

DEMOCRITUS UNIVERSITY OF THRACE

POSTGRADUATE PROGRAMME OF STUDY: "Clinical Pharmacology and Therapeutics"

Tocolytic therapy with magnesium sulphate and perinatal outcome

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PART I: INTRODUCTION

TOCOLYSIS AND PRETERM BIRTH

Prevention of preterm birth

<37 weeks of gestation

PRETERM BIRTH AND PERINATAL OUTCOME

70% of neonatal deaths Respiratory distress syndrome Short-term morbidity Intraventricular haemorrhage Necrotizing enterocolitis Sepsis Retinopathy of prematurity Cerebral palsy Long-term morbidity Learning disabilities Blindness

Chronic lung disease

Adulthood

altered metabolic states

EPIDEMIOLOGY OF PRETERM BIRTH

- 5-12% of all births (worldwide)
- Preterm birth rate in the United States:
 12.3% in 2008 (12.8% 2006)





-safe in utero transfer to a Neonatal Intensive Care Unit (NICU)

-prevent prematurity-associated morbidities

TOCOLYSIS

Classes

- Magnesium sulphate
- β-agonists
- ■Ca⁺² channel blockers
- COX-inhibitors
- Oxytocin antagonists
- Nitric Oxide donors
- ■*hCG*

Considered as a first-line tocolytic agent in the United States

Associated with perinatal mortality

Newly-established role of neuroprotection

ACTION OF Mg⁺² ON THE MYOMETRIUM

- **+** NOS (nitric oxide synthase)

- cAMP (cyclic adenosine monophosphate)

Moreover, there might be a role for magnesium to prevent fetal hypoxia during preterm and term labour, by promoting periodic relaxation between contractions.

ACTION OF Mg⁺² ON THE MYOMETRIUM



MAGNESIUM SULPHATE AND NEUROPROTECTION

PRETERM BRAIN

susceptiple to periventricular white matter injury

such as periventricular leucomalacia



MAGNESIUM SULPHATE AND NEUROPROTECTION

Magnesium sulphate's action

X NMDA Receptors (*N*-methyl *D*-aspartate)

Excitotoxicity, Demyelination

Oxygen free radicals — Hypoxic damage

Cytokines

4 Inflammation

Metalloproteinases

Degradation of Blood-Brain Barrier Demyelination

ADVERSE EFFECTS- *MOTHER*

Dose-dependent

Physiologic effect	Serum Magnesium concentration (mg/dl)
Inhibition of myometrial contractility	5-8
Diminishment of deep tendon reflexes	9-13
Respiratory depression	14-18
Cardiac arrest	>18

FETAL/NEONATAL SIDE EFFECTS

Short-term administration:	Central Nervous System
• Hypermagnesaemia	— Lethargy,
 Motor and Respiratory depression 	Hypotonicity,
	Depressed Apgar score

System depression:

Long-term administration:

- Hypocalcaemia
- Demineralization of fetal bone
- Decreased fetal heart rate variability

PART II: META-ANALYSIS

META-ANALYSIS

AIM OF STUDY

 Primary: impact of magnesium sulphate on perinatal outcome, in the settings of tocolysis

Secondary: tocolytic efficacy

METHODS

Search strategy:

OvidSP, including Medline, all EBM Reviews- Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED Pubmed, CINAHL, and <u>www.clinicaltrials.gov</u>.

Selection criteria:

women in threatened preterm labour

Data collection and analysis:

Cochrane Collaboration's Software, Review Manager (RevMan 5)

PERINATAL OUTCOME

> Perinatal Morbidity:

 Respiratory Distress Syndrome •Need for assisted ventilation •IntraVentricular Haemorrhage (IVH)- total •Periventricular Leucomalacia (PVL) •Severe IVH (grade 3 or 4)/or PVL •Cerebral Palsy •Neonatal Infection or Sepsis •Necrotising Enterocolitis (NEC) •Patent Ductus Arteriosus (PDA) •Transient Tachypnea of the Newborn (TTN) •Fetal distress •Pulmonary Hypertension •Chronic Lung Disease Blindness •Deafness

