Thieme

Does Antenatal $MgSO_4$ Administration to the Mother in the Event of Imminent Premature Birth Reduce the Occurrence of Infantile Cerebral Palsy in the Child? – An Umbrella Review

Verringert die antenatale $MgSO_4$-Gabe an die Mutter bei drohender Frühgeburt das Auftreten einer infantilen Zerebralparese beim Kind? – Ein Umbrella Review

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Key words
neuroprotection, preterm birth, magnesium sulfate, evidence, umbrella review, PRISMA, AMSTAR score

Schlüsselwörter
Neuroprotektion, Frühgeburt, Magnesiumsulfat, Evidenz, Umbrella Review, PRISMA, AMSTAR-Score

received 16.9.2022
accepted after revision 4.3.2023

Bibliography
Geburtsh Frauenheilk 2023; 83: 602–611
DOI 10.1055/a-2049-2976
ISSN 0016-5751

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Deutsche Version unter:
https://doi.org/10.1055/a-2049-2976.
Additional material is available at
https://doi.org/10.1055/a-2049-2976.

ABSTRACT

Introduction Premature births have a significantly increased risk of developing cerebral palsy. This clinical picture involves great restrictions and impairments in the lives of the children and their families. Its prevention is therefore of great importance. One method of neuroprotection to reduce the rate of infantile cerebral palsy is the antenatal administration of magnesium sulfate to the mother. The aim of this paper is to present the current state of research of existing reviews and meta-analyses on the topic and to review the evidence for this intervention.

Material and Methods A literature search was conducted within the framework of an umbrella review in the electronic database PubMed in February 2022 to identify all relevant publications on the topic. The search was structured using the PRISMA statement. The important methodological characteristics and the results of the studies were then extracted. In addition, a quality assessment of the studies was performed using the AMSTAR score.

Results Two systematic reviews with meta-analysis, one systematic review, and one individual participant data meta-analysis were included in this study. The total number of subjects

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was n = 6178. The publications conclude that the antenatal administration of magnesium sulfate to the mother significantly reduces the risk of cerebral palsy in preterm infants. Due to the high quality of 3 of the 4 studies, a high level of evidence can be assumed.

Conclusion The evidence for antenatal magnesium sulfate administration for the prophylaxis of cerebral palsy in preterm infants is high. However, further research is needed to determine which doses of magnesium and up to which gestational age the administration is useful.

ZUSAMMENFASSUNG

Einleitung Frühgeborene haben gegenüber Reifgeborenen ein deutlich erhöhtes Risiko, eine Zerebralparese zu erleiden. Dieses Krankheitsbild birgt große Einschränkungen und Beeinträchtigungen im Leben der Kinder und ihrer Familien. Die antenatale Verabreichung von Magnesiumsulfat an die Mutter vor Entbindung stellt eine Maßnahme dar, um das Risiko für eine infantile Zerebralparese zu senken. Ziel dieser Arbeit ist die Darstellung des aktuellen Forschungsstands bestehender Reviews und Metaanalysen zum Thema und die Überprüfung der Evidenz dieser Maßnahme.

Material und Methoden Im Februar 2022 wurde eine Literaturrecherche im Rahmen eines Umbrella Reviews in der elektronischen Datenbank PubMed durchgeführt, um alle relevanten Veröffentlichungen zum Thema zu identifizieren. Die Suche wurde mithilfe des PRISMA-Schemas strukturiert. Daraufhin wurden die wichtigen methodischen Kennzeichen sowie die Ergebnisse der Studien herausgelesen. Außerdem wurde eine Qualitätsbewertung der Studien mit dem AMSTAR-Score durchgeführt.

Ergebnisse Insgesamt wurden 2 systematische Reviews mit Metaanalyse, 1 systematisches Review und 1 Individual-Participant-Data-Metaanalyse in diese Arbeit eingeschlossen. Es ergab sich eine Gesamtprobandinnenzahl von n = 6178. Die Publikationen kommen zu dem Ergebnis, dass eine antenatale Magnesiumsulfatgabe an die Mutter das Risiko für das Erleiden einer Zerebralparese bei Frühgeborenen signifikant mindert. Aufgrund der hohen Qualität von 3 der 4 Studien kann eine hohe Evidenz angenommen werden.

Schlussfolgerung Die Evidenz für die antenatale Magnesiumsulfatgabe zur Prophylaxe von Zerebralparesen des Frühgeborenen ist hoch. Jedoch muss weiter erforscht werden, welche Dosen an Magnesium und bis zu welchem Gestationsalter die Gabe sinnvoll ist.

