



REVIEW ARTICLE



Antenatal Magnesium Sulfate and adverse gastrointestinal outcomes in Preterm infants—a systematic review and meta-analysis

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INTRODUCTION: To evaluate the effect of antenatal magnesium sulfate (MgSO₄) on mortality and morbidity outcomes related to the gastrointestinal system (GI) in preterm infants.

METHODS: Data sources: A systematic literature search was conducted in November 2022. PubMed, CINAHL Plus with Full Text (EBSCOhost), Embase (Elsevier), and CENTRAL (Ovid) were searched. There were 6695 references. After deduplication, 4332 remained. Ninety-nine full-text articles were assessed and forty four articles were included in the final analysis.

STUDY ELIGIBILITY CRITERIA: Randomized or quasi-randomized clinical trials and observational studies that evaluated at least one of the pre-specified outcomes were included. Preterm infants whose mothers were given antenatal MgSO₄ were included and whose mothers did not receive antenatal MgSO₄ were the comparators. The main outcomes and measures were: Necrotizing enterocolitis (NEC) (stage ≥ 2), surgical NEC, spontaneous intestinal perforation (SIP), feeding intolerance, time to reach full feeds, and GI-associated mortality.

STUDY APPRAISAL AND SYNTHESIS METHODS: A random-effects model meta-analysis was performed to yield pooled OR and its 95% CI for each outcome due to expected heterogeneity in the studies. The analysis for each predefined outcome was performed separately for adjusted and unadjusted comparisons. All included studies were assessed for methodological quality. The risk of bias was assessed using elements of the Cochrane Collaboration's tool 2.0 and the Newcastle–Ottawa Scale for randomized controlled trials (RCTs) and non-randomized studies (NRS), respectively. The study findings were reported as per PRISMA guidelines.

RESULTS: A total of thirty-eight NRS and six RCTs involving 51,466 preterm infants were included in the final analysis. There were no increased odds of stage ≥2 NEC, (NRS : $n = 45,524$, OR: 0.95; 95% CI: 0.84–1.08, $I^2 = 5\%$ & RCT's: $n = 5205$ OR: 1.00; 95% CI: 0.89–1.12, $I^2 = 0\%$), SIP ($n = 34,186$, OR: 1.22, 95% CI: 0.94–1.58, $I^2 = 30\%$), feeding intolerance ($n = 414$, OR: 1.06, 95% CI: 0.64–1.76, $I^2 = 12\%$) in infants exposed to antenatal MgSO₄. On the contrary, the incidence of surgical NEC was significantly lower in MgSO₄ exposure infants ($n = 29,506$ OR:0.74; 95% CI: 0.62–0.90, ARR: 0.47%). Studies assessing the effect on GI-related mortality were limited to make any conceivable conclusion. The certainty of evidence (CoE) for all outcomes was adjudged as 'very low' as per GRADE.

CONCLUSION: Antenatal magnesium sulfate did not increase the incidence of gastrointestinal-related morbidities or mortality in preterm infants. With the current evidence concerns, regarding the adverse effects of MgSO₄ administration leading to NEC/SIP or GI-related mortality in preterm infants should not be a hurdle in its routine use in antenatal mothers.

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INTRODUCTION

Magnesium sulfate (MgSO₄) is widely used in obstetric patients for indications such as treatment for preeclampsia, tocolysis, and neuroprotection when preterm delivery is imminent [1, 2]. Recent evidence suggests that antenatal magnesium sulfate is effective in the reduction of moderate to severe cerebral palsy by up to 40% [3, 4]. The American College of Obstetricians and Gynecologists (ACOG) in 2010 and the World Health Organization (WHO) in 2015 endorsed the use of MgSO₄ administration to antenatal women to reduce the risk of cerebral palsy (CP) when delivery is anticipated before 32 weeks [5, 6]. A recent meta-analysis found a number

needed to treat of 42 to prevent CP [7]. When used as a tocolytic in preterm deliveries, MgSO₄ was shown to prolong the delivery despite its safety concerns as compared to other tocolytic agents such as calcium channel blockers and betamimetics [8]. MgSO₄ in preeclampsia is known to reduce the risk of seizures by 50% which makes it an effective treatment in women to prevent eclampsia [9].

When administered to antenatal mothers, MgSO₄ can rapidly cross the placenta resulting in an increase in fetal and newborn magnesium levels in the serum [10]. Magnesium is known to produce fecal impaction and intestinal atony in infants by

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Table 1. Summary table.

No	Study ID, Country	Study Type	Sample Size (Case vs Control)	Gestational Age (weeks)	Gastrointestinal outcomes (Primary vs Secondary)	Magnesium Sulfate Regimen	Indication for Magnesium Sulfate	Antenatal steroids (Case vs Control)	Confounding factors
1.	De Veciana 1995, USA	Retrospective	48 vs 32	<33	Secondary	4 to 6 g load followed by 2 to 4 g/h ^a for at least 48 h and no longer than 7 days	Tocolysis	70% vs 0%	No steroids in the control group
2.	Wiswell 1996, USA	Retrospective	61 vs 76	<33	Primary	NI	Tocolysis/ Preeclampsia	NI	NI
3.	Schanler 1997, USA	Prospective	22 vs 19	<34	Secondary	6 g ^b load followed by 2 g/h infusion.	Tocolysis	NI	NI
4.	Kimberlin 1998, USA	Retrospective	124 vs 184	>20	Secondary	NI	Tocolysis	48.3% vs 10.8%	NI
5.	Elimian 2002, USA	Retrospective	190 vs 211	23–34	Secondary	4 g load followed by 2–3 g/h	Tocolysis	95.8% vs 61.6% (<i>p</i> < 0.0001)	NI
6.	Jazayeri 2003, USA	Retrospective	36 vs 36	<34	Secondary	NI	Tocolysis	100% vs 100%	NI
7.	Crowther 2003(ACTOMgSO ₄), Australia	RCT ^c	535 vs 527	<30	Secondary	4 g load followed by maintenance for 24 h	Neuroprotection	NI	NI
8.	Marret 2006 (PREMAG), France	RCT	352 vs 336	<33	Secondary	4 g loading dose infused over 30 minutes	Neuroprotection	95.1% vs 94.6%	NI
9.	Rouse 2008 (BEAM), USA	RCT	1174 vs 1244	24–31	Secondary	6 g load followed by 2 g/h infusion	Neuroprotection	96.9 vs 97.5 (<i>p</i> - 0.49)	NI
10.	Yokoyama 2010, Japan	Retrospective	58 vs 59	<35	Secondary	4 g/h for load followed by 1–2 g/h for prevention of preterm labor	Tocolysis	NI	Late preterm infants included in the study
11.	Paradisi 2011, Australia	RCT	48 vs 39	<30	Secondary	4 g load followed by 1 g/h for 24h	Neuroprotection	77% vs 79% (<i>p</i> -0.8)	NI
12.	Havranek T 2011, USA	Prospective	27 vs 29	<37	Primary	4–6 g load followed by 2–3 g/h	Tocolysis/ Preeclampsia	70% vs 52%	Late preterm infants included in the study
13.	Basu SK 2012, USA	Retrospective	289 vs 186	24–32	Secondary	6 g load followed by 2 g/h till delivery	Neuroprotection	NI	GA and prematurity
14.	Lee 2013, Korea	Retrospective	20 vs 61	<34	Secondary	NI	Preeclampsia	NI	NI
15.	Weisz 2014, Canada	Retrospective	1387 vs 3868	<32	Secondary	4 g load followed by 1 g/h up to 24h	Neuroprotection	97.1% vs 83.4%	NI
16.	Rattray BN 2014, USA	Retrospective	132 vs 23	24–32	Primary	6 g load followed by 2 g/h	Neuroprotection	94.6% vs 100% (NI)	GA, prematurity, NSAIDS
18.	James 2015, Ireland	Prospective	19 vs 19	<29	Secondary	4 g load over 20 min	Neuroprotection	74% vs 37%	NI
19.	Suh 2015, Korea	Retrospective	110 vs 40	<37	Secondary	NI	Preeclampsia	70.5 % vs 42.1 %	NI