> Perinatal Mortality

fetal/neonatal/infant deaths

>Factors reflecting the perinatal outcome

Neonatal birth weight (gr)
Apgar Score at 1 minute
Apgar score at 5 minutes
Umbilical cord pH
Admission to Neonatal Intensive Care Unit (NICU)
Length of stay in the NICU

TOCOLYTIC OUTCOME

Gestational age at delivery

Time to uterine quiescence (hours)

Days gained in utero

Admission for recurrent preterm labour

Birth <48 hours after trial entry

Very preterm birth (<34 weeks)

Preterm birth (<37 weeks)



Identified: 41 RCTs

Included: 20 RCTs

MAGNESIUM SULPHATE VERSUS COMPARISON- all trials

PERINATAL OUTCOME

•

Statistically significant difference in the number of total deaths in the magnesium sulphate group

	Magnesium Sulph	ate	Cont	rol	Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Cotton 1984	1	15	1	19	7.1%	1.27 [0.09, 18.62]			
Cox 1990	8	77	2	79	15.8%	4.10 [0.90, 18.71]			
Floyd 1992	0	40	1	50	10.7%	0.41 [0.02, 9.91]			
Fox 1993	0	45	0	45		Not estimable			
Glock 1993	0	41	2	39	20.5%	0.19 [0.01, 3.85]	• • • • • • • • • • • • • • • • • • •		
Larmon 1999	0	65	0	57		Not estimable			
Lorzadeh 2007	0	55	0	54		Not estimable			
Lyell 2007	1	106	0	110	3.9%	3.11 [0.13, 75.56]			
McWhorter 2004	4	102	0	92	4.2%	8.13 [0.44, 148.91]			
Mittendorf (MAGNET) 1997	8	55	0	51	4.2%	15.79 [0.93, 266.72]	· · · · · · · · · · · · · · · · · · ·		
Morales 1993	1	52	1	49	8.3%	0.94 [0.06, 14.65]			
Parilla, 1999	1	18	1	14	9.0%	0.78 [0.05, 11.37]			
Suricharmorn 2001	1	36	2	35	16.3%	0.49 [0.05, 5.12]			
Total (95% CI)		707		694	100.0%	2.17 [1.12, 4.22]	•		
Total events	25		10						
Heterogeneity. $Chi^2 = 9.60, r$									
Test for overall effect: Z = 2.	29 (P = 0.02)						Favours MgSO ₄ Favours control		

BUT...

The difference no longer remained statistically significant when we excluded deaths not related to the use of tocolytic agents such as congenital malformations and twin-twin transfusion.

	Magnesium Su	lagnesium Sulphate		rol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
Cox 1990	5	77	2	79	18.7%	2.56 [0.51, 12.83]	_		
Floyd 1992	0	40	1	50	12.7%	0.41 [0.02, 9.91]	· · ·		
Fox 1993	0	45	0	45		Not estimable			
Glock 1993	0	41	2	39	24.3%	0.19 [0.01, 3.85]	· •	<u> </u>	
Larmon 1999	0	65	0	57		Not estimable			
Lorzadeh 2007	0	55	0	54		Not estimable			
Lyell 2007	1	106	0	110	4.6%	3.11 [0.13, 75.56]	1	• •	
McWhorter 2004	3	102	0	92	5.0%	6.32 [0.33, 120.74]		<u> </u>	
Mittendorf (MAGNET) 1997	5	55	0	51	4.9%	10.21 [0.58, 180.21]		<u> </u>	
Parilla, 1999	1	18	1	14	10.7%	0.78 [0.05, 11.37]			
Suricharmorn 2001	1	36	2	35	19.2%	0.49 [0.05, 5.12]			
Total (95% CI)		640		626	100.0%	1.72 [0.81, 3.64]		•	
Total events	16		8						
Heterogeneity: $Chi^2 = 6.87$, (df = 7 (P = 0.44);	$ ^2 = 0\%$							
Test for overall effect: Z = 1.	41 (P = 0.16)						0.02 0.1 Eavours MaSO4	1 10 50 Eavours control	