Introduction/Background

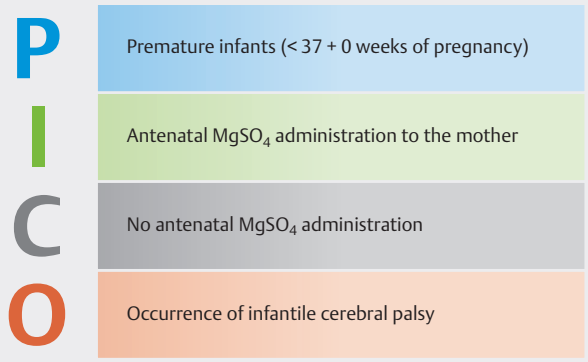
Epidemiology of premature births and cerebral palsy

Globally, more than 1 in 10 newborn is born prematurely [1, 2]. In Germany, the number of premature infants is over 8%, with 1.5% of all children being born as extremely or very premature infants before 32+0 weeks of pregnancy [3, 4, 5]. Premature infants have a significantly higher morbidity and mortality risk compared to full-term infants. Among other things, the probability of premature infants suffering from cerebral palsy is increased compared to children born full-term [6]. The prevalence of cerebral palsy depends on gestational age. For children with a gestational age > 36+0 weeks of pregnancy, the literature gives the prevalence as 1.35/1000, for a gestational age between 32+0 and 36+0 weeks of pregnancy it is 6.75/1000, for premature infants between 28+0 and 31+0 weeks of pregnancy 43.15/1000, and before 28+0 weeks of pregnancy it is even 82.25/1000 [6]. In the United States, cerebral palsy is diagnosed annually in 1 in 345 children [7], in Germany 3042 patients were treated in 2016 for the ICD-10 main diagnosis G80 (infantile cerebral palsy) [8], the prevalence of cerebral palsy in premature infants is tending to decrease (with the exception of extremely premature infants) in Europe [9]. In countries with a lower standard of living (developing and emerging countries) there is a higher prevalence than in industrialized countries [10, 11].

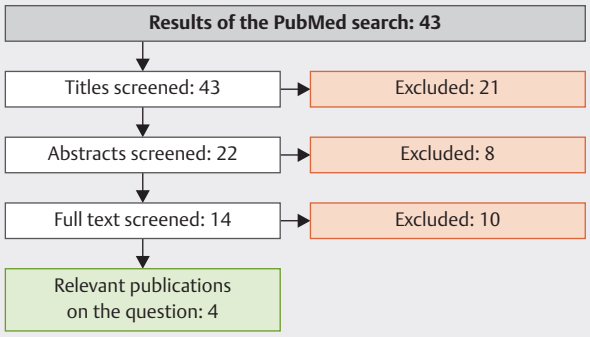
Definition and etiology of cerebral palsy

Cerebral palsy describes a group of differently pronounced symptoms, which always include movement disorders and spasticity and originate in the brain. The clinical manifestation of cerebral palsy differs in the type of movement disorder, the degree of functional abilities and limitations, and the body parts affected. In 10% of cases, the cause of cerebral palsy is impaired brain development. 90% result from a damaging effect on the brain just before, during or just after birth, which results in lesions of healthy brain tissue. Because the area of the periventricular white matter is a highly active proliferative zone in the immature brain, this area is particularly prone to injury in premature infants. In addition, development-related metabolic and molecular factors increase the susceptibility of the periventricular white matter in the prematurely born child [12].

Disorders of the metabolism in the brain caused by ischemia, inflammatory processes, or oxygen-deficient states, which can often occur in premature infants, trigger a cascade that ultimately leads to apoptosis or necrosis of glial cells and neurons [13]. Due to the reduced supply, the function of the adenosine triphosphate (ATP)-dependent processes decreases, resulting in a loss of membrane potential. As a result, voltage-gated calcium channels open. The high intracellular level of calcium causes glutamate to be released and accumulate in the extracellular space, thereby activating glutaminergic n-methyl-D-aspartate channels (NMDA channels). Additional calcium flows into the cell through the activated NMDA channels. The excess calcium activates proteolytic mechanisms and produces free oxygen radicals, which activates inflammatory and apoptotic automatisms. Since magnesium blocks these NMDA receptors, the administration of magnesium can prevent tissue destruction through excitotoxicity and the resulting apoptosis [12, 14, 15]. Since cerebral palsy is irreversible damage to the brain, which has a significant impact on the lives of the chil-



▶ **Fig. 1** PICO model.



