Effect of Magnesium Sulphate on Fetal Heart Rate Parameters: A Systematic Review

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Abstract

Objective: To examine the potential effects of intravenous magnesium sulphate ($MgSO_4$) administration on antepartum and intrapartum fetal heart rate (FHR) parameters measured by cardiotocography (CTG) or electronic fetal monitoring (EFM).

Methods: We undertook a systematic review of randomized controlled trials, observational studies, and case series. Studies were reviewed independently by two reviewers and qualitatively analyzed with regard to CTG/EFM parameters (baseline FHR, variability and acceleration-deceleration patterns), types of participants, interventions offered, and outcomes reported.

Results: Of 18 included studies, two were RCTs (72 women); 12 were prospective observational studies (269 women), 10 of which were of a pre- and post-intervention design; one was a prospective cohort study (36 women) and three were retrospective cohort studies (555 women). Lower baseline FHR was associated with $MgSO_4$ exposure in seven of nine relevant studies. Decreased FHR variability was reported in nine of 12 relevant studies. Reductions in reactivity or acceleration pattern were seen in four of six relevant studies without an increase in decelerative patterns. All changes were small and not associated with adverse clinical outcomes.

Conclusion: Maternal administration of $MgSO_4$ for eclampsia prophylaxis/treatment, tocolysis or fetal neuroprotection appears to have a small negative effect on FHR, variability, and accelerative pattern, but is not sufficient clinically to warrant medical intervention.

Key Words: Magnesium sulphate, fetal heart rate, non-stress test, cardiotocograph

Competing Interests: None declared.

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Résumé

Objectif : Examiner les effets potentiels de l'administration de sulfate de magnésium ($MgSO_4$) par voie intraveineuse sur les paramètres de la fréquence cardiaque fœtale (FCF) antepartum et intrapartum mesurés par cardiotocographie (CTG) ou monitorage fœtal électronique (MFÉ).

Méthodes : Nous avons mené une analyse systématique ayant porté sur des essais comparatifs randomisés, des études observationnelles et des séries de cas. Ces études ont été analysées de façon indépendante par deux arbitres scientifiques; de plus, elles ont fait l'objet d'une analyse qualitative en fonction des paramètres de la CTG / du MFÉ (FCF initiale, variabilité et profils d'accélération-décélération), des types de participantes, des interventions offertes et des issues signalées.

Résultats : Parmi les 18 études admises à l'analyse systématique, on comptait deux ECR (72 femmes); 12 études observationnelles prospectives (269 femmes), dont 10 comptaient un devis préintervention et postintervention; une étude de cohorte prospective (36 femmes); et trois études de cohorte rétrospectives (555 femmes). Une FCF initiale moindre a été associée à l'exposition au $MgSO_4$ dans le cadre de sept des neuf études pertinentes. Une variabilité moindre de la FCF a été signalée dans neuf des 12 études pertinentes. Des baisses des profils de réactivité ou d'accélération ont été constatées dans quatre des six études pertinentes, sans hausse des profils de décélération. Toutes les modifications ont été faibles et n'ont pas été associées à des issues cliniques indésirables.

Conclusion : Bien que l'administration de $MgSO_4$ à la mère à des fins de prophylaxie / prise en charge de l'éclampsie, de tocolyse ou de neuroprotection fœtale semble exercer un faible effet négatif sur la FCF, la variabilité et le profil d'accélération, cet effet n'est pas suffisant sur le plan clinique pour justifier la tenue d'une intervention médicale.

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INTRODUCTION

Magnesium sulphate has been used for a variety of obstetrical indications, including tocolysis for preterm labour for which it is now recognized to be ineffective.[1] At present, $MgSO_4$ is used for the prevention of eclampsia, for treatment in women with preeclampsia and eclampsia, and for fetal neuroprotection in the setting of imminent preterm birth for any indication at < 32 weeks' gestation in Canada.[2,3]