Table 1. continued

No	Study ID, Country	Study Type	Sample Size (Case vs Control)	Gestational Age (weeks)	Gastrointestinal outcomes (Primary vs Secondary)	Magnesium Sulfate Regimen	Indication for Magnesium Sulfate	Antenatal steroids (Case vs Control)	Confounding factors
20.	Bouet PE 2015, France	Retrospective	81 vs 38	24–33	Secondary	4 g load followed by 1 g/h up to 12 h or delivery.	Neuroprotection	77% vs 30% ($p < 0.01$)	NI
21.	Bozkurt O 2015, Turkey	Retrospective	59 vs 328	24–32	Secondary	6 g load followed by 2 g/h for 24 h	Preeclampsia	NI	NI
22.	De Jesus 2015, USA	Retrospective	1091 vs 453	<29	Secondary	NI	NI	96% vs 76%	NI
23.	Gursoy 2015, Turkey	Prospective	25 vs 25	26–34	Secondary	6 g load followed by 0.8 g/h till delivery	Tocolysis/ Preeclampsia/ Neuroprotection	92% vs 76%	NI
24.	Morag 2015, Israel	Retrospective	145 vs 45	<32	Secondary	5 g load followed by 2 g/h	Neuroprotection /Preeclampsia	92.4 % vs 72.7 % ($p = 0.00$)	NI
25.	Alonso 2016, Spain	Prospective	62 vs 56	<32	Secondary	4 g load followed by 1 g/h up to 24 h or till delivery	Neuroprotection	NI	Variable doses in MgSO ₄ ^d
26.	Lloreda-Garcia 2016, Spain	Prospective	56 vs 51	<32	Secondary	NI	Neuroprotection	80.4 % vs 72.5 %	NI
27.	Shalabi 2017, Canada	Retrospective	2055 vs 2300	<27	Primary	Variable regimen	tocolysis/ Preeclampsia/ Neuroprotection	96.9 % vs 79.1%	NI
28.	Downey 2017, USA	Retrospective	11789 vs 16246	>26	Primary	Variable regimen	Tocolysis/ Preeclampsia/ Neuroprotection	55% vs 35%	NI
29.	Jung 2017, South Korea	Retrospective	143 vs 41	<32	Secondary	6 g load followed by 1 g/h maintain serum Mg ^e of 6 mg/dl	Tocolysis	79.7% vs 43.9 % ($p < 0.0001$)	NI
30.	Narasimhulu 2017, USA	Retrospective	237 vs 67	24–34	Secondary	4 g and 6 g load for preeclampsia and Neuroprotection respectively followed by 2 g/h	Neuroprotection/ Preeclampsia	76.8% vs 28.6% ($p < 0.01$)	NI
31.	Stockley 2018, Canada	Retrospective	173 vs 340	<29	Secondary	NI	Neuroprotection	95.7% vs 95.3% (p. 38, p. 63)	Growth restricted infants
32.	Qasim 2019, USA	Prospective	95 vs 10	<32	Secondary	4 g load followed by 2 g/h up to 12 h	Neuroprotection	78% vs 50% (p 0.12)	Small control size
33.	Mikhael 2019, USA	Retrospective	210 vs 92	<28	Primary	4 g load followed by 2 g/h up to 12 h or till delivery	Neuroprotection	95.2 % vs 64.1%	NI
34.	Özili 2019, Turkey	Retrospective	108 vs 172	<32	Secondary	6 g load followed by 2 g/h	Neuroprotection	100% vs 100%	NI
35.	Valdovinos 2020, Spain	Retrospective	146 vs 55	<32	Secondary	4 g load followed by 1–2 g/h	Neuroprotection	75% vs 53% ($p < 0.002$)	NI
36.	Wolf 2020, Denmark	RCT	343 vs 337	<32	Secondary	4 g loading dose	Neuroprotection	85.1 vs 86.8 (p–0.13)	NI

Table 1. continued

No	Study ID, Country	Study Type	Sample Size (Case vs Control)	Gestational Age (weeks)	Gastrointestinal outcomes (Primary vs Secondary)	Magnesium Sulfate Regimen	Indication for Magnesium Sulfate	Antenatal steroids (Case vs Control)	Confounding factors
37.	Hong 2020, South Korea	Retrospective	247 vs 509	<32	Primary	Variable regimen	Tocolysis/ Preeclampsia/ Neuroprotection	92.1% vs 89% (p 0.048)	NI
38.	Kim 2020, Seoul	Retrospective	109 vs 72	<28	Primary	4–6 g load followed by 2 g/h	Neuroprotection/ Tocolysis	84.4% vs 80.6% (p 0.548)	NI
39.	Üstün 2021, Turkey	Retrospective	186 vs 154	<32	Secondary	4 g load followed by 2 g/h	Neuroprotection	84.4% v 68.2% (p < 0.001)	NI
40.	Bansal V 2021, India	Prospective	50 vs 50	26–34	Secondary	4 g loading dose	Neuroprotection	NI	NI
41.	Chandran S 2021, India	Prospective	56 vs 28	<32	Primary	4 g load followed by 1 g/h up to 24 h or till delivery	Neuroprotection/ Preeclampsia	76.8% vs 28.6% (p < 0.01)	NI
42.	Gupta 2021, India	RCT	50 vs 50	28–36 ⁶⁷	Secondary	4 g load followed by 1 g/h for 12 h	Neuroprotection	NI	NI
43.	Sung 2022, South Korea	Retrospective	91 vs 135	<26	Secondary	4 g load followed by 1 g/h up to 24 h	Neuroprotection/ Preeclampsia	96.7% 92% (p 0.325)	NI
44.	Ayed 2022, Kuwait	Retrospective	47 vs 182	<32	Secondary	4 g loading dose	Neuroprotection	85.1 vs 86.8 (p-0.13)	NI

^aGrams per hour.^bgrams.^cRandomized Controlled Trial.^dMagnesium sulfate, NI- No information.^eMagnesium.

depressing the cholinergic activity in mothers exposed to high levels of magnesium [11, 12]. Hypotonia, hypercalciuria, parathyroid gland suppression, abnormal bone mineralization, and neutrophil dysfunction are some of the side effects reported in infants when mothers are exposed to $MgSO_4$ [13–16]. Intestinal hypomotility with increased meconium overload can lead to increased intraluminal pressure and thinning of intestinal walls which could be exaggerated and increase the risk of NEC or SIP when concomitantly exposed to steroids [17, 18]. $MgSO_4$ acts as a competitive antagonist against calcium and decreases the intracellular calcium and impedes intestinal smooth muscle contractility by interfering with actin-myosin interaction [19]. Studies have shown maternal exposure to $MgSO_4$ resulted in a decrease in intestinal blood flow and an increase in feeding intolerance in infants [11, 20, 21]. The alterations in intestinal blood flow can affect feeding intolerance and subsequent development of necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP) [22–26]. $MgSO_4$ has been associated with increased incidence of NEC in smaller infants and higher doses in recent studies [27, 28]. A few studies also provided evidence to the contrary [29–31]. A recent meta-analysis by Sheperd et al. [32] did not show an association between antenatal $MgSO_4$ and neonatal adverse outcomes.

