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Association between the prolonged use of magnesium sulfate for tocolysis and fracture risk among infants

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Abstract

In 2013, the U.S. Food and Drug Administration issued a safety warning that cautioned against using magnesium sulfate ($MgSO_4$) injections for more than 5 to 7 days to stop preterm delivery due to the bone problems subsequently observed in infants. However, the warning was mainly based on case reports, and further investigation is necessary to determine whether prolonged $MgSO_4$ use increased infant fractures.

To evaluate whether prolonged $MgSO_4$ use for tocolysis increased the risk of subsequent fractures among infants.

A retrospective population-based cohort study was conducted with a new-user study design using the National Health Insurance Database in Taiwan. We included pregnant women aged between 12 and 55 years old who delivered a live-born singleton. The enrollment period was from January 1, 2012 to December 31, 2014. The exposure group was defined as pregnant women who received $MgSO_4$ injection for >5 days during pregnancy, while those not receiving any tocolytics were the reference group. The outcome was any bone fracture among the infants during the 2-year follow-up period. Propensity score matching and Cox proportional hazards regression models were used to estimate the hazard of fractures. We further studied the effect of $MgSO_4$ treatment with varied dosages and durations of treatment in the sensitivity analyses.

Among the 4092 pregnant women in the database, 693 (16.9%) of them were included in the exposure group. The hazard ratio of infant fractures among prolonged $MgSO_4$ users was not significantly different from that of tocolytic nonusers in adjusted models (adjusted hazard ratio (aHR) = 1.48; 95% confidence interval (CI) = 0.59–3.71). A similar lack of significance was found in the sensitivity analyses (aHR = 1.45; 95% CI = 0.40–5.28 for larger treatment dosage; aHR = 2.52; 95% CI = 0.49–12.98 for longer treatment duration).

Prolonged $MgSO_4$ tocolysis use did not increase the risk of infant fractures. Our findings reconfirmed the safety of $MgSO_4$ as a tocolytic treatment.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interv, FDA = The US Food and Drug Administration, HWDC = The Health and Welfare Data Science Center, ICD-10-CM = The International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification, LMP = the last menstrual period, $MgSO_4$ = magnesium sulfate.

Keywords: fractures, infants, $MgSO_4$, National health insurance database, pregnant women, tocolysis

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Y-HW and I-TW contributed equally to this work.

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1. Introduction

Preterm birth, which has a worldwide prevalence of approximately 11.1%, is a considerable health issue in obstetrics.[1–3] It is a major cause of child death and can cause severe physical and mental complications among children younger than 5 years old.[2] Preterm birth can be prevented with tocolytic treatment, which can delay delivery and improve neonatal and maternal outcomes.[4] Magnesium sulfate ($MgSO_4$) is a commonly prescribed tocolytic due to its low side effects, low cost, and neuroprotective benefit for preventing cerebral palsy.[5–7] $MgSO_4$ decreases intracellular calcium, which consequently reduces uterine contractions and delays preterm birth.[8–12]

In 2013, the U.S. Food and Drug Administration (FDA) issued a safety warning that recommended health care providers not use $MgSO_4$ injection for >5 to 7 days to stop preterm labor.[13] Bone abnormalities, such as infant osteopenia and fractures, were observed in several case reports.[14–17] Specifically, these observed bone problems were hypothesized to be due to hypermagnesemia resulting in low calcium levels in fetuses and infants.

Despite the warning, further research with stronger evidence is necessary, because the FDA's review was mainly based on case reports and chart review of individual health institutes.[13–17] None of the studies were from randomized control trials or large observational studies. Findings from individual cases in US institutions may not be generalizable to a larger population or to Asian populations. Furthermore, updated evidence is imperative because most of the references in the warning were >10 years old.[14–16,18–22] No updated studies have been reported since the FDA warning. Thus, studies are needed to evaluate the effects of duration and dose variation of $MgSO_4$ therapy to help clinicians better manage the treatment outcomes.

Given that the prolonged use of $MgSO_4$ remains a common tocolysis treatment,[5–7] a real-world population-based study with greater generalizability is needed to further investigate the impact of $MgSO_4$ tocolytic treatment strategies on the risk of fractures among infants. Therefore, our study aimed to investigate whether prolonged $MgSO_4$ use in tocolysis was associated with the risk of subsequent fractures among infants.