Cardiotocography, or electronic fetal monitoring, is a routine technique for monitoring fetal well-being during the antenatal and intrapartum periods in pregnancies considered at risk for adverse perinatal outcome. Antenatal EFM is considered a "non-stress test" because the fetus is not subjected to the usual stresses associated with regular uterine contractions. EFM records normal and altered fetal cardiovascular function by documenting the baseline fetal heart rate, fetal heart rate variability, and the presence and pattern of fetal heart rate accelerations and/or decelerations along with their temporal relationship to uterine contractions.[4] EFM is used to detect fetal compromise related to fetoplacental pathology, cord compression, or other processes that may result in altered fetal cardiovascular function, such as fetal immaturity or maternal administration of central nervous system-depressant drugs.[5]

While EFM is deeply embedded in Canadian obstetrical practice, evidence indicates that when compared with intermittent auscultation, EFM has been shown only to decrease the incidence of neonatal seizures (without a proven benefit for infant mortality, other standard indicators of newborn wellbeing, or cerebral palsy), and it increases the incidence of Caesarean section and instrumental vaginal deliveries.[6] As such, EFM is recommended only for women with risk factors for adverse perinatal outcome, such as those requiring $MgSO_4$ for either prevention of eclampsia or fetal neuroprotection.[7]

The use of $MgSO_4$ for fetal neuroprotection in the setting of imminent preterm birth for any indication at < 32 weeks is a relatively recent recommendation from the Society of Obstetricians and Gynaecologists of Canada,[7] and a Canada-wide knowledge translation initiative has been undertaken within a quality assurance framework for tertiary obstetrical facilities.[8] This initiative has included educational site visits to these facilities, where questions were raised by physicians, midwives, and nurses about the effects of $MgSO_4$ on EFM, especially related to FHR variability.[8] The current SOGC Fetal Health Surveillance Guidelines (published in 2007) recommend use of EFM for women with risk factors for adverse perinatal outcome (including preeclampsia, eclampsia, and preterm labour), but do not discuss the effect of $MgSO_4$ on EFM parameters.[2]

An effect of magnesium on FHR patterns is plausible because magnesium ions (Mg^{++}) cross the fetal-placental membranes and fetal serum Mg^{++} levels rapidly equilibrate with maternal levels.[9] Magnesium is a peripheral vasodilator and is assumed to cross the fetal blood-brain barrier, as it does in the mother. The FHR could potentially be affected through peripheral and central mechanisms. Although some observational studies have reported adverse effects of $MgSO_4$ on EFM parameters, this may represent "confounding by indication," in that women who are receiving $MgSO_4$ have conditions that may themselves be associated with abnormalities in FHR and FHR pattern.

We undertook a systematic review of controlled studies of $MgSO_4$ administration during pregnancy, in order to understand the potential effects of $MgSO_4$ on EFM.

METHODS

Đoạn này giới thiệu về cách tìm: (1) nguồn - thời gian, (2) Từ khóa để tìm kiếm. (3) các tiêu chuẩn chọn và loại.

We searched PubMed (Medline) (1963 to March 2014), the Cochrane Library (1991 to March 2014), EMBASE (1974 to March 2014), and the bibliographies of retrieved articles addressing the effect of $MgSO_4$ on FHR or FHR pattern. The literature search was conducted using the following search terms: ("magnesium sulfate" OR magnesium sulphate OR "$MgSO_4$") AND ("fetus" OR "fetal" OR "foetus" OR "foetal") AND "heart" OR "fetal cardiotocography" OR "fetal electronic monitoring" OR "fetus heart rate" OR "fetus monitoring" OR "fetus distress." Studies were considered if:

1. they were original articles published in English;
2. they were controlled studies published as randomized controlled trials (RCTs), observational studies, or case series;
3. they described human subjects being exposed to $MgSO_4$ during pregnancy for any indication; and
4. they examined FHR effects by any continuous electronic method, including Doppler, following $MgSO_4$ administration.

Excluded were case reports and studies that measured only parameters other than FHR, FHR variability, and/or FHR accelerations and decelerations after maternal exposure to $MgSO_4$.