▶ **Fig. 2** Flowchart for systematic literature research according to the PRISMA statement (Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1 000 097 doi:10.1371/journal.pmed1000097).

dren affected, the prevention of cerebral palsy is particularly important.

Objective and research question

In 2009, a Cochrane review on the topic "Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus" was published [16]. This review summarized the state of research at the time. The aim of this paper is to develop an update on the current state of knowledge on antenatal magnesium sulfate administration in the event of imminent premature birth, i.e. to determine whether new findings have emerged since the Cochrane review was published and what the current evidence base for this measure is. Therefore, the state of knowledge of all systematic reviews and meta-analyses published since 2009 should be summarized and evaluated. The research question was developed using the PICO model (see ▶ **Fig. 1**). The aim was to determine the neuroprotective effects of magnesium sulfate in premature infants. The occurrence of infantile cerebral palsy is of particular interest. The magnesium sulfate is administered antenatally to the mother in the event of imminent premature birth. This leads to the following research question: *Does antenatal administration of magnesium sulfate to the mother in the event of imminent premature birth reduce the occurrence of infantile cerebral palsy in the child?*

Materials and Methods

Study design, search strategy, and selection of studies

A systematic literature search was attempted in order to answer the research question. On 21 February 2022 (search update on 13 November 2022), an electronic database search was carried out in PubMed. The search was structured using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [17] (see ▶ **Fig. 2**). Since the study was designed as an umbrella review, only systematic reviews and meta-analyses published after the publication of the Cochrane review by Doyle et al. (2009) [16] were considered. The aim of umbrella reviews is to compile the results of existing systematic reviews and to evaluate their results with regard to their evidence [18, 19]. Primary literature in the form of randomized controlled trials (RCT) on the issue was reviewed, but not taken into account in the scientific evaluation.

The search was carried out using previously defined inclusion and exclusion criteria as a collaboration between the two first authors. The results were merged in the next step.

Search term

The search terms "neuroprotection", "cerebral palsy", "preterm birth" and "magnesium sulfate" were combined (for complete search term see Supplementary Material). The filters "Meta-Analysis", "Review", and "Systematic Review" and Meshterms were applied. In addition, only publications after 2009 were considered in order to expand the research state of the Cochrane review [16].

Inclusion and exclusion criteria

In order to obtain an overview of the current state of research on the subject of neuroprotection through antenatal magnesium administration, systematic reviews and meta-analyses were included that show a systematic literature search and were published after the Cochrane review ("Magnesium sulphate for women at risk of premature birth for neuroprotection of the fetus") in 2009 [16]. In addition, the studies included in the reviews and meta-analyses should meet the criteria of a randomized controlled trial. The participants should be women with an acute risk of premature birth (< 37+0 weeks of pregnancy). Further inclusion criteria were defined as follows:

- Neuroprotection through magnesium administration
- Infantile cerebral palsy as the primary outcome,
- Studies conducted on humans,
- Language of publication German or English.

Data extraction

First, the methodological characteristics of the reviews and meta-analyses considered, as well as the RCTs included there, were analyzed and presented. These included the type of study, the country of publication, the dosage of magnesium sulfate, the number and weeks of pregnancy of the subjects, the study objective, the primary outcomes, and the inclusion/exclusion criteria. In addition, the results of the studies for the primary outcome "occurrence of cerebral palsy" were presented. The relative risk (RR) or odds ratio (OR) (95 % confidence interval) was considered as a measure of the results of the included reviews and meta-analyses.

Assessment of evidence

The AMSTAR score [20] was used to systematically evaluate the evidence of the included studies.

Results

Results of the systematic literature search

The literature search in PubMed yielded 43 results. Based on the title, 21 studies could be excluded. Criteria for this were that the publications do not deal with neuroprotection using magnesium sulfate, the development of infantile cerebral palsy was generally treated, neuroprotection was observed in children at term, or risk factors for the negative neurological development in premature infants or very low-birthweight children were the focus. After reviewing the abstracts, another eight studies could be excluded. The reasons for this were duplications and publications in French and Danish, the use of substances other than magnesium sulfate for neuroprotection and the description of biochemical processes in the development of cerebral palsy. The full text of the 14 remaining publications were assessed, of which a further 10 were excluded due to language, a missing or unspecified search strategy, or an inappropriate study design. Four articles were ultimately included in this review [16, 21, 22, 23]. This process is shown in ▶ **Fig. 2**, a representation of the PRISMA statement [17]. One of these articles presented the Cochrane review from 2009 [16], which was intended to serve as a comparative study to determine whether the state of research has changed since then.

