

Association between maternal ritodrine hydrochloride administration during pregnancy and childhood wheezing up to three years of age: The Japan environment and children's study

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Abstract

Background: The effects of maternal ritodrine hydrochloride administration (MRA) during pregnancy on fetuses and offspring are not entirely clear. The present study aimed to evaluate the association between MRA and childhood wheezing using data from a nationwide Japanese birth cohort study.

Methods: This study analyzed the data of the participants enrolled in the Japan Environment and Children's Study, a nationwide prospective birth cohort study, between 2011 and 2014. Data of women with singleton live births after 22 weeks of gestation were analyzed. The participants were divided according to MRA status. Considering childhood factors affecting the incidence of wheezing, including smoking environment and childhood viral infections, a logistic regression model was used to calculate odds ratios for "wheezing ever," diagnosis of asthma in the last 12 months, and "asthma ever" in women with MRA, with women who did not receive MRA as the reference. Additionally, participants were stratified by term births, and odds ratios for outcomes were calculated using a logistic regression model.

Results: A total of 68,123 participants were analyzed. The adjusted odds ratio for wheezing was 1.17 (95% confidence interval, 1.12–1.22). The adjusted odds ratios for the other outcomes did not significantly increase after adjusting for childhood factors. The same tendency was confirmed after excluding women with preterm births.

Conclusion: MRA was associated with a slightly increased incidence of childhood wheezing up to three years, irrespective of term or preterm birth status. It is important that perinatal physicians consider the potential effects of MRA on the offspring's childhood health.

KEYWORDS

birth cohort study, childhood asthma, childhood wheezing, preterm birth, ritodrine, tocolysis

1 | INTRODUCTION

Ritodrine hydrochloride is used as a beta-sympathomimetic agent for controlling unfavorable uterine contractions. It predominantly interacts with beta-2 receptors in the uterus, resulting in the suppression of uterine contractions.¹ It has been used to treat preterm labor (PTL), achieving a lower rate of preterm births (PTB) and lower incidence of neonatal and childhood PTB-related issues, such as respiratory distress syndrome and intraventricular hemorrhage.¹⁻⁴ Most Japanese obstetricians select ritodrine hydrochloride as the first drug for tocolysis in patients with PTL,⁵ as per obstetric practice guidelines in Japan.^{6,7} In Japan, recent studies have shown that approximately 40% of women with PTL and 80% of women with PTL on admission received maternal ritodrine hydrochloride administration (MRA) intravenously.^{4,5} As MRA is approved for administration between 16 and 36 weeks of gestation, the mean gestational age for initiating MRA was 30 weeks.⁵ However, MRA is reported to be effective within 48 h of use, and long-term MRA is reported to be harmful due to its adverse maternal side effects, such as pulmonary edema, granulocytopenia, and rhabdomyolysis.^{5,8-10}

Additionally, fetal tachycardia is a side effect of MRA.^{11,12} However, the clinical significance of this change and the other potential effects of MRA on offspring remain unclear. Moreover, although childhood asthma was reported as a side effect of MRA,¹³ the biological mechanism involved in MRA and offspring asthma or wheezing remains unclear. Furthermore, childhood factors such as smoking environment and childhood viral infections that are reported to have associations with the incidence of childhood asthma¹⁴⁻¹⁶ have not been evaluated. Because asthma is common during childhood, with approximately 10% prevalence in Japan,^{17,18} parents are concerned about the association between prenatal and postnatal factors and the incidence of childhood asthma; therefore, the association of MRA with childhood asthma should be clarified.

Objective diagnosis of childhood asthma is often challenging because its clinical presentation is heterogeneous.¹⁹ Therefore, the present study evaluated the association between MRA and childhood wheezing up to 3 years of age and the diagnosis of childhood asthma using a nationwide Japanese birth cohort dataset.

