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Report

Effect of Long-Term Tocolysis with Magnesium Sulfate on Maternal Renal Function in Patients with Threatened Preterm Labor

Tomoko Shinojima,[a] Takafumi Nakano,[a,b,*] Masahiro Okurano,[a] Kaoru Kihara,[b] Keisuke Sato,[a] Marie Yoshioka,[a,b] Masaya Adachi,[a,b] Mika Higashi,[a,b] Takuya Yamashina,[a,b] Masanobu Uchiyama,[a,b] Susumu Kaneshige,[a] Hidetoshi Kamimura,[a] and Koichi Matsuo[a,b]

[a]*Department of Pharmacy, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0133, Japan;* [b]*Department of Oncology and Infectious Disease Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan*

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In Western countries, magnesium sulfate ($MgSO_4$) for threatened preterm labor is recommended as short-term tocolysis (<48 h) considering potential maternal adverse effects. In Japan, long-term tocolysis exceeding 48 h remains common; however, its maternal renal and fetal effects remain unclear. We evaluated the impact of long-term $MgSO_4$ tocolysis on maternal renal function. This retrospective observational study included pregnant women hospitalized for threatened preterm labor who received $MgSO_4$ therapy at Fukuoka University Hospital between January and December 2021. Eligible patients were ≥18 years old, ≥22 weeks of gestation, and treated with $MgSO_4$ for ≥24 h. A total of 66 patients were classified into short-term (<48 h) group (n = 26) and long-term (≥48 h) group (n = 40). The primary outcome was the incidence of acute kidney injury (AKI). Secondary outcomes included changes in serum creatinine level (ΔCr; peak – baseline) and correlations between ΔCr and Mg exposure (duration, daily dose, serum Mg concentration). Neonatal laboratory values at birth were also assessed. AKI occurred in 0% and 2.5% (1/40) of the short- and long-term groups, respectively; the affected case met creatinine-based AKI criteria but impairment was not clinically significant. ΔCr showed a weak positive correlation with treatment duration (ρ = 0.321, P = 0.009), while daily Mg dose and serum Mg levels were not correlated. Long-term group neonates showed higher serum Mg (P = 0.038) and lower Ca (P = 0.045). Long-term $MgSO_4$ tocolysis may cause mild renal burden but appears unlikely to induce clinically significant maternal renal dysfunction under careful monitoring. Maternal and neonatal electrolyte monitoring is advisable during prolonged $MgSO_4$ therapy.

Key words long-term tocolysis, short-term tocolysis, acute kidney injury, magnesium sulfate therapy

INTRODUCTION

Preterm birth is a leading cause of neonatal mortality and long-term morbidity, with risks increasing as gestational age decreases.[1–3] Preterm infants are particularly vulnerable to complications such as respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis, and may later develop neurodevelopmental impairment or cerebral palsy.[4–6] Threatened preterm labor, defined as regular uterine contractions with cervical shortening or dilation between 22 and 37 weeks of gestation, places pregnancies at high risk for preterm delivery. Its management remains a central challenge in perinatal medicine. To prolong pregnancy and promote fetal maturation, tocolytic therapy is widely used to suppress uterine contractions.[7,8]

Magnesium sulfate ($MgSO_4$) has long been used intravenously as a major agent alongside β-adrenergic agonists and calcium channel blockers. Magnesium acts as a calcium antagonist by blocking voltage-dependent Ca^{2+} channels on the smooth muscle membrane, thereby inhibiting calcium influx, reducing intracellular Ca^{2+} concentration, and suppressing uterine contractions. Moreover, $MgSO_4$ has been reported to have vasodilatory, anti-inflammatory, and antioxidant properties, and is used in perinatal medicine not only as a tocolytic agent but also for fetal neuroprotection.[9] However, recommended dosing duration varies considerably regions. In Western countries, short-term tocolysis, typically limited to within 48 h, is recommended based on considerations of both maternal and fetal efficacy and safety.[10,11] Short-term tocolysis is a treatment strategy that uses tocolytic drugs to relax the uterus for 48 h, during which time corticosteroids are used to promote fetal maturation. Prolonged administration of magnesium sulfate, a commonly used uterine relaxant, can lead to maternal adverse effects such as headaches, flushing, fatigue,