2. Methods

2.1. Data sources

The data source of this study was the Taiwan Health and Welfare Data, which contains 3 major databases, the National Health Insurance Database, the Birth Certificate Application Database, and the Maternal and Child Health Database.[23]

The data in the National Health Insurance Database comes from the National Health Insurance program, which is a compulsory single-payer insurance plan covering approximately 99.6% of the Taiwanese population.[24] The National Health Insurance Database is an administrative claims database that includes beneficiaries' demographic characteristics, disease diagnosis, treatment procedures, and medication prescriptions.[25] In this study, the full population data of the National Health Insurance Database was used. The Birth Certificate Application Database contains information about newborns and mothers,[25,26] including gestational age, birth date, parity, birth weight, type of delivery, and Appearance, Pulse, Grimace, Activity, and Respiration score. The mothers' data includes demographics, education, occupational type, marital status, risk factors of the pregnancy, and type of delivery. The Maternal and Child Health Database includes newborns' and parents' identification numbers, so that mother-child pairs can be linked.[26]

All 3 databases are maintained and supervised by the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare in Taiwan.[23] They are nationally representative and can be linked together to gather comprehensive information about the study population using the unique personal identification number assigned to all Taiwanese beneficiaries. The data were collected from January 1, 2010, to December 31, 2016.

2.2. Study design and participants

This is a retrospective, population-based, cohort study with the new-user study design. Pregnant women were included in the study if they were aged between 12 and 55 years and had a singleton live-born infant. The enrollment period was from January 1, 2012, to December 31, 2014. The period of pregnancy was defined using data from the Birth Certificate Application database, which has complete information (weeks and days) on gestational age and the date of the delivery. The date of the last menstrual period (LMP) was estimated based on the gestational age and the date of infant delivery. The period of pregnancy was defined as the period between the date of the LMP and the date of the delivery. The date of the LMP was marked as the index date. We kept only the first record of pregnancy if women had multiple records of pregnancy during the enrollment period. Figure 1 shows the study design.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code were used to identify the disease diagnosis. The Table S1, Supplemental Digital Content, http://links.lww.com/MD/G550 shows the crosswalk table between ICD-9-CM and ICD-10-CM. Subjects were excluded if any of the following conditions were met: the pregnant woman had a diagnosis with placenta previa, oligohydramnios, placenta abruption, cord prolapse, preeclampsia, antepartum hemorrhage, mild or unspecified pre-eclampsia, or pre-eclampsia or eclampsia superimposed on pre-existing hypertension during pregnancy; the pregnant woman had been exposed to tocolytics ($MgSO_4$, ritodrine, nifedipine, indomethacin, or progesterone) within 1 year before the date of the LMP; the mother-child pair was not complete; or the infant was diagnosed with osteogenesis imperfecta or acute lymphoblastic leukemia between delivery date and the end of follow-up.

Finally, to ensure that the lack of an observation of a medical event was not due to a lack of medical insurance, pregnant women were required to be continuously enrolled from 1 year before the date of the LMP through 6 months after delivery, and infants were required to be continuously enrolled for 3 years after the birth date. Figure 2 shows the enrollment process and the study inclusion/exclusion criteria.

2.3. Exposure: prolonged $MgSO_4$ use

The exposure condition of this study was the prolonged $MgSO_4$ use, which was defined as the pregnant woman receiving $MgSO_4$ injection for >5 days during pregnancy. We used the Inpatient Expenditures by Admissions files and Details of Inpatient Orders files from the National Health Insurance Database to identify the