2 | METHODS

2.1 | Study design

The present study analyzed data from the Japan Environment and Children's Study (JECS), a nationwide, government-funded, prospective birth cohort study initiated in January 2011 that investigated the effects of environmental factors on children's health.^{20,21} Briefly, the JECS is directly funded by the Ministry of the Environment, Japan, and involves collaboration between the Programme Office (ie, National Institute for Environmental Studies), Medical Support Centre (ie, National Center for Child Health and Development), and 15 Regional Centres (namely Hokkaido, Miyagi, Fukushima, Chiba,

Key Message

The effects of maternal ritodrine hydrochloride administration during pregnancy on fetuses and offspring are not entirely clear. The present study revealed maternal ritodrine hydrochloride administration was associated with an increased incidence of childhood wheezing up to three years. It is important that perinatal physicians consider the potential effects of maternal ritodrine hydrochloride administration on the offspring's childhood health.

Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyushu/Okinawa).^{20,21} Expectant mothers who resided in the study areas at the time of recruitment and were expected to continually reside in Japan in the foreseeable future; had an expected delivery date from 1 August 2011 until mid-2014; and were capable of participating in the study without difficulty (i.e., adequate Japanese language comprehension to complete the self-administered questionnaire) were considered eligible for inclusion in the JECS.

The following recruitment strategies were used: recruitment at the first prenatal examination in cooperating healthcare providers and recruitment in local government offices issuing pregnancy journals called Maternal and Child Health Handbooks, which are provided to all expectant mothers in Japan before they receive municipal services for pregnancy, delivery, and childcare. In this study, pregnant women were contacted through cooperating healthcare providers and/or local government offices issuing the handbooks, and those who were willing to participate were subsequently registered. Women completed the self-administered questionnaires during their first and second or third trimester and provided information on demographic factors, medical/obstetric history, physical and mental health, lifestyle, occupation, environmental exposure at home and in the workplace, housing conditions, and socioeconomic status.^{20,21} The median gestational age at enrollment was 12 weeks (interquartile range: 10–16 weeks).

2.2 | Data collection

The 2019 dataset (dataset: jecs-ta-20190930) was used. Specifically, the following types of data were utilized: M-T1, from a self-administered questionnaire completed during the first trimester (first questionnaire), including questions about the maternal medical background; M-T2, from a self-administered questionnaire completed during the second or third trimester (second questionnaire), including information on partner lifestyle and socioeconomic status; Dr-T1 and Dr-0m, from medical record transcripts that were provided by each participant's institution, including information on obstetric outcomes (e.g., gestational age, neonatal birthweight) collected during the first, second, and third trimesters. Medical record

transcripts were performed by physicians, midwives/nurses, and/or research coordinators; C1Y, C2Y, and C3Y were obtained from self-administered questionnaires collected at one, two, or three years after birth, respectively, including descriptions about the infants' allergic diseases and information on childhood environment, including smoking environment, milk feeding, and pet ownership.

Participants with singleton pregnancies after 22 weeks were included in analysis. We excluded those with multiple pregnancies, abortions, stillbirths, and deliveries with missing data. Furthermore, since all missing data were judged to be independent from the exposure and the outcome, we used complete case analysis (CCA). There were no significant differences in characteristics between included and excluded participants (data not shown).

2.3 | Exposure variables

Data on MRA were collected from medical record transcripts. Participants who received MRA intravenously or orally were defined as participants who received MRA, regardless of time point, dosage, duration, and method of MRA; in the JECS, there was no information regarding them.

2.4 | Obstetric outcomes and confounding factors

Outcomes included three variables, namely "wheezing ever," diagnosis of asthma in the last 12 months, and "asthma ever." "Wheezing ever" and "asthma ever" were based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.^{13,22-24} Information regarding "wheezing ever," diagnosis of asthma in the last 12 months, and "asthma ever" were obtained from the questions, "Has your child ever had wheezing or whistling in the chest at any time in the past," "Does your child have immune system disorder diagnosed after age 2: Asthma," and "Has your child ever had asthma," respectively.