OBJECTIVE

We conducted a systematic review and meta-analysis to address three questions: Is there an association between antenatal $MgSO_4$ administration and adverse gastrointestinal outcomes (GI) like NEC, SIP, feeding intolerance, time to reach full feeds, and GI-related mortality in preterm infants? In extreme preterm (<28 weeks) and very preterm infants (<32 weeks) does the administration of antenatal $MgSO_4$ have any adverse gastrointestinal outcomes (GI)? And thirdly, is the association based on the different types of indications of $MgSO_4$ like for neuroprotection, preeclampsia, or tocolysis?

METHODS

The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [33]. Our protocol was registered on the PROSPERO (CRD42022367246), the international prospective register for systematic reviews.

Eligibility criteria

Randomized or quasi-randomized clinical trials and non-randomized studies that reported GI-related morbidities when mothers of preterm infants were given $MgSO_4$ for either neuroprotection, tocolysis, or preeclampsia were included. Studies that did not report prespecified neonatal outcomes were excluded. Preterm infants whose mothers did not receive antenatal magnesium sulfate were considered as comparators. The following outcomes were included in this meta-analysis:

1. Necrotizing enterocolitis (stage ≥ 2 NEC) (defined as per modified Bell's staging) [34]
2. Surgical necrotizing enterocolitis (those needing surgical intervention)
3. Spontaneous intestinal perforation (SIP) (defined as per international standards) [35]
4. Feeding intolerance—as defined by authors.
5. Time to reach full feeds—Minimum of 150 ml/kg/d
6. Gastrointestinal (GI) related mortality—mortality related to NEC/SIP as reported by authors.

Information sources and search strategy

A systematic literature search was conducted in November 2022 using the following databases: PubMed, CINAHL Plus with Full Text (EBSCOhost), Embase (Elsevier), and the Cochrane Central Register of Controlled Trials, or CENTRAL (Ovid). The references of

the identified studies were also screened. No date or language restrictions or search filters were employed. Searches were run by a medical librarian (N.A.) in consultation with authors A.P. and S.D. Details of the search strategy are provided in the online Supplementary File. Results were deduplicated using the SR-Accelerator Deduplicator tool.

Study selection

The deduplicated results were transferred to Rayyan software (www.rayyan.ai) for screening. Title and abstract screening and full-text review of articles were done independently by A.P. and S.D. Any discrepancies were resolved by discussion and consensus (P.C). If necessary, trial authors were contacted by email correspondence to request missing data.

Assessment of risk of bias

All included studies were assessed for methodological quality. The risk of bias was assessed using elements of the Cochrane Collaboration tool 2.0 for randomized studies [36]. For non-randomized studies, the risk of bias for included studies was assessed using a modified Newcastle–Ottawa scale [37]. The following domains were evaluated: selection, comparability, and outcome. A priori, a score of $>7/9$ was deemed low risk, a score of 4–6/9 was deemed a moderate risk, and a score of $\leq 3/9$ was deemed a high risk of bias. Two authors (A.P. and S.D.) performed the risk of bias independently; conflicts were resolved after discussion and consensus. Similarly, A.P. and S.D. assessed the certainty of evidence (confidence in the estimate of effect) for each outcome based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [38]. Any discrepancies were resolved by discussion and consensus.

Data synthesis

All the studies were combined and analyzed using Review Manager V.5.3 (Cochrane Collaboration, Nordic Cochrane Center,

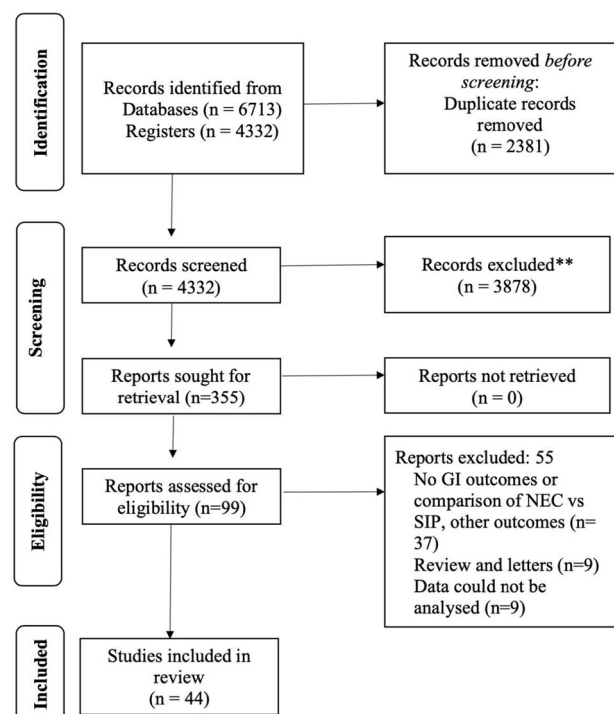


Fig. 1 Flowchart of search results (adapted from PRISMA 2021) [33] GI-gastrointestinal, NEC-Necrotizing enterocolitis, SIP-Spontaneous intestinal perforation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