*To whom correspondence should be addressed. e-mail: naka0625@fukuoka-u.ac.jp

reduced deep tendon reflexes, muscle weakness, nausea, and, in severe cases, respiratory depression.[9,12] Furthermore, the U.S. Food and Drug Administration (FDA) has issued a warning that administration exceeding 7 days may result in fetal or neonatal hypocalcemia and bone demineralization.[13] Consequently, when long-term tocolysis is considered, it should be conducted under strict monitoring in tertiary care settings, balancing the potential benefits of pregnancy prolongation against maternal and fetal risks. In contrast, in Japan, where rates of preterm birth and perinatal mortality are among the lowest globally, long-term $MgSO_4$ tocolysis exceeding 48 h remains common.[14–16] The safety of this approach is generally maintained through careful monitoring of maternal serum Mg concentrations and is influenced by differences in patient characteristics, perinatal care systems, and insurance coverage. However, the the physiological effects of prolonged Mg exposure on maternal and fetal outcomes have not been fully elucidated, and robust evidence supporting the safety of long-term $MgSO_4$ administration remains limited.

Because approximately 30–40% of circulating Mg is excreted renally, prolonged administration may impose renal burden even in women with normal baseline renal function, potentially leading to transient tubular injury or decreased glomerular filtration. However, few studies have systematically evaluated the association between Mg dose or duration and maternal renal dysfunction, and the underlying pathophysiological mechanisms remain unclear.

Given the limited evidence, the impact of long-term $MgSO_4$ tocolysis on maternal renal function remains insufficiently investigated. Clarifying this relationship is essential to ensure the safe use of $MgSO_4$ in obstetric practice. This study therefore focused on maternal renal function to evaluate the effects of prolonged $MgSO_4$ administration during tocolysis on maternal renal outcomes.

MATERIALS AND METHODS

Study Design, Population and Endpoints This retrospective observational study was conducted at Fukuoka University Hospital between January and December 2021 and included pregnant women admitted for threatened preterm labor who received $MgSO_4$ therapy, along with their neonates. The inclusion criteria were: (1) age ≥18 years, (2) gestational age ≥22 weeks, and (3) administration of $MgSO_4$ for at least 24 h. Participants were classified into two groups according to the duration of $MgSO_4$ therapy: those treated for <48 h were assigned to the short-term tocolysis group, and those treated for ≥48 h to the long-term tocolysis group. Patients with hypertensive disorders of pregnancy, multiple gestation, placenta previa, pre-existing renal dysfunction, or with incomplete data were excluded. This study was conducted in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and approved by the Ethics Committee of Fukuoka University (approval number: H24-07-012). As this was a retrospective study, individual informed consent was not obtained. Instead, study information was publicly disclosed on the Fukuoka University website with an opt out option. All personal data was handled confidentially.

The primary endpoint was the incidence of renal impairment during $MgSO_4$ therapy, defined as acute kidney injury (AKI). Secondary endpoints included changes in serum creatinine (Cr) and electrolyte levels during $MgSO_4$ therapy, treatment duration, total Mg dose, correlations between serum Cr and Mg exposure duration (days), daily dose (mg/day), cumulative dose (mg/dL), and neonatal serum electrolyte levels at birth.

Survey Items Patient demographics and clinical data were extracted from medical records using the electronic medical record system. Maternal data included age, gestational age, medical history, medication history (treatment duration and concomitant medications), and laboratory test results, including blood urea nitrogen (BUN), Cr level, estimated glomerular filtration rate (eGFR), total bilirubin (T-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na), potassium (K), calcium (Ca), and magnesium (Mg). Neonatal data included birth weight and laboratory test results at birth, including BUN, Cr, T-Bil, AST, ALT, Na, K, Ca, and Mg.

Definition of AKI Development AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. AKI was considered present if the serum Cr increased by ≥0.3 mg/dL or ≥1.5-fold from baseline during $MgSO_4$ therapy.[17]

Assessment of Changes in Serum Cr Changes in serum Cr level were evaluated by calculating the difference between the baseline Cr value (before initiation of $MgSO_4$) and the highest Cr value observed during the treatment period. This value was expressed as ΔCr (delta Cr).

Statistical Analyses Continuous variables are presented as median (interquartile range; IQR) and categorical variables as *n* (%). Comparisons of medians between two groups were performed using the Mann–Whitney U test, and comparisons of frequencies were performed using the χ^2 test. Correlations between ΔCr and Mg exposure duration (days), daily dose (mg/day), and cumulative serum Mg concentration (mg/dL) were evaluated using Spearman's rank correlation coefficient (ρ). All statistical analyses were conducted using JMP version 12.01, and a P value <0.05 was considered statistically significant.