The following items were analyzed as potential confounding factors during pregnancy: maternal age, maternal body mass index (BMI) before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, PTB before 37 weeks, low-birth-weight (LBW) infants (<2500 g) (gestational age and neonatal birthweight as continuous values were also used as confounding factors instead of PTB and LBW infants, respectively), maternal asthma, and intrauterine infection (IUI). The following items were analyzed as potential confounding factors during childhood: smoking environment, milk feeding at one-year-old, male newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood respiratory syncytial virus infection or lower respiratory infection (childhood viral infections). These confounding factors were selected based on clinical importance.^{14-16,25-29}

Maternal participants were divided into three age groups when reporting childbirth details (nearly equal to the age at childbirth): <20,

20–34, and ≥35 years.^{30,31} Maternal BMI before pregnancy was categorized³² as <18.5, 18.5–24.9, and ≥25.0 kg/m². Parity was categorized as nulliparous and multiparous. Maternal participants provided information about their smoking status by choosing one of the following: "Currently smoking," "Never," "Previously did, but quit before realizing current pregnancy," and "Previously did, but quit after realizing current pregnancy." The smoking category included those who chose "Currently smoking," whereas the non-smoking category consisted of the remainder. Based on the number of years of education, maternal educational status was categorized into junior high school, <10 years; high school, 10–12 years; technical/vocational college or university, 13–16 years; and graduate school, ≥17 years. Annual household income was categorized into <2,000,000, 2,000,000–5,999,999, 6,000,000–9,999,999, and ≥10,000,000 JPY. Mode of delivery was divided into vaginal deliveries and cesarean section based on medical record transcripts. PTB was defined as childbirth before 37 weeks, and LBW infant was weight <2500 g at childbirth. Maternal asthma was defined from the information collected in the first-trimester questionnaire. Paternal asthma was not considered owing to a large amount of missing data. IUI data were derived from medical record transcripts. IUI was clinically diagnosed by physicians at each institution. There were no unified criteria for IUI in the JECS; however, most Japanese obstetricians refer to the criteria recommended in the guidelines for obstetrical practice in Japan (ie, maternal fever and one of the following: maternal tachycardia beyond 100 beats/min, uterine tenderness, abnormal discharge, or elevated maternal white blood cell counts beyond 15,000/μl).³³ Smoking environment, milk feeding, male newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood viral infections were defined according to the questionnaire as yes/no questions; data on milk feeding were collected through the questionnaire administered at one year after childbirth; data on childhood viral infections were collected through the questionnaire administered at two years after childbirth; and other data were collected using the questionnaire administered at three years after childbirth.

2.5 | Statistical analysis

Participants' characteristics were summarized based on MRA status. The chi-square test was used to compare the characteristics (expressed as categorical variables) between the groups. A multiple logistic regression model was used to calculate the crude odds ratios (cORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs) for "wheezing ever," diagnosis of asthma in the last 12 months, and "asthma ever" in women with MRA with women who did not receive MRA as the reference. In Model 1, odds ratios (ORs) were adjusted for potential confounding factors during pregnancy. In Model 2, ORs were adjusted for potential confounding factors during childhood, except for childhood viral infection, in addition to those during pregnancy. In Model 3', ORs were adjusted for potential confounding factors during childhood in addition to those during pregnancy. In Model 3', analysis was performed using

gestational age at delivery and neonatal birthweight as confounding factors rather than PTB and LBW infants, respectively. The difference of confounders used between Model 2 and 3 was based on the idea that the impact of childhood viral infection was the strongest causal factor.^{28,29}

Additionally, participants, excluding those with PTB, were analyzed using a multiple logistic regression model with women who did not receive MRA as the reference and adjusting for confounding factors in Models 1, 2, and 3; here, PTB was removed from the confounding factors.

Statistical analysis was performed using SPSS version 26 (IBM Corp.). $p < .05$ was considered statistically significant.

3 | RESULTS

There were 104,062 fetal records in the JECS, and 68,123 participants met the study inclusion criteria (Figure 1). Missing data were

due to incomplete questionnaire data or medical record transcripts data; detailed information is shown in Figure 1. Herein, 18,141 (26.6%) participants received MRA (MRA group), whereas the remaining 49,982 (73.4%) participants comprised the reference group. After excluding 2,989 participants with PTB, 16,560 (25.4%) participants received MRA, and the remaining 48,574 (74.6%) participants comprised the reference group.