General characteristics of the included studies

The four publications are two systematic reviews with meta-analysis, one systematic review and one individual participant data meta-analysis from Denmark, the USA, Germany, and Australia/New Zealand. Some of the articles overlap completely in the included studies. The studies by Mittendorf et al. (2002) [24], Crowther et al. (2003) [25], Marret et al. (2007) [26], and Rouse et al. (2008) [27] were cited in each of the four publications and their data were used in the meta-analyses. Duley et al. (2007) [28] is cited in three of the four papers. Wolf et al. (2020) [29] is only referenced in Wolf et al. (2020) [21]. All included studies are RCTs with the aim of investigating neuroprotection in premature infants with magnesium sulfate. The exceptions here are the publication by Marret et al. (2007) [26], which also integrates a tocolysis group, as well as the publication by Duley et al. (2007) [28], which primarily deals with the topic of preeclampsia. All six studies use a different dosage of magnesium sulfate. Administration always begins with a bolus (4–6 g $MgSO_4$) followed by a maintenance dose of 0–3 g/h. In the four reviews or meta-analyses, the number of subjects varied from n = 4025 to n = 6178. The aim of the publications is to examine the efficacy and safety of antenatal magnesium sulfate administration for neuroprotection in the event of imminent premature birth. Crowther et al. (2017) [23] examine this issue with regard to different effects of neuroprotection depending on the cause of the premature birth, the initial reason for the magnesium sulfate administration, the gestational age, the dosage, and the timing of the administration. The occurrence of infantile cerebral palsy is the primary outcome in each of the publications. In addition, mortality, other neurological impairments in the child, and negative maternal events are primary outcomes. The general characteristics of the reviews or meta-analyses considered and the RCTs included in these are presented in detail in ▶ **Table 1**.

Results of the included studies with regard to the defined outcomes

The three meta-analyses included refer to a significant risk reduction when using magnesium sulfate in imminent premature birth with comparable outcome measures (RR 0.68, 95 % CI 0.54–0.85 [21], RR 0.68, 95% CI 0.54–0.87) [16, 23]. This applies to any gestational age. The risk of moderate to severe cerebral palsy is also reduced in the magnesium sulfate group compared to the placebo group. The included review states that the five randomized controlled trials and four meta-analyses considered indicate a significant 32% reduction in cerebral palsy with the administration of magnesium sulfate in premature births [22]. An review of the results can be found in ▶ **Table 2**.

Evidence assessment of the included studies

Three of the four included reviews [16, 21, 23] are of high quality according to the AMSTAR rating, resulting in a high level of evidence. In one review, seven out of 11 criteria must be answered with unclear/no/not applicable. The quality can therefore be classified as rather low [22]. The results of this review are therefore of low evidence. ▶ **Table 3** shows the detailed evidence assessment according to the AMSTAR score.

Discussion

Summary of results

A total of two systematic reviews with meta-analysis [16, 21], one systematic review [22], and one individual participant data meta-analysis [23] were included in this paper. These deal with the question to what extent premature infants benefit from neuroprotection by magnesium sulfate compared to a placebo group. The occurrence of infantile cerebral palsy was chosen as the primary outcome. The reviews/meta-analyses came to a clear conclusion: In the magnesium sulfate group, the risk of suffering from cerebral palsy was significantly reduced compared to the placebo group. According to the AMSTAR score, three of the four publications are of high quality, which means that the results can be concluded to be highly evident.

▶**Table 1** Methodical characteristics of the included reviews and meta-analyses and the RCTs considered there, as well as primary outcomes of the included reviews and meta-analyses.