RESULTS

Patient Demographics A flowchart of patient selection is shown in Fig. 1. Among 85 pregnant women who received $MgSO_4$ for threatened preterm labor, 19 met exclusion criteria, leaving 66 women for analysis. Of these, 26 were assigned to the short-term tocolysis group and 40 to the long-term tocolysis group. For neonatal analysis, 16 born to mothers in the short-term group and 23 born to mothers in the long-term group were included.

Comparison of Maternal Baseline Characteristics Maternal baseline characteristics are summarized in Table 1. Maternal age did not differ significantly between the two groups. The median gestational age at admission was 33 weeks (IQR: 28–35) in the short-term tocolysis group and 30 weeks (IQR: 24–32) in the long-term tocolysis group, while the long-term group showing a significantly earlier gestational age (P = 0.007). Baseline laboratory test results did not differ significantly between the groups for any parameter. Baseline serum Mg levels could not be evaluated, as only a few patients had measurements taken prior to treatment initiation.

Comparison of Clinical Outcomes The incidence of AKI, the primary endpoint, defined according to KDIGO criteria, was 0% in the short-term tocolysis group and 2.5%

(1 case/40 cases) in the long-term tocolysis group (Table 2). In the single long-term tocolysis case with AKI, the time to onset was 9 days after the start of therapy, with serum Mg of 7.3 mg/dL and serum Cr of 0.9 mg/dL at the time of AKI (ΔCr = 0.31). For secondary endpoints, total $MgSO_4$ dose, treatment duration, and daily Mg dose were all significantly higher in the long-term tocolysis group compared with the short-term group. However, the maximum serum Cr values did not differ significantly between the groups.

Correlation between ΔCr Level and Mg Exposure parameters Although earlier analyses compared short- and long-term groups, the relationship between Mg exposure and ΔCr was assessed in the entire cohort.

Figure 2 presents the correlations between ΔCr and Mg exposure duration (days), daily dose (mg/day), and cumulative serum Mg concentration (mg/dL). Mg exposure duration was defined as the total number of days of $MgSO_4$ administration, daily dose as the average amount of $MgSO_4$ administered per day, and cumulative level as the highest serum Mg concentration observed during the treatment period. ΔCr showed a weak positive correlation with Mg exposure duration ($\rho = 0.321$, $P = 0.009$), while no significant correlations were observed with the other parameters.

Neonatal Outcomes Neonatal characteristics and laboratory findings at birth for infants born to mothers who received short-term and long-term tocolysis are summarized in Table 3. Because some mothers were transferred to other facilities after symptom resolution, neonatal sample sizes differed from maternal sample sizes.

Birth weight did not differ significantly between neonates born to mothers who received short-term and long-term tocolysis. However, at birth, neonates in the long-term tocolysis