Table 1 summarizes the demographic and clinical characteristics of participants based on MRA status. The difference of confounding factors between the groups was significant, except for the distribution of maternal age and maternal educational status and the ratio of parity and childhood eczema. The ratio of all outcome measures was significantly higher in the MRA group than in the reference group.

Table 2 presents the cORs and aORs for “wheezing ever,” diagnosis of asthma in the last 12 months, and “asthma ever.” The cORs and aORs for all outcomes in Models 1 and 2 significantly increased compared to those in the reference group. Although aORs

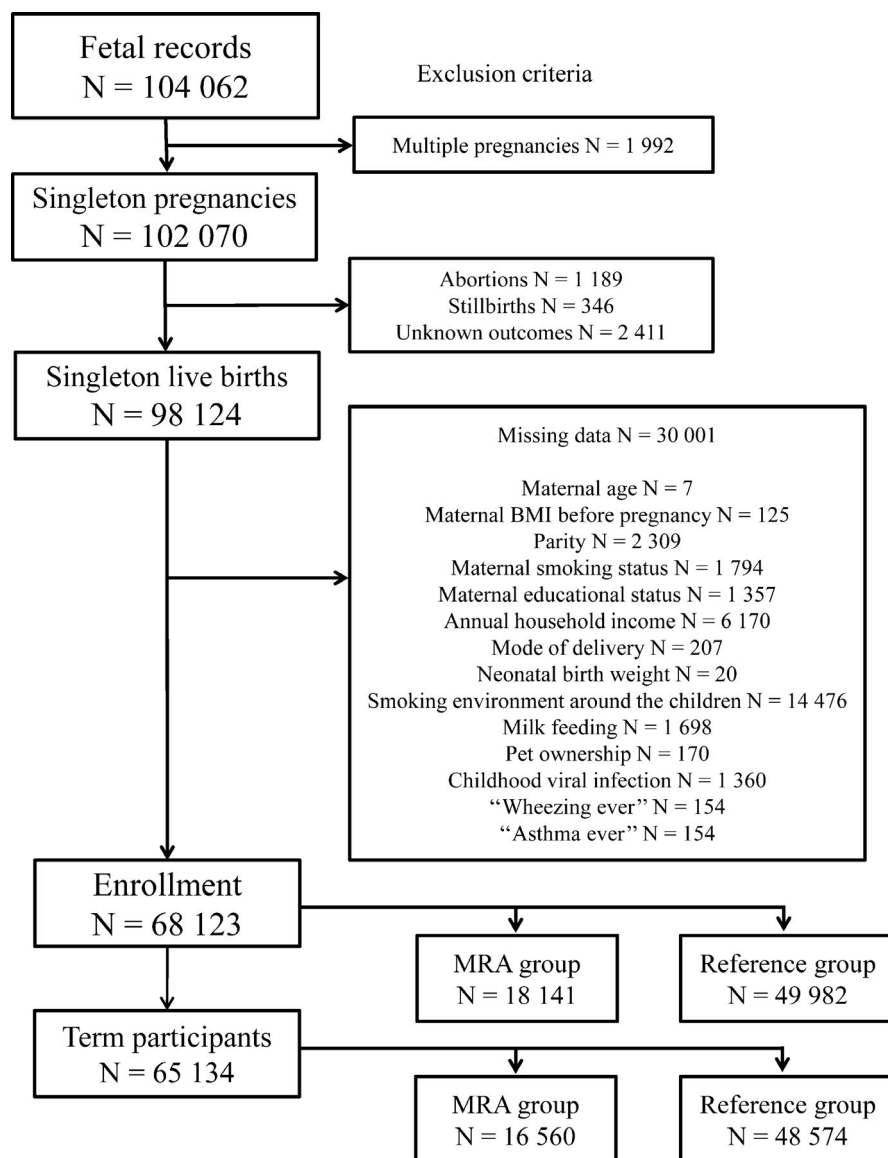


FIGURE 1 Study enrollment flowchart. BMI, Body mass index; MRA, Maternal ritodrine hydrochloride administration