ABBREVIATIONS

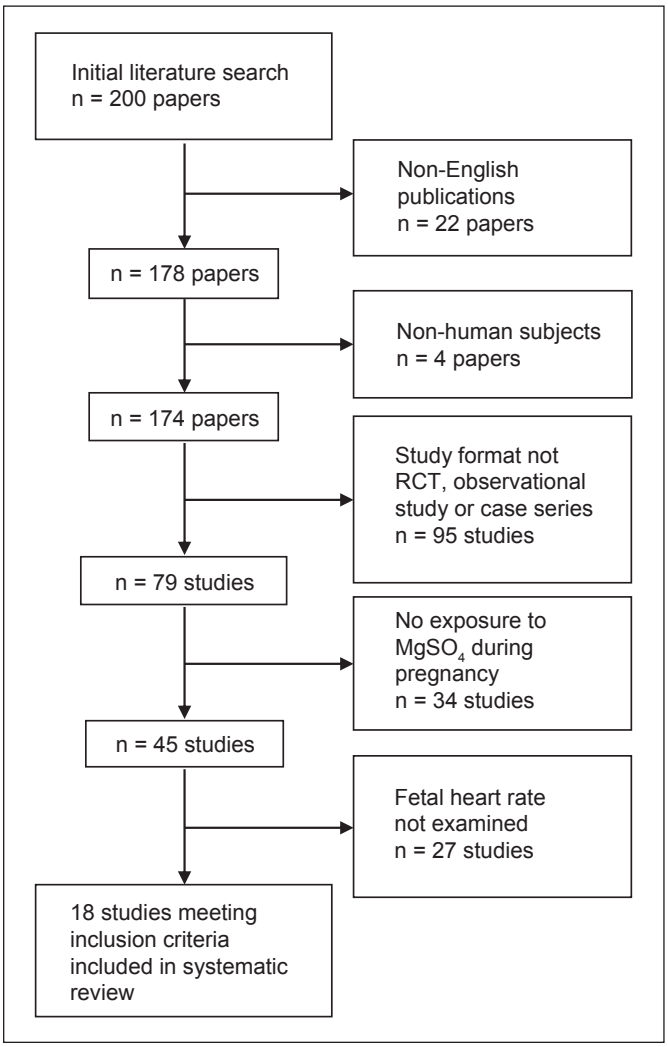
EFM	electronic fetal monitoring
FHR	fetal heart rate
Mg	magnesium
$MgSO_4$	magnesium sulphate

Studies were reviewed independently by two individuals (A.N. and D.D.) and qualitatively analyzed with regard to the types of participants (gestational age, labouring vs. non-labouring, and healthy vs. complicated pregnancy), $MgSO_4$ intervention offered (including indication, dose, route of administration), and reported outcomes. The EFM parameters recorded were type of study (computerized or visual interpretation) and, for each patient, baseline FHR, FHR variability (short-term, long-term, or any), and FHR acceleration/deceleration patterns. Other fetal/neonatal outcomes collected were stillbirth, neonatal death, Apgar scores, cord pH, and need for NICU admission.

For baseline FHR and FHR variability ("short term variability" in the old nomenclature and "variability" in the new nomenclature) a meta-analysis of data was performed, for data including mean and standard deviation, using Review Manager 5.2 (Cochrane Collaboration, Oxford, United Kingdom). Summary mean difference and 95% confidence intervals were calculated. Tests of statistical heterogeneity among pool results were conducted using I^2 and χ^2 tests. Heterogeneity was considered significant if I^2 was greater than 30% or χ^2 P value was less than 0.10. We used fixed-effects models if there was no significant heterogeneity and random-effects models if significant heterogeneity was present. Results were considered to be statistically significant if the 95% confidence interval did not encompass 0.0 for the mean difference or if the P value was less than 0.05.

The study was a review of published literature and did not require research ethics board approval.

Figure 1. Inclusion criteria for papers included in systematic review



RESULTS

Our search of the literature yielded 200 articles published between 1963 and March 2014. Eighteen studies met our inclusion criteria (Figure 1):

1. two RCTs (72 women, median 36/study)[10,11];
2. 13 prospective observational studies (311 women, median 16/study), of which 12 used women as their own control subjects in a pre- and post-intervention design,[12–23] and one used control subjects matched for gestational age[24];
3. three retrospective cohort studies (555 women, median 238/study).[25–27]