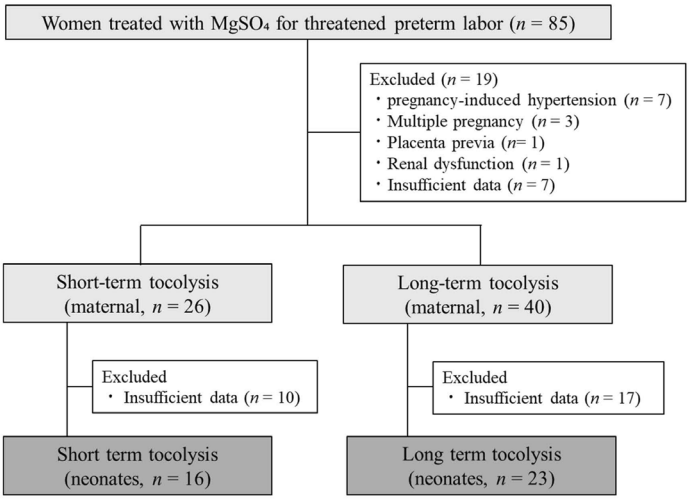

Fig. 1. Patient Selection Flowchart

$MgSO_4$, magnesium sulfate

Table 1. Maternal Baseline Characteristics

	Short-term tocolysis (maternal, *n* = 26)	Long-term tocolysis (maternal, *n* = 40)	*P*-value
Characteristics			
Age (years)	32 (29-38)	32 (28-37)	0.861
Gestational age (weeks)	33 (28-35)	30 (24-32)	0.007
Medical history (*n*, (%))			
Thyroid dysfunction	1 (3.8)	3 (7.5)	0.543
Epilepsy	1 (3.8)	1 (2.5)	0.755
Laboratory data			
Cr (mg/dL)	0.5 (0.4-0.5)	0.5 (0.4-0.5)	0.800
BUN (mg/dL)	7.0 (6.0-9.3)	6.0 (5.0-9.0)	0.226
eGFR (mL/min)	120.3 (102.8-130.3)	124.7 (110.1-134.4)	0.179
T-Bil (mg/dL)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.899
AST (U/L)	18.0 (12.8-22.3)	17.0 (14.0-21.0)	0.839
ALT (U/L)	10.0 (8.0-15.3)	10.5 (7.0-17.0)	0.640
Na (mmol/L)	138.0 (136.0-139.3)	138.0 (137.0-139.0)	0.764
K (mmol/L)	3.6 (3.4-3.9)	3.6 (3.4-3.9)	0.697
Ca (mg/dL)	8.4 (8.0-8.8)	8.4 (7.9-8.8)	0.523

Values are presented as number (%) or median (interquartile range).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; Na, sodium; T-Bil, total bilirubin.

Table 2. Maternal Clinical Outcomes between the Two Groups

	Short-term tocolysis (maternal, n = 26)	Long-term tocolysis (maternal, n = 40)	P-value
Primary endpoint			
Incidence of AKI (n (%))	0 (0)	1 (2.5)	0.417
Secondary endpoints			
Duration of administration (days)	2.0 (1-2)	17.0 (9-30)	<0.001
Total $MgSO_4$ dose (g)	24.0 (17.5-46.5)	475.0 (238.0-852.5)	<0.001
Daily $MgSO_4$ dose (g/day)	15.0 (10.0-23.3)	30.0 (23.5-33.7)	0.001
Peak serum Cr level (mg/dL)	0.5 (0.5-0.6)	0.6 (0.5-0.7)	0.684
Serum magnesium level at peak Cr (mg/dL)	4.5 (3.9-4.0)	5.5 (4.7-6.3)	<0.001

Values are presented as number (%) or median (interquartile range).
AKI, acute kidney injury; Cr, creatinine; $MgSO_4$, magnesium sulfate.