Study	Study type/ type of review	Country and intervention of each included study	$MgSO_4$ administration/dosage	Characteristics of the subjects	Study objective	PICO model	Endpoints/outcomes	Inclusion/exclusion criteria
Wolf et al. 2020 [21]	Systematic review, meta-analysis	Mittendorf 2002 [24], United States	4 g bolus, 0 or 2–3 g/h	149 women, 25–33 weeks of pregnancy	Update of the Cochrane review [2] including own study, which increases the number of subjects in a meta-analysis by 10%	P = premature birth I = antenatal $MgSO_4$ administration C = premature birth without antenatal $MgSO_4$ administration O = Risk for CP	Primary outcome: Occurrence of CP	Studies that compare i. v. treatment with $MgSO_4$ and with placebo in imminent premature birth Study outcomes must include: Neonatal mortality, neurological outcomes with follow-up ≥ 12 months
		Crowther 2003 [25], Australia/ New Zealand	4 g bolus, 2 g/h	1062 women, <30 weeks of pregnancy				
		Duley 2006 [28], 33 countries on 6 continents	4 g bolus, 1 g/h	10 141 women, all weeks*				
		Marret 2006 [26], France	4 g bolus, 0 g/h	573 women, <33 weeks of pregnancy				
		Rouse 2008 [27], United States	6 g bolus, 2 g/h	2241 women, 24–31 weeks of pregnancy				
		Wolf 2020 [29], Denmark	5 g bolus, 1 g/h	560 women, 24–31 weeks of pregnancy				
Doyle et al. 2009 [16]	Systematic review, meta-analysis	Mittendorf 2002 [24], United States	4 g bolus, 0 or 2–3 g/h	149 women, 25–33 weeks of pregnancy	Examining the efficacy and safety of $MgSO_4$ administration as a neuroprotective agent for women at risk of premature birth using the best available evidence	P = pregnancy; adults 19–44 years; premature birth; mean age 45–64 years; young adults 19–24 years; adolescents 13–18 years I = intramuscularly; intravenously; magnesium sulfate; orally C = placebo O = fetal death; motor disorders; neurological impairment; hearing impairment; blindness; respiratory arrest; cardiac arrest; death; death in newborn; cerebral palsy; adverse event	Primary outcomes child: Fetal, neonatal and subsequent death, neurological impairments/disabilities (such as cerebral palsy, blindness, deafness, gross motor impairment), infantile mortality combined with cerebral palsy, combined with gross motor impairment, combined with neurological impairment, combined with neurological impairment Maternal outcomes: Maternal death, respiratory arrest, cardiac arrest, discontinuation of treatment	Randomized trials that compare treatment with $MgSO_4$ and other therapy (e.g. placebo) in the case of imminent premature birth and investigate at least one of the desired outcomes
		Crowther 2003 [25], Australia/ New Zealand	4 g bolus, 2 g/h	1062 women, <30 weeks of pregnancy				
		Duley 2006 [28], 33 countries on 6 continents	4 g bolus, 1 g/h	10 141 women, all weeks*				
		Marret 2006 [26], France	4 g bolus, 0 g/h	573 women, <33 weeks of pregnancy				
		Rouse 2008 [27], United States	6 g bolus, 2 g/h	2241 women, 24–31 weeks of pregnancy				

▶**Table 1** continued

Study	Study type/ type of review	Country and intervention of each included study	$MgSO_4$ administration/dosage	Characteristics of the subjects	Study objective	PICO model	Endpoints/outcomes	Inclusion/exclusion criteria
Jacquemyn et al. 2015 [22]	Systematic review	Mittendorf 2002 [24], United States	4 g bolus, 0 or 2–3 g/h	149 women, 25–33 weeks of pregnancy	An evaluation of the effects and side effects of antenatal i. v. $MgSO_4$ administration for women without preeclampsia and with imminent premature birth Presentation of possible biological mechanisms of action	P = premature birth I = antenatal, intravenous $MgSO_4$ C = premature birth without antenatal, intravenous, $MgSO_4$ administration O = Risk for CP	Primary outcome: Fetal or neonatal neurological outcomes	Randomized controlled trials and meta-analyses with fetal or neonatal neurological outcomes as primary or secondary outcome with intravenous $MgSO_4$ administration in imminent premature birth
		Crowther 2003 [25], Australia/ New Zealand	4 g bolus, 2 g/h	1062 women, <30 weeks of pregnancy				
		Marret 2006 [26], France	4 g bolus, 0 g/h	573 women, <33 weeks of pregnancy				
		Rouse 2008 [27], United States	6 g bolus, 2 g/h	2241 women, 24–31 weeks of pregnancy				
Crowther et al. 2017 [23]	Individual Participant Data (IPD) meta-analysis	Mittendorf 2002 [24], United States	4 g bolus, 0 or 2–3 g/h	149 women, 25–33 weeks of pregnancy	Evaluation of the effects of antenatal $MgSO_4$ administration for women with imminent premature birth and how the effects differ with different causes of imminent premature birth, initial reason for $MgSO_4$ administration, gestational age, dosage, and timing of $MgSO_4$ administration	P = premature birth (<37 weeks) I = antenatal or prenatal $MgSO_4$ administration C = premature birth without antenatal $MgSO_4$ administration O = risk for CP or neuroprotection	Primary outcomes child: Mortality, cerebral palsy Primary outcome mother: Serious maternal complication	Randomized trials examining neuroprotection by $MgSO_4$ in imminent premature birth (<37 weeks of pregnancy) with neurological outcomes as endpoints
		Crowther 2003 [25], Australia/ New Zealand	4 g bolus, 2 g/h	1062 women, <30 weeks of pregnancy				
		Duley 2006 [28], 33 countries on 6 continents	4 g bolus, 1 g/h	10 141 women, all weeks*				
		Marret 2006 [26], France	4 g bolus, 0 g/h	573 women, <33 weeks of pregnancy				
		Rouse 2008 [27], United States	6 g bolus, 2 g/h	2241 women, 24–31 weeks of pregnancy				

* Only 1593 women who meet the criteria for a premature birth are considered in the meta-analysis.