TABLE 1 Demographic and clinical characteristics of participants stratified by MRA status

Variable	Total participants <i>n</i> = 68,123	MRA group <i>n</i> = 18,141	Reference group <i>n</i> = 49,982	<i>p</i> value
Maternal age, % (<i>n</i>)				.075
<20 years	0.4 (247)	0.4 (76)	0.3 (171)	
20–34 years	70.6 (48,125)	71.1 (12,899)	70.5 (35,226)	
≥35 years	29.0 (19,751)	28.5 (5,166)	29.2 (14,585)	
Maternal BMI before pregnancy, % (<i>n</i>)				<.001
<18.5 kg/m ²	15.9 (10,859)	18.5 (3,348)	15.0 (7,511)	
18.5–24.9 kg/m ²	74.1 (50,508)	72.5 (13,148)	74.7 (37,360)	
≥25.0 kg/m ²	9.9 (6,756)	9.1 (1,645)	10.2 (5,111)	
Nulliparous, % (<i>n</i>)	41.6 (28,337)	41.4 (7,513)	41.7 (20,824)	.561
Maternal smoking during pregnancy, % (<i>n</i>)	3.5 (2,401)	3.8 (693)	3.4 (1,708)	.012
Maternal educational status, % (<i>n</i>)				.315
<10 years	3.4 (2,320)	3.5 (633)	3.4 (1,687)	
10–12 years	29.1 (19,828)	29.4 (5,339)	29.0 (14,489)	
13–16 years	65.9 (44,872)	65.6 (11,895)	66.0 (32,977)	
>17 years	1.6 (1,103)	1.5 (274)	1.7 (829)	
Annual household income, % (<i>n</i>)				<.001
<2,000,000 JPY	4.8 (3,290)	4.6 (840)	4.9 (2,450)	
2,000,000–5,999,999 JPY	67.4 (45,930)	66.3 (12,024)	67.8 (33,906)	
6,000,000–9,999,999 JPY	23.3 (15,896)	24.4 (4,430)	22.9 (11,466)	
>10,000,000 JPY	4.4 (3,007)	4.7 (847)	4.3 (2,160)	
Cesarean section, % (<i>n</i>)	18.5 (12,627)	21.8 (3,962)	17.3 (8,665)	<.001
Preterm births, % (<i>n</i>)	4.4 (2,989)	8.7 (1,581)	2.8 (1,408)	<.001
Low-birthweight infants, % (<i>n</i>)	7.7 (5,244)	11.1 (2,009)	6.5 (3,235)	<.001
Maternal asthma, % (<i>n</i>)	10.5 (7,144)	11.5 (2,088)	10.1 (5,056)	<.001
Intrauterine infection, % (<i>n</i>)	0.6 (391)	0.7 (132)	0.5 (259)	.001
Smoking environment around the children, % (<i>n</i>)	18.8 (12,811)	19.7 (3,567)	18.5 (9,244)	.001
Milk feeding at one year old, % (<i>n</i>)	46.2 (31,492)	48.5 (8,807)	45.4 (22,685)	<.001
Male newborn, % (<i>n</i>)	51.1 (34,782)	51.8 (9,397)	50.8 (25,385)	.020
Childhood eczema, % (<i>n</i>)	7.4 (5,013)	7.7 (1,392)	7.2 (3,621)	.058
Childhood rhinitis, % (<i>n</i>)	4.6 (3,150)	4.9 (887)	4.5 (2,263)	.047
Pet ownership, % (<i>n</i>)	17.4 (11,860)	18.3 (3,314)	17.1 (8,546)	<.001
Childhood viral infection, % (<i>n</i>)	12.8 (8,741)	14.9 (2,708)	12.1 (6,033)	<.001
Wheezing ever, % (<i>n</i>)	30.2 (20,541)	33.5 (6,080)	28.9 (14,461)	<.001
Diagnosis of asthma in the last 12 months, % (<i>n</i>)	7.5 (5,128)	8.3 (1,505)	7.2 (3,623)	<.001
Asthma ever, % (<i>n</i>)	9.7 (6,624)	10.6 (1,929)	9.4 (4,695)	<.001

Abbreviations: BMI, Body mass index; JPY, Japanese yen; MRA, Maternal ritodrine administration.

for “wheezing ever” in Model 3 and 3’ significantly increased, aORs for the other outcomes did not significantly increase.