The characteristics of included studies are presented in the Table. Populations studied included labouring (n = 15)[12,13,15–27] and/or non-labouring women (n = 5),[10,11,13–15] who were either healthy (n = 2),[10,24] or had some indication for receiving $MgSO_4$ during their pregnancy: preeclampsia (n = 10),[12–16,19,21,25–27] pre-term labour (n = 6),[11,15,17,18,20,23] or intrapartum fetal distress, with $MgSO_4$ given for intrauterine resuscitation (n = 1).[22] $MgSO_4$ was given as a loading dose of 2 to 8 g IV (median, 4 g), and in most studies was followed by a maintenance dose of 1 to 3.5 g/hour IV (median 2 g/hr). In one study $MgSO_4$ infusion rates were not stipulated, but maternal serum Mg^{++} levels were reported to be between 5.2 and 6.0 mEq/L, considered to be within the therapeutic range.[20] One study described the effects of $MgSO_4$ administered by intramuscular injection.[21] FHR parameters were usually assessed by visual inspection of EFM (n = 15),[10,12–16,18–23,25–27] but one study used electronic interpretation of EFM.[12] Four studies included umbilical Doppler flow velocimetry assessment and reported on FHR[11,17,18,24]; one of the four included biophysical profile[18] and reported on FHR and FHR accelerations only.

Effects of $MgSO_4$ administration on FHR

Reference	Study design (N women)	Characteristics of women	$MgSO_4$ regimen	FHR effects associated with $MgSO_4$ exposure				Reported neonatal outcome*
				Baseline FHR	FHR variability	Accelerations	Decelerations	
Twickler et al. (2010)[11]	RCT (N = 18 $MgSO_4$ treatment, 20 control subjects)	Non-labouring women at risk of preterm labour 24–31 wks	6 g IV then 2 g/hr IV	Lower mean FHR by 8–10 bpm (P = 0.005)	—	—	—	
Hallak et al. (1999)[10]	RCT (N = 18 $MgSO_4$ treatment, 16 control subjects)	Healthy, non-labouring women > 30 wks	6 g IV then: 2 g/hr IV for 3 hr	Lower baseline FHR at 3 hrs: 132.3 ± 7.6 bpm [$MgSO_4$] vs. 134.6 ± 7.1 bpm [control subjects] (P < 0.05)	Lower variability at 3 hrs: 2.67 ± 0.36 [$MgS0_4$] vs. 2.71 ± 0.52 [control subjects] (P < 0.05)	"No significant difference" in N accelerations/hr	No significant decelerations were identified (as for control)	
Kamitomo et al. (2000)[24]	Prospective cohort (with control subjects) (N = 15 $MgSO_4$ treatment, 16 control subjects)	Labouring women 26–34 wks	4 g IV then 1–3 g/hr IV	Lower mean FHR: 131 ± 8 bpm [$MgSO_4$] vs.146 ± 7 bpm [control subjects] (P < 0.001)	—	—	—	
Vigil-de Gracia et al. (2000)[22]	Prospective cohort (pre-post design) (N = 21)	Labouring women with fetal distress 36–42 wks	4 g IV	"Higher" FHR	—	—	—	Apgar > 7 at 1 minute: 18/21 (85.7%) Apgar ≥ 7 at 5 minute: 20/21 (95.2%)
Wright et al. (1996)[23]	Prospective cohort (pre-post design) (N = 48)	Labouring women 24–35 wks	4–8 g IV	Lower baseline FHR at 30 minutes, from 140.8 bpm to 137.3 bpm (P = 0.001)	4/48 (8.3%) developed decreased variability 4 hr after $MgSO_4$	—	—	
Peaceman et al. (1989)[18]	Prospective cohort (pre-post design)† (N = 22)	Labouring women 26–34 wks	4–6 g IV then 1.5–3.5 g/hr IV	Lower baseline FHR, from 144 bpm to 131 bpm (P < 0.0001) 16/22 (73%) fetuses experienced a drop in heart rate ≥ 10 bpm	—	11/22 (50.0%) had NST tracings that became unreactive (P < 0.001)	—	
Miller et al. (1982)[17]	Prospective cohort (pre-post design)* (N = 14)	Labouring women < 37 wks	4 g IV then maintenance then 2 g/hr IV for 2 hr then 1 g/hr IV for 22 hr	"No significant changes" in FHR up to 24 hours after treatment was initiated				
Hiett et al. (1995)[15]	Prospective cohort (pre-post study) (N = 16)	Pre-term labour or preeclampsia > 32 wks	4 g IV then 2 g/hr IV	—	Significant decrease in short-term variability (7.6 ± 0.5 pre Mg vs. 6.4 ± 0.6 post (P = 0.01) 14/16 (87.5%) had significant decrease in long-term variability (P = 0.02)	Fewer accelerations at 60 min from 15.6 ± 3.6 per hr to 10.3 ± 2.6 per hr (P = 0.05)	—	Apgar at 5 minute was (mean) 8.5 + 0.4