▶**Table 2** Key results of the included studies.

Study	Endpoints	Results/conclusion	Heterogeneity
Wolf et al. 2020 [21]	Occurrence of cerebral palsy	Risk of cerebral palsy significantly reduced in the $MgSO_4$ group compared to the placebo group (3.4% vs. 5.0%, RR 0.68, 95% CI 0.54–0.85) Risk of moderate to severe cerebral palsy lower in the $MgSO_4$ group compared to the placebo group (2.1% vs. 3.2%, RR 0.63, 95% CI 0.45–0.89) $MgSO_4$ has the same preventive effect for all gestational ages.	$I^2 = 0\%$, not statistically significant
Doyle et al. 2009 [16]	Fetal, neonatal, subsequent death; neurological impairments (including cerebral palsy); severe neurological disability; severe maternal side effects	$MgSO_4$ reduces the risk of developing cerebral palsy (RR 0.68; 95% CI: 0.54–0.87; 5 studies; 6145 newborn) More moderate to severe cerebral palsy occurred in the placebo group compared to the $MgSO_4$ group (RR 0.64; 95% CI 0.44 to 0.92; 3 studies; 4387 neonates).	for CP: $I^2 = 0\%$-25%
Jacquemyn et al. 2015 [22]	Neuroprotection of the newborn	significant 32% reduction in cerebral palsy	not calculated
Crowther et al. 2017 [23]	Child's death or CP, severe maternal side effects	The risk of developing cerebral palsy is reduced in the $MgSO_4$ group compared to the placebo group (RR 0.68, 95% CI 0.54–0.87, 4601 neonates, 5 studies). Reduction of moderate and severe CP (RR 0.63, 95% CI 0.44–0.90), as well as only severe CP (RR 0.54, 95% CI 0.30–0.94) in the $MgSO_4$ group compared to the placebo group.	I^2 not stated, but indication that heterogeneity is not statistically significant

Side effects in the child

Jaquemy et al. (2015) [22] describe the potential negative outcomes for the child after magnesium sulfate therapy: Hypermagnesemia theoretically poses a risk of respiratory arrest, hypotension, reduced or absent peripheral reflexes, and stupor or coma to the newborn. Such effects on the newborn have been described after extremely high doses of magnesium sulfate to prevent eclampsia [22]. In the Mittendorf study [24], administration of high doses of magnesium sulfate for long-term tocolysis or long-term preeclampsia treatment was shown to result in higher infant mortality, more brain hemorrhage, and more brain lesions. Doses of more than 50 g magnesium are critical for the newborn [22]. However, with an administration schedule of 4 g bolus and 1 g/h maintenance dose over 12 h and repeated if necessary, this critical value is not even remotely reached. Neonatal hypotension was also only observed after administration of high doses of magnesium sulfate [22]. Wolf et al. (2020) [21], Doyle et al. (2009) [16], and Crowther et al. (2017) [23] were able to show in their meta-analyses that the secondary neonatal outcomes show no signs of damage from antenatal magnesium sulfate administration. Doyle et al. (2009) [16] found no significant statistical differences between groups for intraventricular hemorrhage (RR 1.01; 95% CI 0.87–1.18), cystic periventricular leukomalacia (RR 0.99; 95% CI 0.68–1.45), Apgar 5′ < 7 (RR 1.12; 95% CI 0.89–1.40), neonatal seizures (RR 0.77; 95% CI 0.49–1.21) or sustained respiratory support (RR 0.99; 95% CI 0.89–1.11). Crowther et al. (2017) [23] also found no significant differences between groups for the neonatal morbidity such as Apgar 5‘ < 7, active resuscitation at birth, intraventricular hemorrhage, cystic periventricular leukomalacia, neonatal convulsions, neonatal encephalopathy, chronic lung diseases, NEC, patent ductus arteriosus, and retinopathy. Likewise, Wolf et al. (2020) [21] found no negative side effects for the newborn. Rather, positive effects could be observed: The risk of a major intraventricular brain hemorrhage was borderline significantly reduced in the magnesium sulfate group (RR 0.77; 95% CI 0.60–1.00). The risk of intubation, cardiopulmonary resuscitation, or endotracheal intubation being necessary during the initial steps of newborn care was also marginally significantly reduced in the magnesium sulfate group. Giving magnesium sulfate at the lowest dose that has been shown to be effective is therefore safe for the newborn and has no negative consequences if an overdose does not occur.