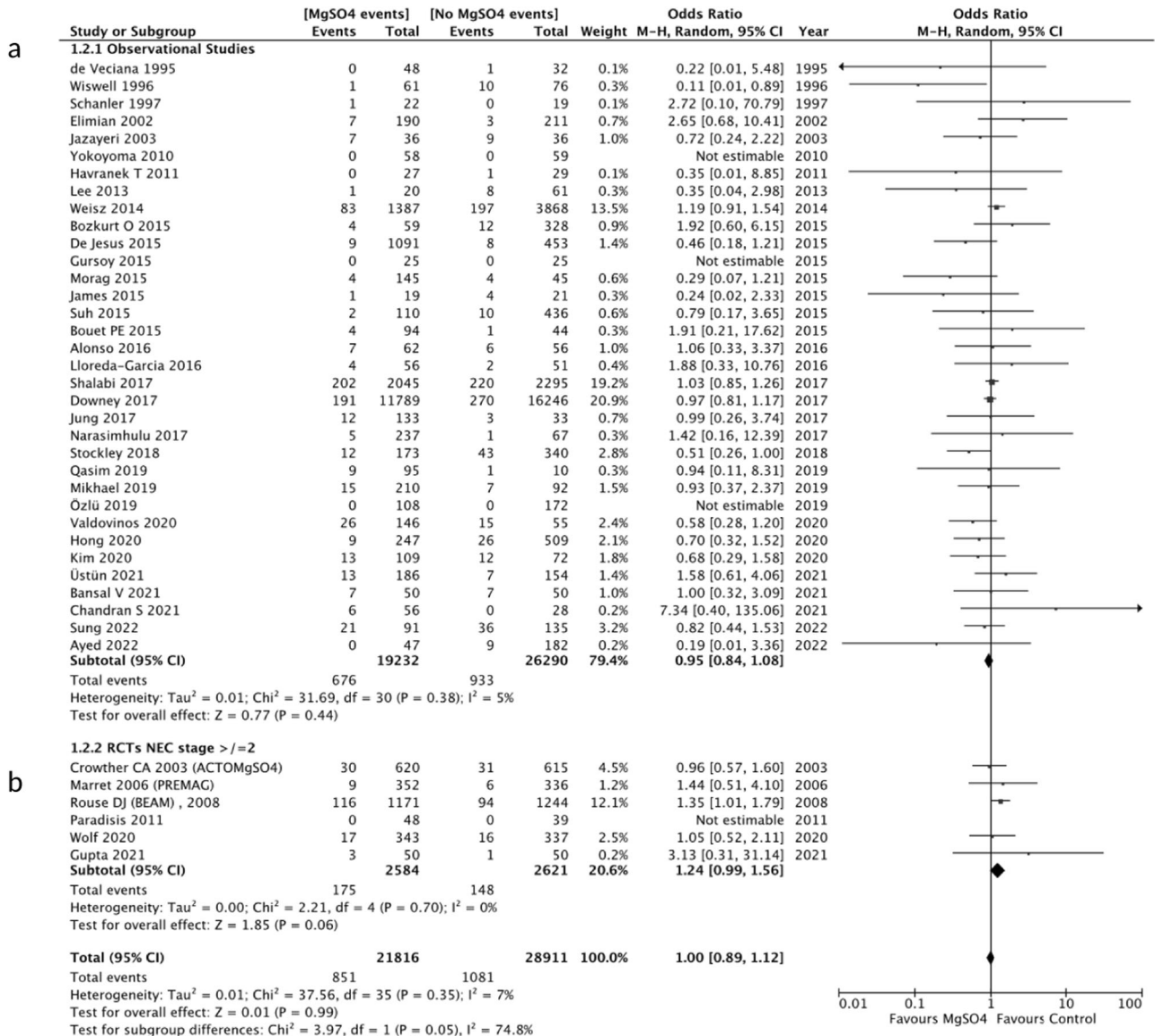


Fig. 2 Forest plots for primary outcomes. a Necrotizing enterocolitis (Stage ≥ 2) of observational studies. **b** Necrotizing enterocolitis (Stage ≥ 2) of Randomized Controlled Trials. **c** Surgical Necrotizing enterocolitis. **d** Spontaneous Intestinal Perforation (SIP). **e** Time to reach full feeds (150 cc/kg/d). **f** Feeding intolerance.

Copenhagen, Denmark). The mean difference with 95% CI was calculated for continuous outcomes. For dichotomous outcomes, the OR with 95% CI was calculated from the data provided in the studies. Adjusted odds ratios for potential confounders were extracted from the studies reporting these data. Studies reporting continuous variables as median and range or interquartile range were converted to mean and SD using a published calculator [39]. The random effects model was used to calculate summary statistics owing to anticipated heterogeneity. For some variables like gestational age, a fixed outcome model was used. Statistical heterogeneity was assessed by use of the Cochran Q statistic and by use of the I² statistic, which is derived from the Q statistic and describes the proportion of total variation that is due to heterogeneity beyond chance. We used the Egger regression test and funnel plots to assess publication bias if more than 10 studies were available for that particular outcome.

Sensitivity analysis was performed for studies based on the different type of indications for MgSO₄ (neuroprotection, pre-eclampsia, tocolysis) and based on gestational age (<28 weeks, <32 weeks)

RESULTS

Study selection and Study characteristics

A total of 6695 articles were identified through database searching. After duplicates were removed, 4332 articles underwent title and abstract screening. Ninety-nine full-text articles were assessed. A final total of 44 articles including 6 RCTs [40–45] and 38 non-randomized studies [20, 21, 27, 29–31, 46–76] were deemed eligible to be included in the final meta-analysis (Summary Table 1). The PRISMA flow diagram [33] is shown in Fig. 1a. A list of excluded studies and search strategies are provided in the Online Supplementary File.

i. Medical necrotizing enterocolitis (Stage ≥ 2 NEC) was reported in 40 included studies [20, 21, 29–31, 40–44, 46–51, 53–64, 68, 72] involving 51,466 infants. The pooled effect estimate favored the MgSO₄ group but was not statistically significant between the two groups in non-randomized studies (n = 45,524, OR: 0.95; 95% CI: 0.84–1.08, I² = 5%) and randomized controlled trials (n = 5205 OR: 1.24; 95% CI: 0.99–1.56, I² = 0%) (shown in Fig. 2a, b). Sensitivity

