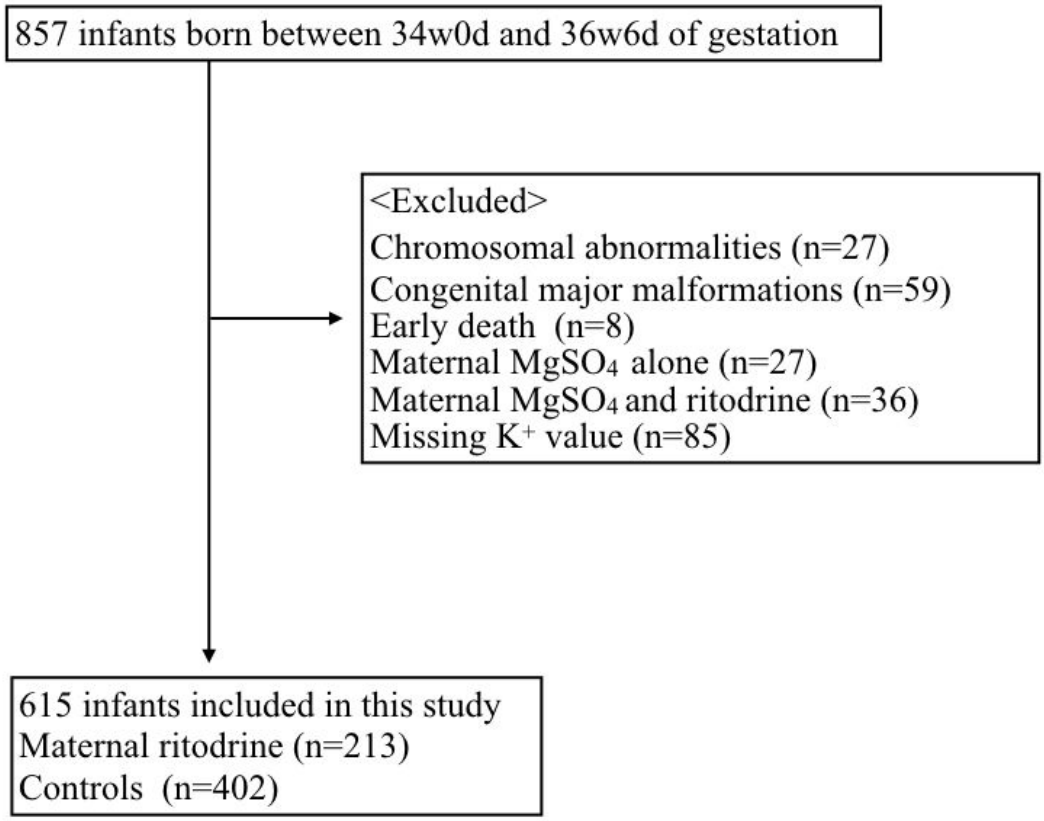

Figure 1

Enrollment flowchart