Side effects in the mother

Doyle et al. (2009) [16] found significantly more frequent maternal hypotension (RR 1.51; 95% CI 1.09–2.09) and tachycardia (RR 1.53; 95% CI 1.03–2.29) in the magnesium group compared to the placebo group, and significantly more treatment discontinuations due to side effects in the magnesium sulfate group (RR 3.26; 95% CI 2.46–4.31). They found no significant differences for maternal respiratory depression, postpartum hemorrhage, Caesarean section delivery, or ICU transfer. Also, for serious maternal outcomes, such as maternal death (RR 1.25; 95% CI 0.51–3.07), cardiac arrest (RR 0.34; 95% CI 0.04–3.26), and respiratory arrest (RR 1.02; 95% CI 0.06–16.25) no significant differences were shown. Crowther et al. (2016) [23] reported no case of severe maternal consequences of the therapy (death, respiratory arrest, cardiac arrest). Negative side effects that led to premature discontinuation of therapy were significantly more frequent (RR 1.95; 95% CI 1.44–2.65). There were no differences in type of delivery, post-

▶ **Table 3** Evidence assessment of the included studies according to the AMSTAR score.

Study	A priori design	Study selection and data extraction by two independent persons	Systematic literature search	Unpublished and gray literature included	References of included and excluded literature	Characteristics of the included studies specified	Quality of studies assessed according to risk of bias	Adequate consideration of the risk of bias in the interpretation of the results	Appropriate methodology/ statistically adequate evaluation	Potential publication bias assessed	Disclosure of conflicts of interest
Wolf et al. 2020 [21]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Doyle et al. 2010 [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes
Jacquemyn et al. 2015 [22]	Yes	Uncertain	Yes	Uncertain	No	No	No	Yes	Not applicable	No	Yes
Crowther et al. 2017 [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes

natal hemorrhage, or maternal infection. Jaquemy et al. (2015) [22] pointed out that when magnesium sulfate is combined with nifedipine, the risk of serious maternal side effects such as hypotension and respiratory depression is increased. The data on this are insufficient, so caution and strict indications are required when combining nifedipine and magnesium sulfate.

Dosage

The studies included in the meta-analyses included different administration regimens, which is why the total dose administered also varies. In subgroup analyses it could be determined that there are no significant differences in the efficacy of the doses and no linear trends that speak in favor of a higher dose. Therefore, in the event of imminent premature birth, the smallest effective dosage should be selected, i.e., a bolus of 4 g over 15–30 minutes and a maintenance dose of 1 g/h for 12 hours or until delivery [16, 21, 22, 23].

Gestational age

The inclusion criterion of weeks of pregnancy varied considerably between the studies considered in the meta-analyses. Crowther et al. (2017) [23] created subgroups by gestational age (< 26 weeks of pregnancy, 26–27 weeks of pregnancy, 28–29 weeks of pregnancy, 30–31 weeks of pregnancy, 32+ weeks of pregnancy). In the subgroup analysis, there were no obvious trends of a difference in the effect of therapy on the main outcomes and no statistically significant differences. Magnesium sulfate thus has similar effects over a wide range of gestational ages up to 34 weeks of pregnancy. Also, Doyle et al. (2009) [16] reported a reduction in cerebral palsy for all studies with women under 34 weeks of pregnancy and no clear differences in the subgroups by gestational age. Jaquemy et al. (2015) [22] recommended the therapy for all impending premature births under 32 weeks of pregnancy and pointed out the decreasing effect with increasing weeks of gestation. Wolf et al. (2020) [21] showed that the optimal range of gestational ages for therapy is a matter of interpretation, since the rate of cerebral palsy decreases with increasing gestational age and thus the number needed to treat (NNT) increases. The weighing of the benefit against the maternal side effects can therefore not only be answered with the available data. With the gestational-age-dependent prevalence of infantile cerebral palsy according to Oskoui et al. (2013) [6] and the RR calculated by Doyle et al. (2009) [16] for cerebral palsy after magnesium sulfate administration, the NNT can be calculated for the respective gestational age: For premature births < 28 weeks of pregnancy, it is 38, for 28–31 weeks of pregnancy 73 and for 32–36 weeks of pregnancy 463. This consideration is weighed differently at the international level: The AWMF [4], the ACOG [30], and the World Health Organization (WHO) [31] recommend therapy for the acute risk of premature birth < 32 weeks of pregnancy, the National Institute for Health and Care Excellence (NICE) Guideline [32] and the Queensland Clinical Guidelines [33] recommend therapy for women < 30 weeks of pregnancy and considering therapy for women < 34 weeks of pregnancy with an acute risk of premature birth. The disagreement about the therapy between 30 and 34 weeks of pregnancy could not be conclusively clarified by