Table 3 presents the cORs and aORs for “wheezing ever,” diagnosis of asthma in the last 12 months, and “asthma ever” in participants without PTB. The cORs and aORs for all outcomes in Models 1 and 2 significantly increased compared to those in the reference group. Although aOR for “wheezing ever” in Model 3 significantly increased, aORs for the other outcomes did not significantly increase.

4 | DISCUSSION

In summary, MRA was associated with an increased incidence of childhood wheezing in children up to 3 years of age even considering childhood factors; however, there was only a slight increase in aOR, and aORs for diagnosis of childhood asthma did not increase. In a recent study, there was a significant association between MRA and childhood asthma, considering confounding factors during pregnancy.¹³ This previous study concluded that exposure to ritodrine

	Wheezing ever	Diagnosis of asthma in the last 12 months	Asthma ever
Childhood outcomes	Odds ratios (95% CI)		
Ritodrine hydrochloride usage			
cORs	1.24 (1.19–1.28)	1.16 (1.09–1.23)	1.15 (1.09–1.21)
aORs (Model 1)	1.20 (1.16–1.25)	1.12 (1.05–1.19)	1.11 (1.05–1.17)
aORs (Model 2)	1.19 (1.15–1.24)	1.10 (1.03–1.17)	1.09 (1.03–1.15)
aORs (Model 3)	1.16 (1.11–1.20)	1.06 (0.99–1.13)	1.06 (0.99–1.12)
aORs (Model 3')	1.15 (1.11–1.20)	1.05 (0.98–1.12)	1.05 (0.99–1.11)

Abbreviations: aOR, Adjusted odds ratio; CI, Confidence interval; cOR, crude odds ratio.

Note: In Model 1, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low-birthweight infants (below 2500 g), maternal asthma, and intrauterine infection

In Model 2, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low-birthweight infants, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn, childhood eczema, childhood rhinitis, and pet ownership

In Model 3, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low-birth-weight infants, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood viral infection

In Model 3', Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, gestational age of delivery, neonatal birthweight, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood viral infection

TABLE 2 Odds ratios for outcomes in the maternal ritodrine administration group

	Wheezing ever	Diagnosis of asthma in the last 12 months	Asthma ever
Childhood outcomes	Odds ratios (95% CI)		
Ritodrine hydrochloride usage			
cORs	1.21 (1.17-1.26)	1.13 (1.06-1.21)	1.13 (1.06-1.19)
aORs (Model 1)	1.20 (1.16-1.25)	1.11 (1.04-1.19)	1.11 (1.05-1.18)
aORs (Model 2)	1.19 (1.14-1.24)	1.10 (1.02-1.17)	1.09 (1.03-1.16)
aORs (Model 3)	1.16 (1.11-1.20)	1.06 (0.99-1.13)	1.06 (0.99-1.13)

Abbreviations: aOR, Adjusted odds ratio; CI, Confidence interval; cOR, crude odds ratio.

Note: In Model 1, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, low-birthweight infants (below 2500 g), maternal asthma, and intrauterine infection

In Model 2, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, low-birthweight infants, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn, childhood eczema, childhood rhinitis, and pet ownership

In Model 3, Multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity, maternal smoking status, maternal educational status, annual household income, mode of delivery, low-birthweight infants, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood viral infection

TABLE 3 Odds ratios for outcomes in the maternal ritodrine administration group without preterm births

hydrochloride *in utero* was a risk factor for childhood asthma, with a dose-dependent association. In contrast, considering childhood factors like strong determinants of the incidence of childhood wheezing^{14–16} as confounders, we found an association between MRA and the incidence of childhood wheezing, although MRA seemed to affect just the fetal condition during pregnancy. The association between MRA and the increased incidence of childhood asthma was not confirmed after adjusting for childhood viral infection. In our univariable analysis, significant associations were noted between MRA status and childhood confounders that strengthened the validity of the use of these factors as confounding factors. Immune responses to airway exposures, including tobacco smoke, allergens, and viruses, can stimulate prolonged pathogenic inflammation and aberrant repair of injured pulmonary tissues.