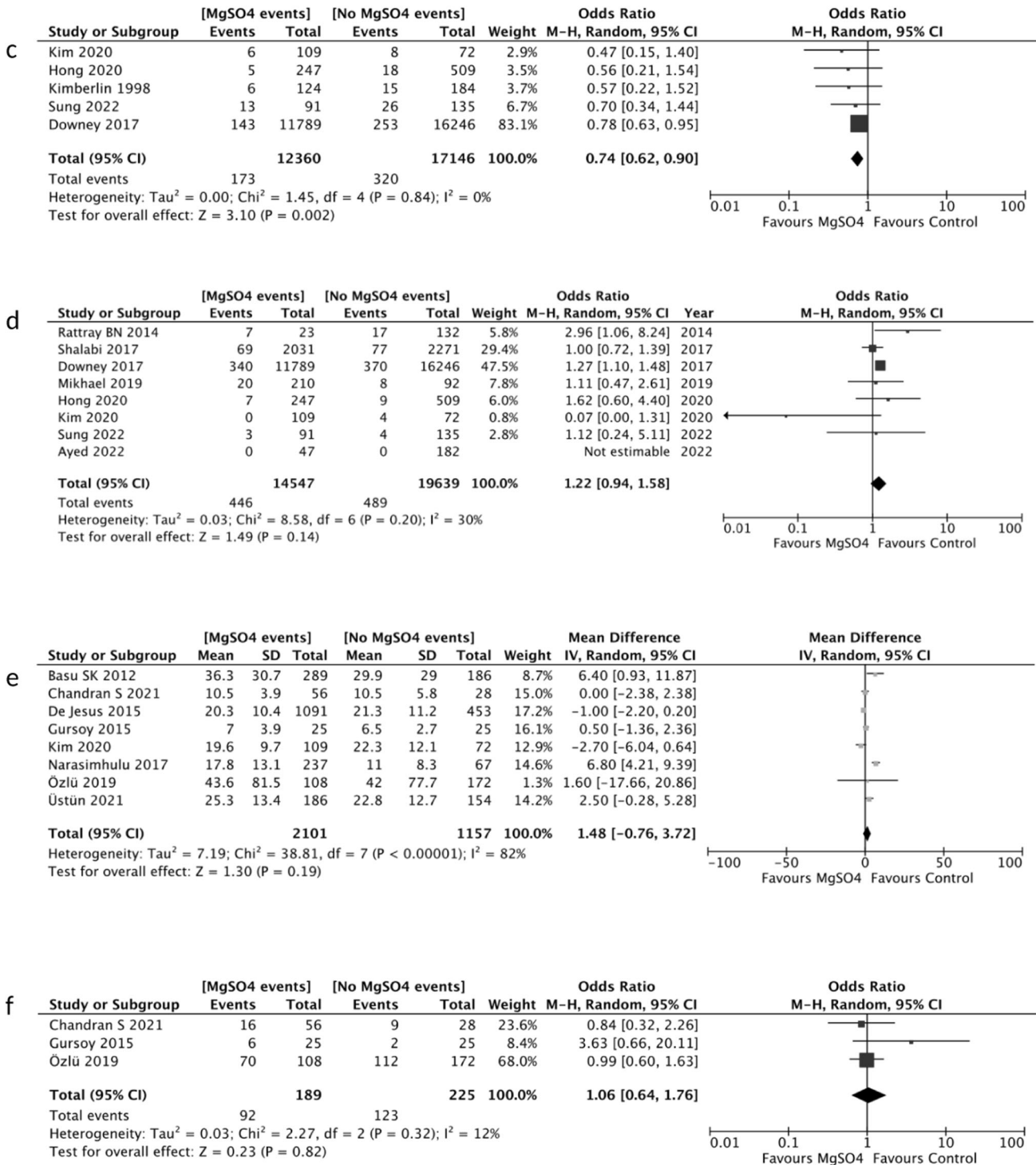


Fig. 2 Continued

analysis of infants <28 weeks reported in 5 studies ($n = 5133$, OR: 1.0; 95% CI: 0.83 to 1.20, $I^2 = 0\%$) reported no difference between the two groups (shown in Fig. 3a)

ii. Surgical NEC was reported in 5 studies [48, 63, 70, 71, 75] of the 44 studies involving 29,506 infants. The incidence of surgical NEC was significantly lower in the MgSO₄ group compared with controls ($n = 29,506$ OR:0.74; 95% CI: 0.62–0.90, ARR: 0.47%) (shown in Fig. 2c). There was no heterogeneity noted between the studies. Sensitivity analysis revealed no significance for infants <32 weeks

including 3 studies [70, 71, 75] ($n=1163$, OR: 0.60; 95% CI: 0.36 to 1.01, $I^2 = 0\%$) (shown in Fig. 3c).

iii. Spontaneous intestinal perforation was reported in 8 out of the 44 studies [27, 29, 31, 48, 63, 70, 71, 75] including 34,186 infants. Antenatal exposure of MgSO₄ did not increase the incidence of SIP in preterm infants ($n = 34,186$, OR: 1.22, 95% CI: 0.94–1.58, $I^2 = 30\%$) (shown in Fig. 2d). Subgroup analysis of the incidence of SIP in infants <32 weeks was analyzed in 5 studies [27, 70, 71, 74, 75] and there was no difference between groups ($n=1,610$ OR: 1.54, 95% CI: 0.67 to 3.55, $I^2 = 34\%$) (shown in Fig. 3d).

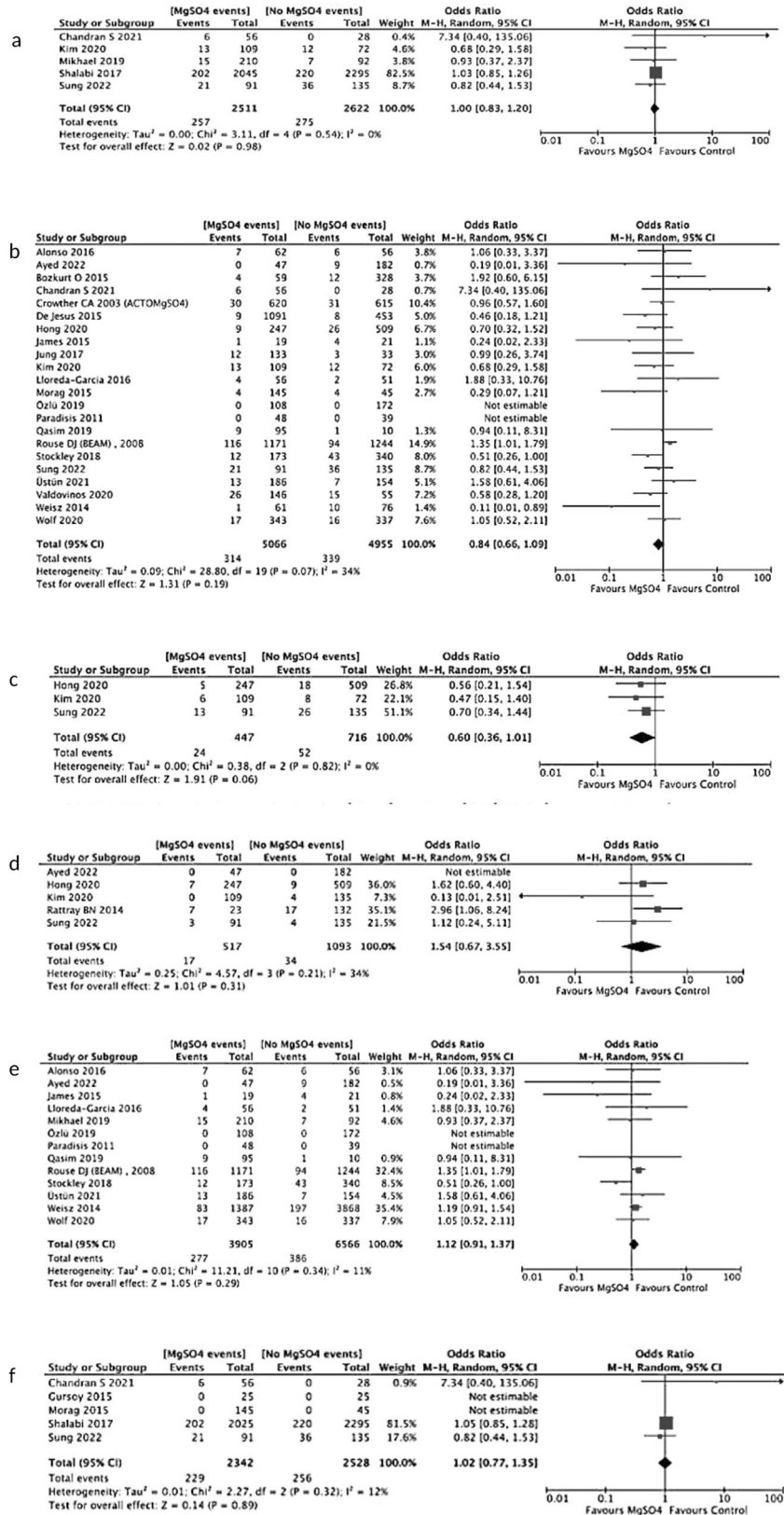


Fig. 3 Forest plots for various sub-group analysis. a Necrotizing enterocolitis (Stage ≥ 2) (≤28 weeks). **b** Necrotizing enterocolitis (Stage ≥ 2) (≤32 weeks). **c** Surgical Necrotizing enterocolitis (≤32 weeks). **d** Spontaneous intestinal perforation (SIP) (≤32 weeks). **e** Necrotizing enterocolitis (Stage ≥ 2) (Neuroprotection & ≤32 weeks). **f** Necrotizing enterocolitis (Stage ≥ 2) (Neuroprotection & Preeclampsia & ≤32 weeks). **g** Spontaneous intestinal perforation (Neuroprotection). **h** Spontaneous intestinal perforation (≤32 weeks). **i** Time to reach full feeds (150 cc/kg/d) (≤32 weeks). **j** Time to reach full feeds (150 cc/kg/d) (Neuroprotection).