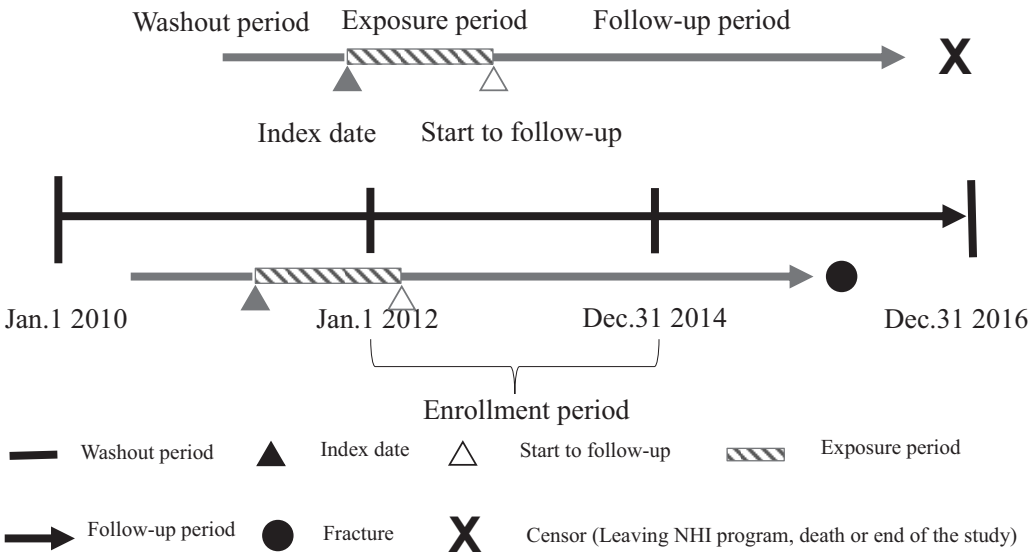

Figure 1. Study design.

quantity of $MgSO_4$ use. For the use of $MgSO_4$ in tocolysis, clinicians typically give a loading dose of 4 to 6 g for 20 minutes in the first hour, followed by a maintenance dose of 1 to 2 g per hour until uterine quiescence is established.[17,21,27] Therefore, we calculated the total quantity of the $MgSO_4$ use during 1 hospitalization and the daily dosage of $MgSO_4$ to measure the exposure. The usual daily dose of $MgSO_4$ was estimated through the following formula:

First hour:
(Loading dose + maintenance dose)

$$4\,\mathrm{g} + (1\,\mathrm{g/h} \times \tfrac{40 minutes}{60 minutes}) = 4.67\mathrm{g}$$

Next 23 hours:

$$1\,\mathrm{g/h} \times 23\,\mathrm{hours} = 23\mathrm{g}$$

Daily dose per day:

$$4.67\,\mathrm{g} + 23\mathrm{g} = 27.67 \cong 27.7\mathrm{g}$$

Based on the calculation, we estimated that the daily dosage of $MgSO_4$ was approximately 27.7 g. We then estimated the number of days of $MgSO_4$ use by dividing the total quantity of $MgSO_4$ use by 27.7. Pregnant women were included in the exposure group if they received $MgSO_4$ injection for >5 days, whereas pregnant women were included in the reference group if they did not receive any tocolytic agents during pregnancy.

2.4. Outcomes

The main outcome of this study was the incidence of fracture among infants during the follow-up period, which was the 2-year period following birth. Fractures were identified using inpatient or outpatient diagnosis codes associated with fractures, which included vertebral fractures and nonvertebral fractures. All related ICD-9-CM and ICD-10-CM codes are listed in the Appendix. Pathological fractures and fractures due to transport accident were excluded. Infants were censored at the date of leaving the NHI program coverage, death from any cause, or at the end of the 2-year follow-up period.

2.5. Covariates

Covariates were classified into 4 major groups: demographic variables, comorbid diseases, medication-related variables, and infant-related variables. Demographic variables, including age and region, were obtained from the Registry for Beneficiaries file on the index date. Age was calculated by the index year (the year of pregnancy) minus the patient's birth year. The region variable was divided into 6 parts according to the geographic area of Taiwan. Comorbid diseases were defined based on at least one inpatient or outpatient record of disease diagnosis in the 1-year preindex period or during pregnancy. Comorbid diseases included asthma, diabetes, hypertension, hyperlipidemia, gestational hypertension, gestational diabetes, renal diseases, liver diseases, depression, and anxiety disorders. They were identified from data collected during the 1-year preindex period or during pregnancy. Medication-related variables were obtained from data collected during this same time period and required at least one prescription record from contracted pharmacies, inpatient visit, or outpatient visit. Medications included antidepressants, antipsychotics, benzodiazepines, Z-drugs, antihypertension drugs, antidiabetic drugs, antiasthmatic drugs, antibiotics, and nonsteroidal anti-inflammatory drugs. In addition, the use of vitamin D or calcium supplements was collected only during pregnancy. Infant-related variables that were obtained during the follow-up period included gender, birth weight, gestational age at birth, and the number of outpatient visits.