continued

Continued

Reference	Study design (N women)	Characteristics of women	$MgSO_4$ regimen	FHR effects associated with $MgSO_4$ exposure				Reported neonatal outcome*
				Baseline FHR	FHR variability	Accelerations	Decelerations	
Atkinson et al. (1994)[12]	Prospective cohort (pre-post study) (N = 12)	Labouring women with preeclampsia > 28 wks GA	6 g IV then 2 g/hr IV	—	Decreased short-term variability at 60 min from 9.8 ± 3.3 msec to 6.7 ± 2.0 msec (P = 0.003) "No significant difference" in medium- or long-term variability			
Guzman et al. (1993)[14]	Prospective cohort (N = 18 $MgS0_4$ treatment, 18 control subjects)	Non-labouring women with preeclampsia 27–41 wks	6 g IV then 3 g/hr IV	—	Reduced short-term variability: 8.0 ± 1.6 [$MgSO_4$] to 7.0 ± 1.5 [control subjects] (P = 0.03) Reduced long-term variability: 40.0 ± 7.0 to 35.0 ± 6.0 msec (P = 0.01)	Reduced reactivity (accelerations of 15 bpm over 20 minutes) of 4 ± 3 to 1.4 ± 1.4 (P = 0.003)	—	
Lin et al. (1988)[16]	Prospective cohort (pre-post study) (N = 42)	Labouring women with preeclampsia 36–41 wks	4 g IV then 2 g/hr IV	—	Reduced variability: in 12/30, 40.0% cases	—	—	Apgar < 6 at 1 minute: 3/27 (11.1%) among women with no change in variability, and 1/10 (10.0%) among women with decreased variability
Canez et al. (1987)[13]	Prospective cohort (pre-post study) (N = 57)	Labouring women with hypertensive disorders of pregnancy Gestational age not stated	2–4 g IV then 1–3 g/hr IV	—	"No significant change" in variability with increasing Mg levels	—	—	Mg++ 2.0–3.9 mEq/L: Apgar at 1 minute (mean) 7.5 + 1.6 [$MgSO_4$] vs. 6.7 + 2.0 [control subjects] (NS) $MgSO_4$ serum level 4.0–7.4 mEq/L: Apgar at 5 minute (mean) 8.7 + 0.8 [$MgSO_4$] vs. 8.4 + 0.9 [control subjects]
Stallworth et al. (1981)[21]	Prospective cohort (pre-post study) (N = 10)	Labouring women with preeclampsia "Term"	3 g IV then 1.25 g/hr IV	—	No significant change in short-term or long-term variability	—	—	