As another strength, the present study analyzed both total participants with term births and PTB and stratified participants with term births. The previous study excluded participants with PTB before 34 weeks and did not perform stratification.¹³ Since PTB was independently positively associated with childhood asthma,²⁵ the stratified analysis strengthened the association between MRA and incidence of childhood wheezing, regardless of gestational age of birth. The reason why PTB increased the likelihood of childhood wheezing is unclear; however, long-term bronchopulmonary dysplasia may increase impedance and resistance of the small airways.^{34,35} Regarding term births in which gestational age was forcefully prolonged by MRA, infants from mothers who received long-term MRA might have suffered from “excessive” uterine contractions that were not completely controlled by MRA; this may result in fetal stress and influence the secretion of fetal pituitary adrenocorticotrophic hormone, potentially leading to future asthma development in the offspring.³⁶

The biological mechanism of MRA on childhood wheezing remains unclear; the underlying mechanism regarding the MRA-associated childhood wheezing may be associated with pathological impairment in the trachea of children, hyper-responsiveness, and beta-receptor desensitization.^{37–39} As maternal inflammation increases the risk of childhood asthma via maternal type-2 cytokines in maternal asthma cases,⁴⁰ IUI, which frequently coexists in mothers with PTL, may affect the incidence of childhood wheezing by changing the maternal and the child's inflammatory condition.

The present study has some limitations. First, diagnosis of childhood asthma is often unsatisfactory¹⁹; the diagnosis of asthma may be less accurate than “wheezing ever” because of the ambiguities regarding the classification and diagnosis of childhood asthma. Results should be interpreted carefully. Second, this study did not include data regarding the time point, dosage, duration, and method of administration (intravenous or oral) of MRA use. Characteristics of women with earlier uterine contractions in PTL may be substantially different from those of women having PTL closer to term. Additionally, since a dose-dependent effect of MRA on childhood asthma was reported,¹³ the dosage and duration of MRA may significantly impact the grade of childhood effects. In this study, we

could not clarify a cause-and-effect relationship. Third, there were unmeasured confounding factors that have not been fully discussed. Detailed data on daily maternal drug use, including anti-asthmatic medications, antioxidative supplements, and antipyretic analgesics, were not considered. Similarly, the present study did not include data on PTL severity, such as cervical dilatation, frequency of uterine contractions, fetal fibronectin, or IUI severity. Finally, CCA performed in this study may have led to potentially biased results. Although CCA was judged to be suitable because the missing data were not jointly dependent of exposure and outcome^{41,42} and there were no significant differences in characteristics between included and excluded participants, careful interpretation of results may be needed.

In conclusion, MRA was associated with an increased incidence of childhood wheezing, regardless of term births or PTB, although this impact was slight. Further studies are needed to clarify the relationship between MRA and the incidence of childhood wheezing while considering the dosage and duration of MRA, clinical factors regarding PTL, and biological effects of MRA on fetuses. It is important that perinatal physicians consider the potential effects of MRA on the offspring's childhood health.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTION

Tsuyoshi Murata: Conceptualization (equal); Formal analysis (equal); Writing-original draft (equal). **Hyo Kyojuka:** Validation (supporting). **Shun Yasuda:** Validation (supporting). **Toma Fukuda:** Validation (supporting). **Akiko Yamaguchi:** Validation (supporting). **Hajime Maeda:** Validation (supporting). **Akiko Sato:** Data curation (equal); Validation (equal). **Yuka Ogata:** Data curation (equal); Validation (equal). **Kosei Shinoki:** Data curation (equal); Validation (equal). **Mitsuaki Hosoya:** Validation (equal); Writing-review

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ETHICAL APPROVAL

The JECS was conducted according to the Declaration of Helsinki and local regulations. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (100910001) and by the ethics committees of all participating institutions. All participants provided written informed consent.

PEER REVIEW

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