2.6. Statistical analyses

The analysis began with calculating the prevalence of $MgSO_4$ use and the incidence rate of fractures among infants in both the prolonged $MgSO_4$ users and tocolytic nonusers. Then, the

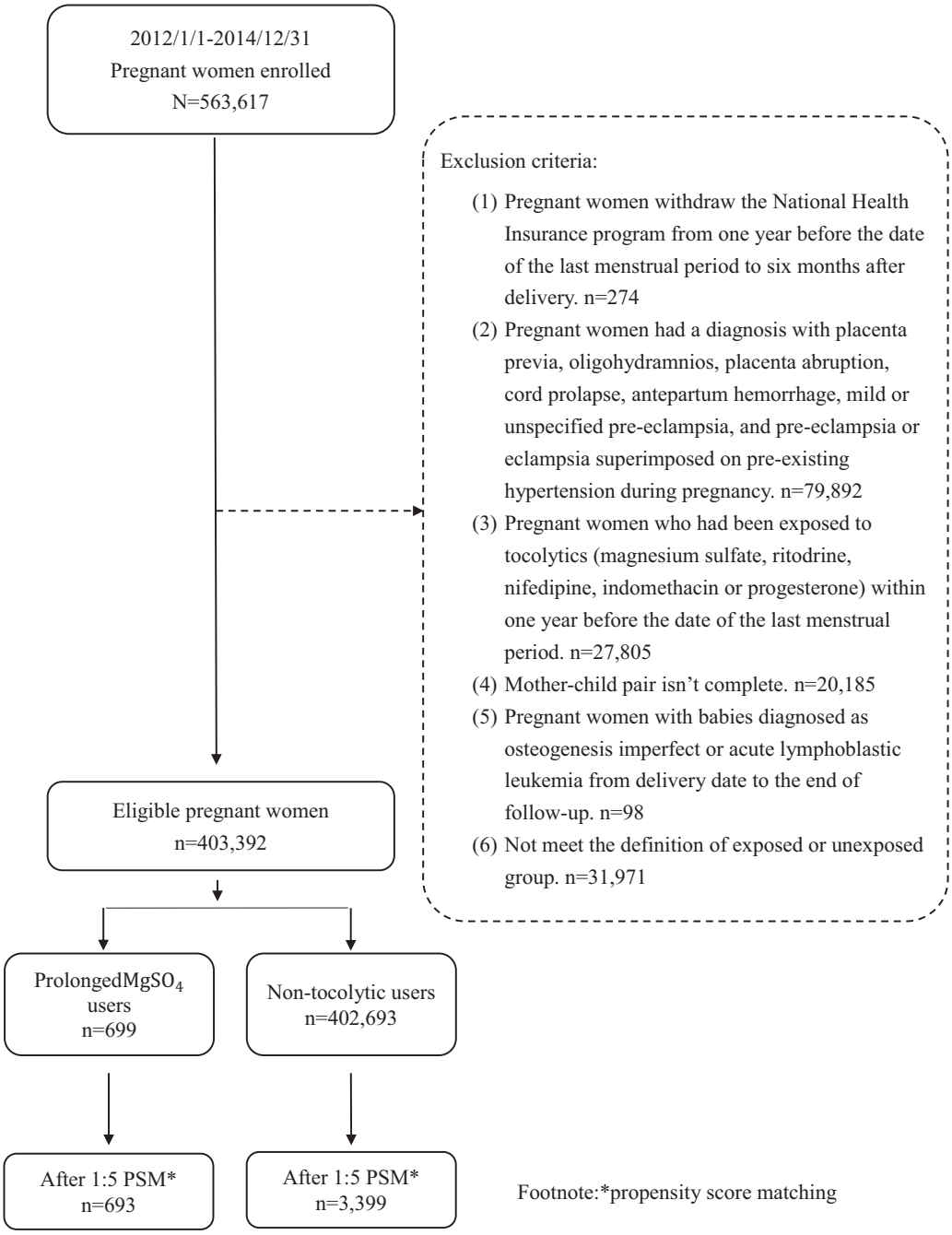

Figure 2. The enrollment processes.

baseline characteristics in the exposure and reference groups were compared by using the independent sample *t* test for continuous variables or chi-square test for categorical variables. To balance measurable confounders between 2 groups, we used propensity score matching.[28] Each patient's propensity score was defined as the probability that a pregnant woman would receive prolonged $MgSO_4$ treatment. The propensity score was obtained from a logistic regression model that contained the variables listed above as covariates. The variables were used to generate a propensity score for each patient, which predicted the probability of receiving the exposure treatment. Then, the prolonged $MgSO_4$ users and tocolytic nonusers were 1:5 matched through a greedy matching algorithm with caliper width equal to 0.2 times the standard deviation of the logits of the propensity scores.[28,29] Cox proportional hazards regression analyses were then used to estimate the adjusted hazard ratio for fractures. A 2-tailed *P*-value $<.05$ was considered statistically significant. All data management, analyses, and statistical procedures were performed using SAS software version 9.4 (SAS Institute, Cary, NC). This study was reviewed, approved, and obtained the exemption from the Taipei Medical University Joint Institutional Review Board (TMU-JIRB No: N201702066). The study was granted the exemption because this is a secondary data analysis study. All patient information was deidentified. No informed consent was

given. The investigators did not have any human contact with the patients.