continued

Continued

Reference	Study design (N women)	Characteristics of women	$MgSO_4$ regimen	FHR effects associated with $MgSO_4$ exposure				Reported neonatal outcome*
				Baseline FHR	FHR variability	Accelerations	Decelerations	
Petrie et al. (1978)[19]	Prospective cohort (pre-post study) (N = 10)	Healthy labouring women "Term"	2 g IV	—	"Statistically significant increase" in short and long term variability at multiple 5 min intervals post-$MgSO_4$	—	—	
Sherer (1994)[20]	Prospective cohort (pre-post study) (N = 5)	Labouring women 31–36 wks	Doses not stated (Mg levels were 5.2–6.0 mEq/L)	—	—	Reduced rates of acceleration in response to vibro-acoustic stimulation	—	
Duffy et al. (2012)[25]	Retrospective cohort (N = 248 $MgSO_4$ treatment, 5139 control subjects)	Labouring women with severe preeclampsia > 37 wks	6 g IV then 2 g/hr IV	Lower FHR: 136.9 ± 12.3 bpm [$MgSO_4$] vs. 139.0 ± 13.5 bpm [control subjects] (P = 0.02)	Increased risk of absent or minimal variability (adjusted OR 2.41, 95% CI 1.78–3.27)		Fewer pro-longed decelerations (OR 0.64 [0.49–0.84)	Cord blood pH < 7.1: "1.2%" [$MgSO_4$] vs. "1.1%" [control subjects] (P = 0.75) Adverse composite neonatal outcome‡: 8.1% [$MgSO_4$] vs. 5.6% [control subjects] (P = 0.11)
Petrikovsky & Vintzileos (1990)[26]	Retrospective cohort (N = 15 $MgSO_4$ treatment, 54 control subjects)	Labouring women with preeclampsia "Term"	4 g IV then 2 g/hr IV	-	Reduced variability: "77%" [$MgSO_4$] vs. "24%" [control subjects] (P < 0.001)			
Stewart et al. (2013)[27]	Retrospective cohort (N = 238)	Labouring women with severe preeclampsia > 37 wks	4 g IV then 2 g/hr IV	Lower FHR: mean 139.91bpm before $MgS0_4$ to 137.54 post (P < 0.01)	Minimal/absent variability increased during bolus infusion (OR 2.4, 95% CI 1.10 to 5.62), but corrected during steady state (OR 1.44, 95% CI 0.76–2.80)	"No significant difference" (P = 0.76)	"No significant difference" (P = 0.08)	

FHR: fetal heart rate; NST: non-stress test

*Results are expressed as the event rate in $MgS0_4$-exposed vs. controls other than for the pre-post study design publications for which the fetal/neonatal outcomes associated with $MgSO_4$ treatment are reported (as the woman's pre-treatment status served as her 'control').

†In the pre-post study design, women acted as their own controls.

‡The composite neonatal outcomes was one/more of the following: cord blood pH < 7.1, base excess ≤ 12, or neonatal special or intensive care admission.

Outcomes related to FHR and associated with $MgSO_4$ therapy are presented in the Table.

Changes in baseline FHR following the administration of $MgSO_4$ were reported in nine studies. Lower baseline FHR associated with $MgSO_4$ exposure was reported in seven of the nine studies: two RCTs (72 women),[10,11] three prospective studies (79 women),[18,23,24] and two retrospective cohort studies (436 women).[25,27] Despite statistically significant decreases in baseline FHR, the mean FHR remained within the normal physiologic range (110 to 160 bpm), even in the study with the largest absolute drop of approximately 15 bpm.[24] One study reported associated perinatal outcomes, which did not differ between groups despite a significant decrease in FHR associated with $MgSO_4$ exposure.[25] One prospective study of 14 women[17] found no significant change in baseline FHR associated with $MgSO_4$ administration. Another study of 21 women[22] found FHR to be increased when $MgSO_4$ was used as a tocolytic to facilitate intrauterine resuscitation in women who developed intrapartum fetal distress (defined as repetitive late decelerations, persistent loss of baseline variability, severe variable decelerations, or fetal bradycardia) and who were awaiting emergency Caesarean section.

Twelve studies reported the effect of $MgSO_4$ on FHR variability (Table). The definitions varied widely, from a four-tiered classification system (n = 4 studies),[10,16,23,27] to a seven-tiered one,[13] and four studies classified FHR using the older terminology of "short" and "long-term" variability.[12,14,15,21] Three studies provided no definition of variability.[17,18,22] Eight studies with variable study designs reported a significant relative decrease in FHR variability associated with $MgSO_4$ exposure: one RCT (34 women),[10] four prospective observational studies (106 women),[12,14–16] and three retrospective cohort studies (555 women).[25–27] One of the retrospective cohort studies reported more frequent absent or minimal FHR variability as a composite outcome associated with $MgSO_4$ use (OR 2.41; 95% CI 1.78 to 3.27),[25] but no other study reported absent FHR variability. A low Apgar score at one minute was not associated with the observed reduction in FHR variability in one study[16] (Table). Petrikovsky et al. reported that $MgSO_4$ administration was associated with significant diminished variability in the Cycle C category or "quiet awake" fetal behavioural state, with characteristic FHR variability in the 6 to 10 bpm range ($P < 0.01$).[26] Variability characteristic of quiet and active sleep (FHR variability between 0 and 5 bpm) was not significantly different between the study and control groups, and there were no differences in adverse fetal or neonatal health outcomes (Table). Two prospective observational studies (115 women) found no effect of $MgSO_4$ on FHR variability,[13,21] and another (10 women) reported an increase in FHR variability.[19]