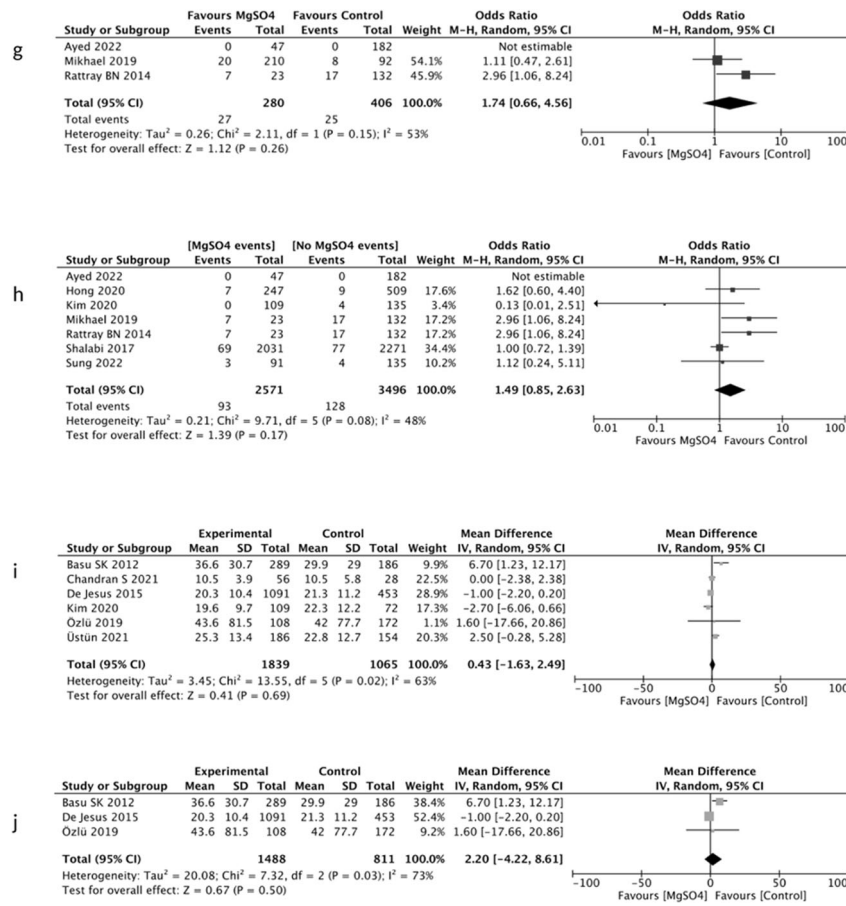


Fig. 3 Continued

- iv. Time to reach full feeds was also analyzed and was reported in 8 [21, 52, 59, 65, 68, 71–73] of the 44 included studies involving 3,258 infants. Full enteral feeds were defined as a minimum of 150 cc/kg/day for analysis. There was no difference in time taken to achieve full feeds (20.3 d vs 20.7 d in the MgSO₄ group vs the control group (MD:1.48; (95% CI: -0.76 to 3.72) (shown in Fig. 2e).
- v. Feeding intolerance was reported in 3 studies [21, 29, 73] out of the 44 involving 414 infants ($n = 414$, OR: 1.06 (95% CI: 0.64–1.76, I² = 12%) (shown in Fig. 2f).
- vi. GI-related mortality (NEC/SIP related) was reported in only one study ($n = 4355$) [29]. There was no statistically significant difference between the two groups (4.6% vs 3.8%, $p = 0.18$) in mortality. Stratified analysis based on gestational age (22–25 weeks & 26–27 weeks) did not show any significance either between the two groups.

Sensitivity and adjusted analysis

Sensitivity analysis was performed separately for all studies including infants less than 32 weeks of gestation. Seventeen studies involving 10,021 infants were analyzed [40, 43–45, 54, 55, 58–62, 64, 66–75]. The incidence of medical NEC was similar among the MgSO₄ group as compared to controls (OR: 0.84; 95% CI: 0.66 to 1.09) (shown in Fig. 3b). Studies that used MgSO₄ for neuroprotection alone (13 studies, $n = 10,471$) were analyzed, and neuroprotection or preeclampsia (5 studies, $n = 4870$) were analyzed separately. Both analyses did not show any statistical difference between the two groups (shown in Fig. 3e, f). For the outcome of SIP, sensitivity analysis was performed for very preterm infants and studies that used MgSO₄ for

neuroprotection. A total of 3 studies for neuroprotection [27, 31, 74] (shown in Fig. 3g) and seven studies [27, 29, 31, 70, 71, 74, 75] for <32 weeks were included (shown in Fig. 3h) and there was no difference between the two groups. For other indications like tocolysis and preeclampsia, not enough studies were available for meta-analysis. For the outcome of time to reach full feeds subgroup analysis on preterm infants <32 weeks [52, 59, 71–73, 77] (shown in Fig. 3i) and studies that used MgSO₄ for neuroprotection [52, 59, 77] (shown in Fig. 3j) showed no difference between two groups.

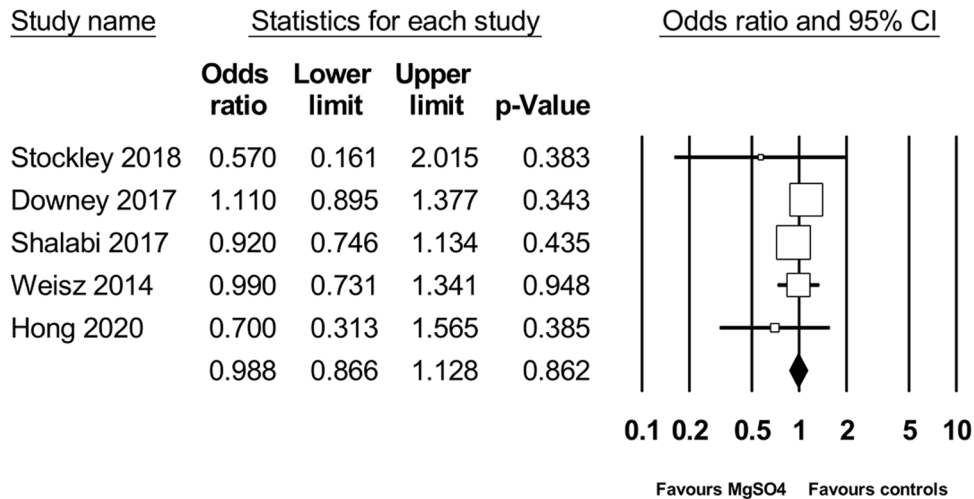
We performed an adjusted odds ratio analysis for medical NEC (5 studies) and surgical NEC (3 studies) and SIP (4 studies) (shown in Fig. 4a–c). None of the analysis showed any statistical significance between the two groups. Analysis for superior mesenteric artery (SMV) blood flow velocity (cm/s) indices like mean velocity (MV), peak systolic velocity (PSV), and end-diastolic velocity (EDV) was reported in only 2 studies [21, 73]. There was no difference between the two groups for all the indices (online supplementary file).