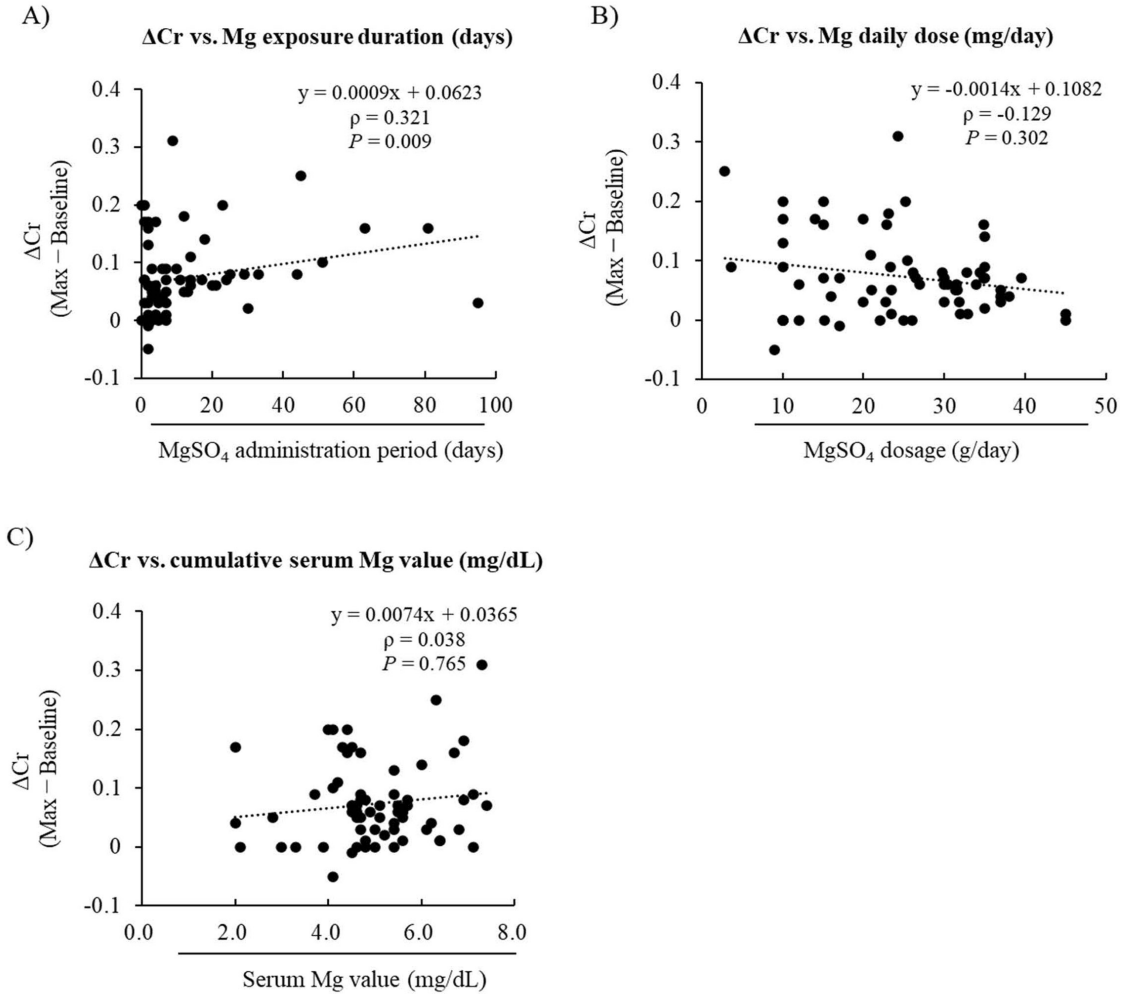

Fig. 2. Correlation between Changes in Serum Creatinine (ΔCr) Level and Magnesium Exposure Parameters in All Patients

ΔCr vs. Mg exposure duration (days) (A), daily dose (mg/day) (B), and cumulative serum Mg concentration (mg/dL) (C).

group had significantly higher serum Mg levels (P = 0.038) and significantly lower serum Ca levels (P = 0.045) compared with those in the short-term group. Additionally, serum K levels tended to be higher in neonates from the long-term tocolysis group (P = 0.074).

DISCUSSION

This retrospective study primarily investigated the impact of long-term $MgSO_4$ tocolysis on maternal renal function in pregnant women with threatened preterm labor and also evaluated its effects on fetal electrolyte balance. In Japan, although short-term tocolysis has recently become the standard of care, long-term $MgSO_4$ administration is still frequently performed in clinical settings.[14–16] However, its safety, particularly regarding maternal renal function, remains insufficiently established. To our knowledge, this study is among the first to systematically monitor maternal renal function during prolonged $MgSO_4$ administration, thereby providing novel insight into its renal safety profile.

Table 3. Comparison of Neonatal Characteristics at Birth between the Two Groups

	Short-term tocolysis (neonates, *n* = 16)	Long-term tocolysis (neonates, *n* = 23)	*P*-value
Birth information			
Male, (*n* (%))	8 (50.0)	11 (47.8)	0.894
Birth weight (g)	1327.0 (827.3-2023.0)	1637.0 (796.0-2223.0)	0.530
Laboratory findings at birth			
Cr (mg/dL)	0.5 (0.4-0.6)	0.6 (0.5-0.6)	0.853
BUN (mg/dL)	7.0 (5.0-9.8)	7.0 (5.0-8.0)	0.943
T-Bil (mg/dL)	2.3 (1.8-2.6)	2.1 (1.9-2.5)	0.909
AST (U/L)	27.0 (22.3-36.0)	29.0 (21.0-40.0)	0.627
ALT (U/L)	3.5 (3.0-6.0)	4.0 (3.0-6.0)	0.855
Na (mmol/L)	138.0 (136.3-139.0)	137.0 (135.0-138.0)	0.391
K (mmol/L)	3.7 (3.3-4.1)	4.1 (3.6-4.3)	0.074
Ca (mg/dL)	9.1 (8.3-9.5)	8.5 (8.0-9.0)	0.045
Mg (mg/dL)	3.8 (2.8-4.8)	4.5 (4.0-5.3)	0.038

Values are presented as number (%) or median (interquartile range).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; Mg, magnesium; Na, sodium; T-Bil, total bilirubin.