Six studies described FHR acceleration patterns[10,14,15,18,20,27] (Table). Four prospective observational studies (72 women) with gestational age ranging from 26 weeks to term reported significant reductions in the number of FHR accelerations associated with $MgSO_4$ exposure.[14,15,18,20] However, reactivity was still present in all studies. Sherer[20] described the FHR accelerations as "blunted" following vibroacoustic stimulation in five women presenting in preterm labour, as FHR accelerations reached a maximum that was 5 to 10 bpm less than the peak accelerations seen in those women who had not received $MgSO_4$. The only RCT (34 women)[10] in women greater than 30 weeks' gestation and one retrospective cohort study of 238 women in labour with preeclampsia[27] reported no effect of $MgSO_4$ administration, assessed by the number of FHR accelerations per hour. One study described associated perinatal outcome in the form of a mean Apgar score that was within the normal range.[15]

Three studies commented on FHR deceleration patterns after treatment with $MgSO_4$[10,25,27] (Table). The RCT reported by Hallak et al.[10] (34 women) and the retrospective study reported by Stewart et al.[27] (238 women) described an absence of FHR decelerations, but in a retrospective cohort study Duffy et al.[25] (248 women exposed to $MgSO_4$) found *fewer* prolonged late FHR decelerations. Duffy et al.[25] reported no significant difference in neonatal outcomes overall.

A total of three studies provided mean and standard deviations for baseline FHR[10,24,25] (Figure 2), and four studies provided mean and standard deviation for FHR variability[10,12,14,15] (Figure 3).

Our meta-analysis found that there was no significant difference in baseline FHR with administration of $MgSO_4$ (mean difference −6.19 beats per minute, 95% CI −13.46 to 1.07). However, these results are limited by the number of studies providing mean and standard deviation data to allow combination of the results. Our meta-analysis did find a small reduction in FHR variability with administration of $MgSO_4$ (−0.99 beats per minute, 95% CI −1.91 to −0.08).

DISCUSSION

Our review of controlled studies examined patterns of parenteral administration (usually IV) of $MgSO_4$, at loading doses ranging from 2 to 8 g IV and maintenance doses ranging from 1 to 3.5 g IV or adjusted to achieve serum Mg^{++}

Figure 2. Meta-analysis of baseline fetal heart rate.

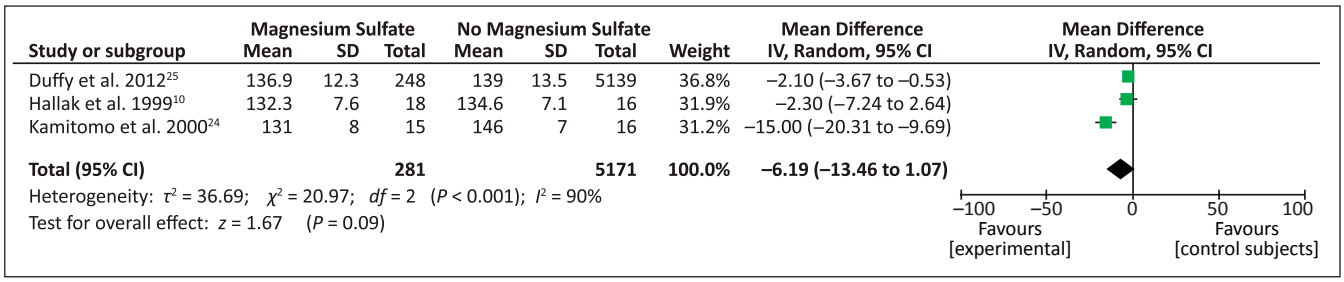
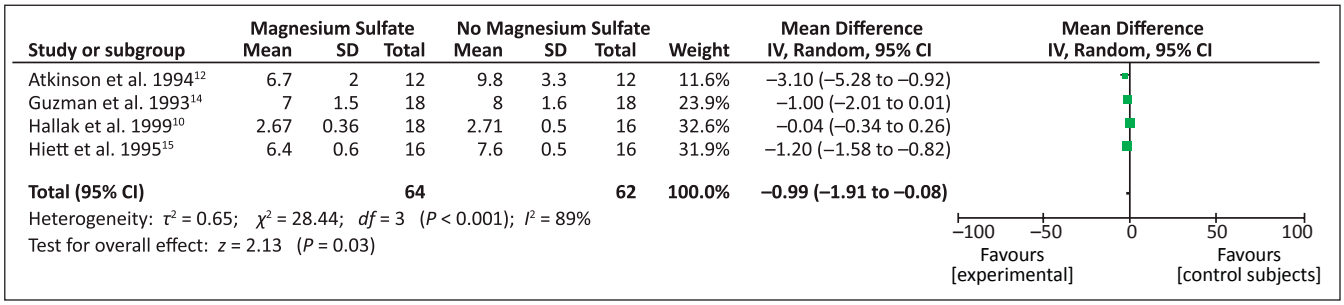