Risk of bias (RoB) and Certainty of Evidence (CoE)

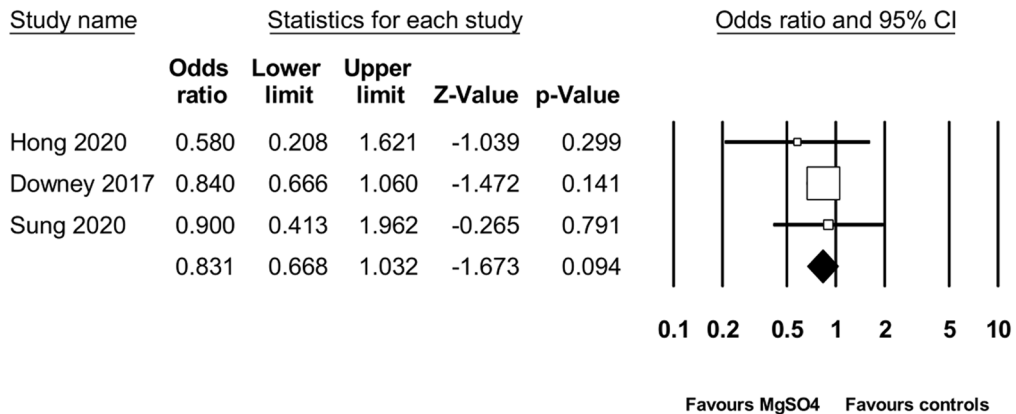
All the non-randomized studies were assessed for quality of evidence using the Newcastle-Ottawa scale [37]. All 38 studies were scored as good (>6) (Online supplementary file). The risk of bias assessment for RCTs was performed as per the Cochrane Risk of Bias 2.0 tool [78] in five domains (shown in Fig. 5). Of the six RCTs included, two studies were adjudged as high risk of bias [41, 42], one with some concerns [43], and two studies with low risk of bias (shown Fig. 5) [40, 45].

The certainty of evidence (CoE) as per GRADE [38] for all outcomes is provided in Table 2. For outcomes of medical and

a



b



c

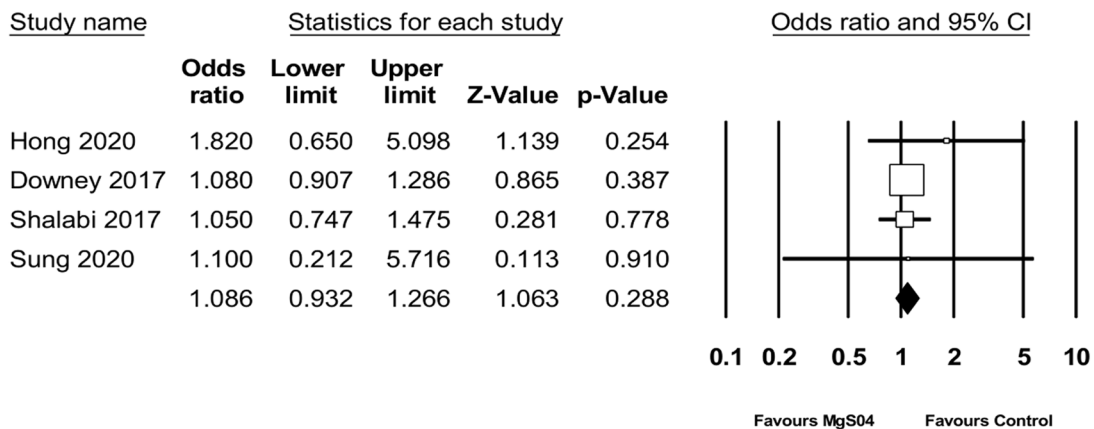


Fig. 4 Adjusted Odds Ratio (aOR) analysis. **a** Necrotizing enterocolitis (Stage ≥ 2). **b** Surgical Necrotizing enterocolitis. **c** Spontaneous intestinal perforation (SIP).

surgical NEC, SIP, and GI-related mortality, the CoE was determined to be “very low”.

Neither visual inspection of funnel plots nor the Egger test suggested publication or selection bias for the outcome of medical NEC [20, 21, 30, 31, 40–51, 53–72, 74–76] (41 studies) (shown in Fig. 6). The number of studies was insufficient to evaluate publication bias for the other outcomes.

DISCUSSION

Our review demonstrates that there is no difference in the incidence of medical necrotizing enterocolitis SIP, feeding intolerance, or time to reach full feeds in infants exposed to antenatal magnesium sulfate as compared to no exposure. We did not find any adverse association between the use of antenatal $MgSO_4$ and GI morbidities in extreme preterm or very preterm infants. On the contrary, infants

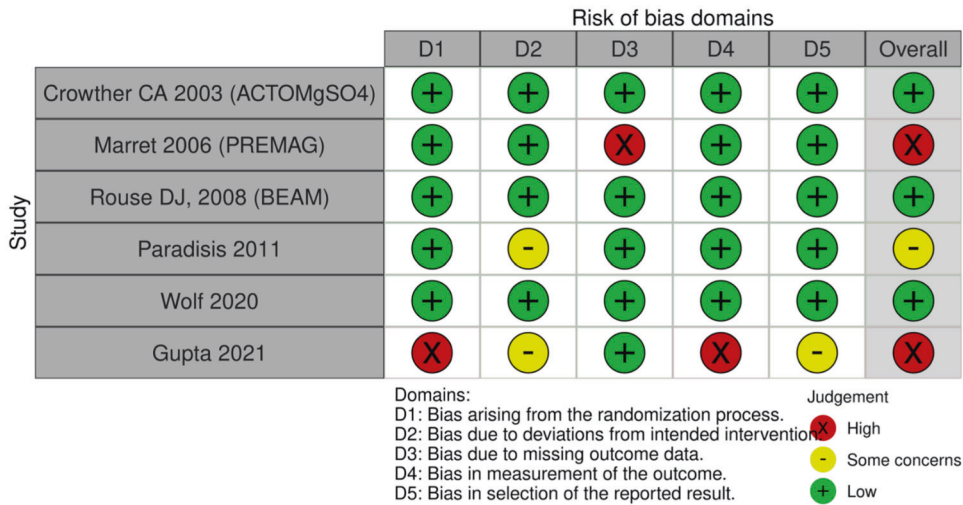


Fig. 5 Risk of Bias 2.0 for randomized controlled trials.