Several previous studies have evaluated the safety of $MgSO_4$ therapy in the management of threatened preterm lab or.[16,18,19] The most commonly reported maternal adverse effects include nausea and vomiting, whereas more serious complications, such as loss of patellar reflexes and respiratory depression, are associated with elevated serum magnesium levels but typically occur at concentrations above 10 mEq/L. Maintaining serum Mg within the therapeutic range for threatened preterm labor (4.0–7.0 mEq/L) is therefore considered unlikely to result in severe maternal complications.[20] Emerging evidence also suggests that prolonged $MgSO_4$ administration may be associated with an increased risk of pregnancy- and lactation-associated osteoporosis.[19] Nevertheless, reports that systematically evaluate maternal renal function during long-term $MgSO_4$ therapy are scarce.

In the present study, only one patient in the long-term tocolysis group met the KDIGO criteria for AKI. Even in this case, the increase in serum Cr, from 0.57 to 0.88 mg/dL, did not result in clinically significant renal dysfunction. A weak but statistically significant positive correlation was observed between $MgSO_4$ administration duration and serum Cr changes, suggesting that prolonged exposure may impose a subtle renal burden. Overall, these findings indicate that while long-term $MgSO_4$ tocolysis may cause mild renal stress, it is unlikely to induce overt renal impairment in women with normal baseline renal function under careful monitoring and appropriate dosage.

Regarding neonatal outcomes, compared with infants born to mothers receiving short-term tocolysis, those born to mothers receiving long-term tocolysis showed significantly higher serum Mg and lower serum Ca levels at birth, along with a trend toward higher K levels. These changes were consistent with those reported previously and remained within clinically acceptable ranges.[20,21] However, our results were based solely on laboratory values at birth, and we did not evaluate long-term outcomes in the infants. Therefore, these findings should not be interpreted as evidence of complete safety of long-term $MgSO_4$ tocolysis for neonates; rather, they should be considered as observations limited to the neonatal period. In 2013, the U.S. FDA issued a safety warning against using $MgSO_4$ injections for more than 7 days to stop preterm labor due to concerns regarding subsequent bone abnormalities in infants.[13] However, this warning was mainly based on case reports, and whether long-term $MgSO_4$ tocolysis truly increases the risk of fractures in neonates remains debatable. Reports from the 1990s and 2000s frequently suggested that prolonged maternal $MgSO_4$ administration could lead to impaired bone mineralization in neonates.[22–25] In contrast, more recent population-based studies have not found a significant increase in fracture risk. For example, a retrospective cohort study using the National Health Insurance Database in Taiwan evaluated infants born to mothers who received $MgSO_4$ for more than 5 days during pregnancy. After adjusting for potential confounders, the hazard of fractures in infants exposed to prolonged $MgSO_4$ did not differ significantly from that in infants whose mothers did not receive tocolytic therapy (adjusted hazard ratio = 1.48; 95% confidence interval, 0.59–3.71), and similar findings were observed across analyses considering treatment dosage and duration.[26] Thus, while historical concerns exist, current evidence does not indicate a major skeletal risk from long-term $MgSO_4$ tocolysis, although continued vigilance and further studies are warranted.

This study has some limitations. First, this was a single-center retrospective study with a limited sample size, which may affect both statistical power and generalizability. Second, renal function was evaluated only by serum Cr, which has low sensitivity for early renal injury. Future research using more sensitive biomarkers, such as cystatin C or urinary NGAL, is warranted. Third, potential confounding factors, such as hydration status, body mass index, concomitant medications, and comorbid conditions, were not fully controlled. Fourth, neonatal outcomes were assessed only at birth, and long-term effects on infant growth, bone health, or neurodevelopment were not evaluated. Thus, the long-term safety of prolonged $MgSO_4$ exposure for the child cannot be confirmed. Despite these limitations, this study provides valuable clinical insight into the effects of long-term $MgSO_4$ tocolysis on maternal renal function. Our findings suggest that while long-term administration may slightly influence renal and electrolyte dynamics, the overall risk of clinically significant renal dysfunction appears low when patients are carefully monitored.

In conclusion, although this single-center retrospective

study does not allow for definitive conclusions, the findings indicate that long-term $MgSO_4$ tocolysis, when carefully monitored, is unlikely to cause clinically significant renal impairment, though a mild renal burden cannot be completely ruled out. Moreover, transplacental Mg transfer may transiently affect neonatal electrolyte balance. Therefore, close maternal and neonatal monitoring is recommended during prolonged $MgSO_4$ therapy, and larger prospective studies are needed to validate these results and establish evidence-based clinical guidelines.

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Conflict of Interest The authors declare that they have no competing interests.

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