2.7. Sensitivity analyses

We also conducted 2 sensitivity analyses to ensure the robustness of the study findings. First, we varied the estimated usual daily dosage of $MgSO_4$ from 27.7 to 40.0 g to consider the effect of a larger treatment dosage of $MgSO_4$ exposure, as physicians may consider using a higher dose of $MgSO_4$ to reduce uterine contractions. In the first sensitivity analysis, we used the maximum daily dosage of $MgSO_4$ of 40 g to evaluate the association. In the second sensitivity analysis, since there were limited evidence examining duration of $MgSO_4$ tocolytic treatment,[27] we used the active comparator design (treatment duration >5 days vs <5 days) to evaluate the association between the duration of therapy and the risk of infant fracture.[30] We varied the duration of therapy and defined enrolled pregnant women who received the $MgSO_4$ injection for <5 days during pregnancy as a reference group.

3. Results

A total of 403,392 pregnant women who delivered a singleton from January 1, 2012, to December 31, 2014, were enrolled in the study. There were 699 prolonged $MgSO_4$ users and 402,693 tocolytic nonusers remaining in the study after removing subjects who met the study exclusion criteria. After 1:5 propensity score matching, 693 participants were in the prolonged $MgSO_4$ user group and 3399 participants were in the tocolytic nonuser group. The characteristics of the prolonged $MgSO_4$ users and the tocolytic nonusers and their respective infants are shown in Tables 1 and 2.

Table 1 presents the characteristics of the pregnant women before and after propensity score matching. Before matching, $MgSO_4$ users were older than tocolytic nonusers (33.0 vs 31.2 years old, $P < .01$). The rate of comorbid conditions, except liver diseases, was significantly higher in prolonged $MgSO_4$ users than in tocolytic nonusers. In addition, compared with tocolytic nonusers, prolonged $MgSO_4$ users were significantly more likely to be prescribed antihypertensive, antidiabetic, antidepressant, benzodiazepine, and antipsychotic drugs, z drugs, and antibiotics. After matching, all characteristics were balanced between prolonged $MgSO_4$ users and tocolytic nonusers.

Table 2 shows the characteristics of the infants born to prolonged $MgSO_4$ users and tocolytic nonusers. Infants born to pregnant women who were prolonged $MgSO_4$ users had a higher preterm birth rate, lower birth weight, and shorter gestational age. The rate of preterm birth was significantly higher in prolonged $MgSO_4$ users than in tocolytic nonusers (52.4% vs 12.9%, $P < .01$). Furthermore, compared with tocolytic nonusers, the average birth weight in prolonged $MgSO_4$ users was lower (2568.3 vs 3024.9 g, $P < .01$). The mean gestational age was significantly shorter in $MgSO_4$ users than in tocolytic nonusers (35.5 vs 37.9 weeks, $P < .01$).

Table 3 shows the results of the Cox proportional hazard models. In the first model, the demographic variables, comorbidity variables, and medication-related variables were used to calculate the propensity score and adjusted in the Cox proportional hazards model. Although the hazard of infant fractures was higher among pregnant women who received prolonged $MgSO_4$ treatment, the difference was not statistically significant (=1.50; 95% confidence interval (CI) = 0.60–3.73). In the second model, the infant-related variables were adjusted for in the regression model. Again, the hazard ratio of the infant fracture was not found to be significantly different between prolonged $MgSO_4$ users and tocolytic nonusers (adjusted hazard ratio (aHR) = 1.48; 95% CI = 0.59–3.71).

Finally, the results from the first sensitivity analysis, which applied the maximum daily dosage of $MgSO_4$ to reevaluate the association, showed that the hazard ratio of infant fracture was not significantly different between prolonged $MgSO_4$ users and tocolytic nonusers (aHR = 1.45; 95% CI = 0.40–5.28). A similar nonsignificant result was also observed in the second sensitivity analysis, in which we compared $MgSO_4$ users with a treatment duration of >5 days to $MgSO_4$ users with a treatment duration of <5 days (aHR = 2.52; 95% CI = 0.49–12.98) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G551).