Table 2. GRADE: Summary of findings (SoF) for main outcomes.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with MgSO ₄ group			
NEC - Stage ≥2	35 per 1000	34 per 1000 (30 to 38)	OR 0.95 (0.84 to 1.08)	45522 (34 studies)	⊕○○○ Very low ^a
NEC - Stage ≥ 2 (RCTs)	56 per 1000	69 per 1000 (56 to 85)	OR 1.24 (0.99 to 1.56)	5205 (6 studies)	⊕⊕○○ Low ^b
Surgical NEC	19 per 1000	14 per 1000 (12 to 17)	OR 0.74 (0.62 to 0.90)	29506 (5 studies)	⊕○○○ Very low ^c
Spontaneous Intestinal Perforation (SIP)	25 per 1000	30 per 1000 (23 to 39)	OR 1.22 (0.94 to 1.58)	34186 (8 studies)	⊕○○○ Very low ^d

^aWe downgraded evidence by three levels due to the serious risk of bias, heterogeneity, and indirectness.

^bWe downgraded the evidence by two levels due to indirectness, and imprecision.

^cWe downgraded evidence by three levels due to serious risk of bias, heterogeneity and indirectness and inconsistency.

^dWe downgraded evidence by three levels due to heterogeneity, indirectness, and inconsistency.

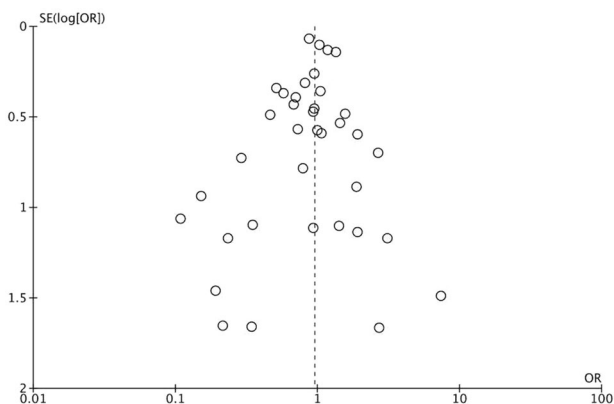


Fig. 6 Funnel plot assessing publication bias for Necrotizing enterocolitis (Stage ≥ 2).

born to mothers who received antenatal MgSO₄ had a lower incidence of surgical NEC by 26%. There was no difference in outcomes of NEC based on the type of indication like neuroprotection, preeclampsia, or tocolysis. Antenatal MgSO₄ exposure did not increase gastrointestinal-related mortality in preterm infants.

Magnesium Sulfate has been used in imminent preterm deliveries less than 32 weeks for neuroprotection as a routine practice for the past decade after the large clinical trials [42, 44] and endorsement by ACOG and WHO [5, 6]. Its role in preeclampsia and as a tocolytic had been established long before [8, 9]. Concerns about maternal adverse effects were highlighted for the last 50 years but red flags were raised for its association with NEC and SIP in preterm infants since 2014 [27]. MgSO₄ at higher cumulative doses and smaller infants (<25 weeks) increased the odds of NEC and SIP by 2–9 times [27, 28]. Contrasting evidence with absolutely no association was found in large observational studies [29, 63]. This difference could be explained by the adjustment of confounding factors for SIP/NEC in the later studies, for example, the use of steroids, indomethacin, small for gestational, and use of mechanical ventilation. We found no association between MgSO₄ and NEC when adjusted odds ratio (aOR) was analysed, with a caveat that the adjusted confounding factors were not uniform across all studies and only 7 studies [29, 53, 54, 63, 66, 70, 75] reported the adjusted data (Shown in Fig. 4).

Various hypotheses were proposed for the association between antenatal MgSO₄ and adverse GI-outcomes. These include calcium antagonism and decreasing actin-myosin interaction, intestinal hypomotility, increased resistance, and reduction of blood flow in

the mesenteric artery. Our results are consistent with the results of the previous meta-analysis [4, 32]. Zeng et al reported on cerebral palsy and overall mortality with ten studies included and Shepherd et al reported on NEC, SIP and NEC/SIP-related death as a part of an overall review of neonatal outcomes of antenatal MgSO₄. However the previous reviews [4, 32] were not specific to the GI-outcomes, the number of included studies were significantly less compared to the current review which justifies the need for extensive and updated review.

We found that the antenatal MgSO₄ group had decreased the incidence of surgical NEC by 26%. This finding is contrary to the conventional reports from previous studies [27, 28]. The reduced incidence of surgical NEC in preterm infants exposed to antenatal MgSO₄ had been reported in previous observational studies [31, 63]. This positive effect could be due to the attenuation of peroxide-induced vasoconstriction by inhibiting thromboxane synthesis [79]. Thromboxane is an inciting agent for NEC [34]. MgSO₄ also increases the blood flow by vasodilatation [79]. We also attribute the beneficial effects due to the overall benefit of MgSO₄ in preterm infants and the fact that infants in the MgSO₄ group could be less sick and more hemodynamically stable. This observation needs further exploration by larger studies.

The effect of MgSO₄ on intestinal blood flow indices is inconclusive. Theoretically, MgSO₄ will induce vasodilatation by calcium antagonism, attenuation of peroxide-induced vasoconstriction, inhibition of platelet activation induced by adenosine diphosphate, and release of vasoactive substances [79, 80]. Studies reporting on blood flow velocities in mesenteric arteries were limited [20, 21, 73] and none reported any significant change in mean velocity, end-diastolic velocity, peak systolic velocity, or the resistivity index between the two groups (online supplementary file).

CONCLUSIONS AND IMPLICATIONS

Our study findings do not support any clear association between antenatal magnesium sulfate administration and adverse gastrointestinal morbidities or gastrointestinal-related mortality in preterm infants. Concerns regarding the adverse effects of antenatal MgSO₄ administration on GI morbidity or mortality should not be a hurdle in its routine use when indicated. This review should encourage clinicians to not deviate from feeding practices in the neonatal units when premature infants are exposed to antenatal MgSO₄. The biological plausibility of MgSO₄ causing NEC or SIP by decreased blood flow in mesenteric arteries needs further studies.

Strengths and limitations

The strength of this meta-analysis was that we used a comprehensive search strategy for our literature search, published our protocol a priori, and assessed the certainty of evidence using GRADE. To our knowledge, this is the largest meta-analysis on adverse neonatal GI outcomes and antenatal MgSO₄. Nonetheless, there were several limitations. The majority of the studies were non-randomized, studies were heterogeneous, variable doses of MgSO₄ were used in different studies and dose-related associations were not evaluated.

DATA AVAILABILITY

All data included in the analysis are available in public domain. The details including search strategy, list of excluded studies with reason for exclusion, risk of bias assessment and quality assessment of included studies are all available in the online supplementary file.

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AUTHOR CONTRIBUTIONS

AP: conceptualized, formulated the research methodology, performed formal analysis, curated data, and wrote the original draft, reviewed and edited the manuscript. Nell Aronoff participated in formulating the research methodology and provided resources for the literature search. She also contributed to writing, reviewing, and editing the manuscript. PC: administered the project and also contributed to manuscript writing, reviewing and editing. SD: conceptualized, formulated the research methodology, performed formal analysis, curated data, wrote the original draft, reviewed, edited the manuscript, supervised/administered

the whole project and guarantor for the project. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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