Figure 3. Meta-analysis of fetal heart rate variability



levels of 5.2 to 6.0 mEq/L, and the impact of administration of $MgSO_4$ on FHR. We found that most studies of various designs support a modest adverse effect of $MgSO_4$ on EFM parameters. The changes observed consisted of:

1. a statistically significant decrease in FHR of up to 15 bpm, but all FHRs remained within the normal range of 110 to 160 bpm (7/9 studies that reported baseline FHR)[10,11,18,23,24,25,27];
2. a decrease in short-term and/or long-term FHR variability (9/12 relevant studies)[10,12,14–16,23,25–27]; and
3. a decrease in the number and/or frequency of FHR accelerations by not more than 5 to 10 bpm (4/6 relevant studies),[14,15,18,20] without an increase in deceleration patterns (3/3 relevant studies).[10,25,27]

The two RCTs that reported on these outcomes had findings that mirrored those for all studies.

Current clinical practice guidelines in Canada,[2] the United States,[28] and the United Kingdom[29] do not outline the effects of $MgSO_4$ on FHR and FHR pattern. Because $MgSO_4$ is a commonly used drug in modern obstetric practice, in both preterm and term pregnancies, this review makes an important contribution to clinical care.

Strengths of our study include the comprehensive literature search and the description of all reported FHR and FHR pattern effects (and associated neonatal outcomes) associated with parenteral $MgSO_4$ administration. Limitations include the fact that 15 of 18 studies in this review were published in or before 2000. There was considerable variation in the dosage of $MgSO_4$ administered, and there was no reported examination of a dose–response relationship. There was a wide range of definitions of FHR "variability" in the included studies, with only one study[27] classifying variability according to the currently accepted National Institute of Child Health and Human Development definition.[30] Most studies used visual interpretation of EFM, and this is less reliable than computerized analysis.[31] Finally, only one study[16] reported newborn outcomes according to FHR effects, and most study cohorts were too small to have sufficient statistical power to comment on these outcomes; however, there is a wide body of literature on $MgSO_4$ effects on neonatal outcomes, and there have been no demonstrated adverse effects.[32]

CONCLUSION

This meta-analysis of the current evidence suggests that maternal administration of $MgSO_4$ for eclampsia prophylaxis or treatment, tocolysis, or fetal neuroprotection does indeed have a modest adverse effect on baseline FHR, FHR variability, and the accelerative/decelerative pattern of the FHR. However, the effects are small and do not appear to be associated with adverse outcomes. It would be prudent for clinicians to obtain a baseline FHR assessment prior to administration of $MgSO_4$; any substantive changes in EFM parameters after administration of $MgSO_4$ should be regarded as reflective of fetoplacental pathology (and requiring the appropriate response) rather than reflective of $MgSO_4$ administration.

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APPENDIX.
MAGNESIUM SULPHATE FOR FETAL NEUROPROTECTION OF THE PRETERM INFANT (MAG-CP) COLLABORATIVE GROUP

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