4. Discussion

4.1. Principal findings

To our knowledge, this is the first study using real-world large administrative data to investigate the prolonged use of $MgSO_4$ during pregnancy and its impact on fractures in infants. In the study, infants born to women with prolonged $MgSO_4$ use for tocolysis were not found to be at a significantly increased risk of subsequent fractures compared with infants born to pregnant women who did not receive tocolytic treatment. The findings were also consistent in the sensitivity analyses with different definitions of dosage and treatment duration.

4.2. Results

The results from our study were corroborated by a prior cohort study which showed no association between prolonged $MgSO_4$ use for tocolytic treatment among pregnant women and bone abnormalities among infants in the United States.[21] The cohort study used the database from American University of Beirut Medical Center to investigate the association between $MgSO_4$ use and bone abnormalities that were identified and defined based on X-rays.[21] The study showed that $MgSO_4$ use was not found to be significantly associated with a higher rate of bone abnormalities among infants when compared with nonprolonged $MgSO_4$ use. This finding was similar to the results of our study.

Furthermore, a more recent Cochrane systematic review conducted by McNamara et al[27] evaluated the health outcomes in the mothers and infants after intravenous or oral magnesium sulphate were given for tocolysis from 3 randomized trials. They concluded that the risk of fetal hypocalcaemia, osteopenia, or fracture was not different between pregnant women with high-dose and low-dose $MgSO_4$. Finding of our study from the observational study design was consistent with results from clinical trials.

4.3. Research implications

The major finding of our study was not consistent with those of two other cohort studies that indicated the harmful effect of $MgSO_4$ use on infant bone.[18,19] However, the previous studies could have been limited by the confounding bias[19] and a relatively small sample size.[18] Specifically, failure to adjust for confounders could introduce bias. For instance, one of the two

Table 1

Characteristics of prolonged $MgSO_4$ users and non-tocolytic users before and after propensity score matching.

	Before propensity score matching					After propensity score matching				
	Prolonged $MgSO_4$ users (N = 699)		Non-tocolytic users (N = 402,693)			Prolonged $MgSO_4$ users (N = 693)		Non-tocolytic users (N = 3,399)		
Characteristics	**n**	**%**	**n**	**%**	***P*-value**	**n**	**%**	**n**	**%**	***P*-value**
Maternal age (y, mean ± SD*)	33.0 ± 4.9		31.2 ± 4.7		<.01	33.0 ± 4.9		33.0 ± 4.7		.81
Maternal age (y, median)	33		31			33		33		
Region					<.01					.83
Northern	410	58.7	193,688	48.1		408	58.9	2,021	59.5	
Northwest	57	8.2	58,464	14.5		57	8.2	299	8.8	
Central	55	7.9	61,483	15.3		55	7.9	302	8.9	
Southwestern	75	10.7	38,552	9.6		73	10.5	338	9.9	
Southern	62	8.9	36,161	9.0		61	8.8	275	8.1	
Eastern and the other	40	5.7	14,345	3.6		39	5.6	164	4.8	
Comorbidities										
Asthma	17	2.4	6321	1.6	<.05	17	2.5	84	2.5	.98
Hypertension	13	1.9	1281	0.3	<.01	12	1.7	52	1.5	.70
Diabetes	17	2.4	1646	0.4	<.01	16	2.3	63	1.9	.43
Depression	19	2.7	3878	1.0	<.01	19	2.7	74	2.2	.36
Anxiety	25	3.6	6835	1.7	<.01	25	3.6	105	3.1	.48
Hyperlipidemia	14	2.0	3235	0.8	<.01	14	2.0	67	2.0	.93
Renal diseases	4	0.6	864	0.2	<.01	4	0.6	14	0.4	.53
Liver diseases	11	1.6	3319	0.8	.07	11	1.6	47	1.4	.68
Medication										
Antihypertensives	25	3.6	5851	1.5	<.01	25	3.6	108	3.2	.56
Antidiabetic drugs	26	3.7	2311	0.6	<.01	24	3.5	106	3.1	.64
Antidepressants	29	4.2	9262	2.3	<.01	29	4.2	134	3.9	.77
Benzodiazepines	129	18.5	45,484	11.3	<.01	128	18.5	614	18.1	.80
Z drugs	36	5.2	10,037	2.5	<.01	36	5.2	160	4.7	.58
Antipsychotics	17	2.4	4991	1.2	<.01	16	2.3	65	1.9	.49
Antibiotics	258	36.9	108,870	27.0	<.01	256	36.9	1,255	36.9	.99
Antiasthmatic drugs	187	26.8	108,552	27.0	.90	187	27.0	900	26.5	.78
NSAIDs	480	68.7	263,279	65.4	.07	477	68.8	2,303	67.8	.58
Comorbidities										
Asthma	20	2.9	6044	1.5	<.01	20	2.9	92	2.7	.79
Hypertension	12	1.7	1111	0.3	<.01	12	1.7	48	1.4	.52
Gestational hypertension	39	5.6	1768	0.4	<.01	39	5.6	184	5.4	.82
Diabetes	24	3.4	1525	0.4	<.01	22	3.2	96	2.8	.62
Gestational diabetes	19	2.7	747	0.2	<.01	17	2.5	85	2.5	.94
Depression	18	2.6	3601	0.9	<.01	18	2.6	72	2.1	.43
Anxiety	23	3.3	6297	1.6	<.01	23	3.3	96	2.8	.48
Hyperlipidemia	13	1.9	2954	0.7	<.01	13	1.9	64	1.9	.99
Renal diseases	4	0.6	803	0.2	.05	4	0.6	14	0.4	.53
Liver diseases	16	2.3	3111	0.8	<.01	16	2.3	68	2.0	.60
Medication										
Antihypertensives	591	84.6	29,822	7.4	<.01	585	84.4	2,862	84.2	.89
Antidiabetic drugs	54	7.7	2297	0.6	<.01	49	7.1	222	6.5	.60
Antidepressants	11	1.6	3205	0.8	<.05	11	1.6	56	1.7	.91
Benzodiazepines	78	11.2	26,131	6.5	<.01	74	10.7	315	9.3	.25
Z drugs	88	12.6	5004	1.2	<.01	82	11.8	359	10.6	.33
Antipsychotics	56	8.0	22,445	5.6	<.01	56	8.1	278	8.2	.93
Antibiotics	127	18.2	51,630	12.8	<.01	126	18.2	544	16.0	.16
Antiasthmatic drugs	221	31.6	63,743	15.8	<.01	217	31.3	1,056	31.1	.90
NSAIDs	531	76.0	283,845	70.5	<.01	526	75.9	2,605	76.6	.68
Vitamin D or Ca	78	11.2	16,039	4.0	<.01	75	10.8	339	10.0	.50