the present study either. In 2013 the (still ongoing) MAGENTA study was announced, which aims to answer this question [34].

Limitations

This paper contains some limitations, which result from both the included studies and the methodical procedure. The included studies were evaluated using the AMSTAR score. As already shown in the Results section, three of the four studies considered were of very high quality. In three of the four studies, however, the category "potential publication bias assessed" could not be answered with yes. There is a possibility that potentially existing publication bias is not sufficiently considered in the conclusions and the reported effect of antenatal magnesium sulfate administration appears greater than it possibly is. Also, for the point "References of the included and excluded literature", the answer to two studies was not yes, which makes it difficult to check whether the specified inclusion and exclusion criteria have been applied correctly. One of the included studies is of low quality, as only four of the 11 AMSTAR endpoints could be answered with yes. The poor quality of this study was taken into account in the results section. Deficiencies in the methodological approach in the present study are the fact that no two-fold, independently performed data extraction was carried out, but the literature search was carried out in teamwork. The evaluators were therefore not independent of each other. In addition, the literature search was carried out exclusively in PubMed and therefore does not meet the AMSTAR criterion of a systematic literature search, which has only a limited influence, however, since an umbrella review was carried out in the present paper. In addition, the probability of publication bias could not be assessed. Finally, possible distortions also resulted from the fact that the search was exclusively in PubMed and only English and German-language studies were considered.

Answering the research question

Does antenatal $MgSO_4$ administration to the mother in the event of impending premature birth reduce the occurrence of infantile cerebral palsy in the child? – Due to the consistent results of the included studies and their good quality, the above research question can be answered positively. The antenatal administration of magnesium sulfate reduces the risk of cerebral palsy in premature infants. There is very good evidence for this, as the included meta-analyses and reviews are mostly of very high quality and contain a reasonably large number of cases.

Conclusions

The meta-analyses published since 2009 confirm the results of the Cochrane review [16]. Due to the high level of evidence on the protective effect of antenatal magnesium sulfate in preventing cerebral palsy, there is a clear recommendation to protect the child's brain by administering magnesium sulfate to the mother in the event of an acute risk of premature birth. Since the side effects depend on the dose, the lowest dose that has been shown to be effective of an initial bolus of 4 g over 15–30 minutes followed by a maintenance dose of 1 g/h for 12 h or until the birth of the child should be chosen. If birth of the child does not occur, the therapy can be repeated at a later date if necessary.

There is also sufficient high-quality data on the potential side effects for mother and child. The therapy is safe for the child. The mother may experience undesirable side effects such as hypotension and tachycardia, some of which require discontinuation of therapy. However, severe maternal side effects do not occur more frequently with the therapy than in the placebo group, which is why the therapy can also be classified as safe for the mother. Maternal vital signs and their reflex status should be monitored during administration. Checking maternal magnesium levels can also be useful. Particular care should be taken when combining nifedipine and magnesium sulfate. However, the combination of the two drugs is rated more critically in the AWMF guideline "Prevention and therapy of premature birth" [4] than in the AWMF guideline "Hypertensive pregnancy diseases: Diagnostics and therapy" [35]. Based on the data, no clear statement can be made as to the gestational age up to which neuroprotection with magnesium sulfate should take place. Due to the high prevalence of cerebral palsy < 30 weeks of pregnancy, therapy up to this point is always indicated. Therapy should be offered and recommended between 30 and 32 weeks of pregnancy. Even between 32 and 34 weeks of pregnancy, an effect of neuroprotection with magnesium sulfate can still be demonstrated, but the prevalence is so low that it should only be offered here after the mother has been given detailed information (NNT, side effects for the mother). The current AWMF guideline "Prevention and therapy of premature birth" [4] does not recommend this. The question of the conditions under which neuroprotection with magnesium sulfate should take place is therefore still relevant for research and clinical practice [36].

Conflict of Interest

The authors declare that they have no conflict of interest.

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