* Standard deviation.

previous studies that was conducted reviewed medical charts to identify pregnant women receiving intravenous $MgSO_4$ as tocolytic treatment.[19] The study found that infants born to pregnant women who received intravenous $MgSO_4$ treatment were associated with a higher risk of the bone abnormalities when compared with infants born to pregnant women who did not receive $MgSO_4$ treatment.[19] Although a significant association between $MgSO_4$ use and the bone abnormalities was found, the study did not adjust for any covariates in the regression analysis, which can lead to bias from confounders. By applying propensity score matching, our analytic models adjusted for 4 groups of covariates, specifically, demographic variables, comorbid diseases, medication-related variables, and infant-related variables; this reduced the possibility of confounding effects and further

Table 2

Characteristics of infants among prolonged $MgSO_4$ users and non-tocolytic users before and after propensity score matching.

	Before propensity score matching					After propensity score matching				
	Prolonged $MgSO_4$ users (N = 699)		Non-tocolytic users (N = 402,693)			Prolonged $MgSO_4$ users (N = 693)		Non-tocolytic users (N = 3,399)		
Characteristics	n	%	n	%	*P*-value	n	%	n	%	*P*-value
Sex					<.05					.12
Male	395	56.5	208,922	51.9		394	56.9	1,823	53.6	
Female	304	43.5	193,771	48.1		299	43.2	1,576	46.4	
Birth weight (g, mean ± SD*)	2,569.1 ± 771.2		3,110 ± 394.6		<.01	2,568.3 ± 768.7		3,024.9 ± 511.3		<.01
Birth weight					<.01					<.01
>2500 g	442	63.2	383,470	95.2		439	63.3	3,022	88.9	
1500–2500 g	177	25.3	18,514	4.6		175	25.3	328	9.6	
<1500 g	80	11.4	709	0.2		79	11.4	49	1.4	
Gestational age (weeks, mean ± SD*)	35.5 ± 3.6		38.5 ± 1.3		<.01	35.5 ± 3.6		37.9 ± 2.0		<.01
Preterm birth†	367	52.5	19,375	4.8	<.01	363	52.4	437	12.9	<.01
Visit (times, mean ± SD*)	40.0 ± 28.0		37.6 ± 26.0		<.05	40.2 ± 28.1		41.4 ± 27.6		.29
Follow up time (days, mean ± SD*)	712.1 ± 107.9		725.7 ± 48.2		<.01	713.0 ± 105.0		725.3 ± 53.1		<.01
Follow up time (days, median)	730		730			730		730		
Fracture	6	0.9	3,710	0.9	.86	6	0.9	20	0.6	.43

* Standard deviation.
† Gestational age <37 weeks.

clarified that prolonged $MgSO_4$ use for tocolysis was not associated with bone abnormalities in infants. The other study that found a significant association between $MgSO_4$ use and infants' bone fractures was conducted on a limited sample size.[18] The study only included 33 participants identified from a review of chest radiographs. The small sample size of the study lowered the representation of the patient population, and the finding was unlikely to be generalizable. However, our study's sample was obtained from a real-world setting and provides more reliable and compelling evidence of the safety of prolonged $MgSO_4$ treatment for pregnant women. Furthermore, the 2 studies were published >2 decades ago.[18,19] Updated evidence is necessary to further evaluate the use of $MgSO_4$ as the tocolytic treatment and to inform obstetricians the safety of the treatment.

4.4. Clinical implications

From a clinical perspective, health professionals should have a conservative attitude toward the harmful effect of prolonged $MgSO_4$ use. This study did not find evidence of a long-term effect of the prolonged $MgSO_4$ use on bone abnormalities. The basis of the safety warning that FDA issued in 2013 came mainly from several case reports with chart reviews at several individual health institutes.[13–17] The current study was a large observational study using administrative claims data and provided updated evidence that prolonged $MgSO_4$ use did not increase the risk of infants' fractures. Regarding the effectiveness of $MgSO_4$ use on the prevention and delay of uterine contractions, further research is needed to evaluate the risks and benefit of $MgSO_4$ use in tocolytic treatment, as it remains a common treatment for tocolysis in typical clinical practice.[5–7]

4.5. Strength and limitations

Our study has several strengths. This is the first study to use a large administrative dataset to investigate the impacts of prolonged $MgSO_4$ use in pregnant women on subsequent fractures in their infants after the FDA issued a warning in 2013. Several analytic approaches and research designs were applied in this study to address bias and confounding factors.[30,31] In this study, for example, the new $MgSO_4$ user design helped to eliminate the prevalent user bias.[30,31] The active comparator design used in the second sensitivity analysis reduced the bias from confounding by indication.[30,32] Propen-

Table 3

The association between prolonged magnesium sulfate use and the risk of infant fractures: results from Cox proportional hazard models.

Groups	Hazard ratio	95% CI	Variables used to obtain the propensity score
Model 1			
Prolonged magnesium sulfate users	1.5	(0.60–3.73)	Demographic variables Comorbid diseases Medication-related variables
Non-tocolytic users	Reference	Reference	
Model 2			
Prolonged magnesium sulfate users	1.48	(0.59–3.71)	Demographic variables Comorbid diseases Medication-related variables Infant-related variables
Non-tocolytic users	Reference	Reference	

sity score matching and multivariable regression models adjusted for confounders and provided compelling evidence for the connection between exposure and outcome.

Despite these strengths, there are several acknowledged limitations in this study. First, the duration of $MgSO_4$ use was estimated by calculating the total quantity of $MgSO_4$ use divided by the usual daily dosage of $MgSO_4$ during the hospital stay because the actual number of days of $MgSO_4$ use was not provided in the database. Variation in the dosage and duration of treatment may still exist and lead to a potential misclassification of the exposure. Second, bias from unmeasured confounders cannot be completely eliminated, because the propensity score matching can only balance the measurable confounders.[28] Third, information regarding the smoking status, exercise habits, and diet could not be obtained from the current claims databases; residual confounding effects may still have been present. Finally, the generalizability of this study is limited to the Taiwanese population.

5. Conclusions

In conclusion, in this large population-based cohort study, prolonged $MgSO_4$ use for tocolysis among pregnant women did not significantly increase the risk of fractures in infants. Our findings reasserted the safety of $MgSO_4$ use as tocolytic treatment. Physicians can still prescribe $MgSO_4$ for tocolysis with caution. Randomized control trials with a large population are needed to determine the causal relationship between prolonged $MgSO_4$ use and the bone abnormalities, which can provide more compelling evidence for future clinical practice.

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