MAGNESIUM SULPHATE VERSUS COMPARISONall trials

• Increased neonatal birth weight in the magnesium sulphate group

	Magnesi	um Sulpł	nate		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borna 2007	2,511	654	52	2,448	632	52	0.9%	63.00 [-184.19, 310.19]	· · · · · · · · · · · · · · · · · · ·
Chau 1992	2,821	640	46	2,536	759	52	0.7%	285.00 [7.94, 562.06]	│→
Cotton 1984	1,651	591	15	1,841	678	19	0.3%	-190.00 [-617.07, 237.07]	← →
Cox 1990	2,264	93	75	2,204	77	79	76.9%	60.00 [32.96, 87.04]	
Fox 1993	2,741	495	45	2,761	585	45	1.1%	-20.00 [-243.90, 203.90]	← ← →
Glock 1993	2,508	693	41	2,434	716	39	0.6%	74.00 [-235.02, 383.02]	← →
Haighighi 1999	2,405	674	40	2,452	532	34	0.7%	-47.00 [-321.96, 227.96]	←
Larmon 1999	2,475	636	65	2,449	729	57	0.9%	26.00 [-218.38, 270.38]	← →
Lorzadeh 2007	2,287.25	498.7	55	2,334	631.03	54	1.2%	-46.75 [-260.52, 167.02]	← ← →
Lyell 2007	2,550	802	106	2,650	698	110	1.4%	-100.00 [-300.81, 100.81]	← →
McWhorter 2004	2,530	902	102	2,585	778	92	1.0%	-55.00 [-291.46, 181.46]	← →
Morales 1993	2,030	627	52	1,808	390	49	1.4%	222.00 [19.60, 424.40]	│
Parilla, 1999	1,581	1,005	18	1,622	589	14	0.2%	-41.00 [-598.45, 516.45]	← →
Suricharmorn 2001	2,511	654	35	2,448	602	33	0.6%	63.00 [-235.55, 361.55]	← →
Taherian 2007	2,014	164	63	2,002	213	57	12.0%	12.00 [-56.54, 80.54]	
Total (95% CI)			810			786	100.0%	50.59 [26.88, 74.30]	•
Heterogeneity. Chi ² = 13.18, df = 14 (P = 0.51); l ² = 0%									-100 -50 0 50 100
, est tel everal effect.									Favours control Favours MgSO

• No benefit for magnesium sulphate in improving perinatal outcomes:

-Necrotising enterocolitis

	Magnesium Sul	phate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	0	15	1	19	15.6%	0.42 [0.02, 9.55]	
Cox 1990	4	75	3	79	34.1%	1.40 [0.33, 6.07]	
Fox 1993	0	45	0	45		Not estimable	
Lyell 2007	0	106	0	110		Not estimable	
McWhorter 2004	0	102	2	92	30.7%	0.18 [0.01, 3.71]	← ■ −
Parilla, 1999	0	18	1	14	19.6%	0.26 [0.01, 6.01]	
Total (95% CI)		361		359	100.0%	0.65 [0.23, 1.84]	-
Total events	4		7				
Heterogeneity: Chi ² –							
Test for overall effect:	Z = 0.81 (P = 0.4)	42)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS COMPARISONall trials

• Intraventricular haemorrhage

	Magnesium Sul	Magnesium Sulphate				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	1	15	2	19	5.8%	0.63 [0.06, 6.34]	
Cox 1990	4	75	4	79	12.9%	1.05 [0.27, 4.06]	_
Fox 1993	0	45	0	45		Not estimable	
Lyell 2007	3	106	2	110	6.5%	1.56 [0.27, 9.13]	
McWhorter 2004	7	102	б	92	20.9%	1.05 [0.37, 3.02]	+
Mittendorf (MAGNET) 1997	8	54	б	51	20.4%	1.26 [0.47, 3.38]	
Morales 1993	4	52	4	49	13.6%	0.94 [0.25, 3.56]	
Parilla, 1999	б	18	4	14	14.9%	1.17 [0.41, 3.35]	
Schorr 1997	0	43	1	45	4.9%	0.35 [0.01, 8.33]	• • •
Total (95% CI)		510		504	100.0%	1.07 [0.67, 1.71]	•
Total events	33		29				
Heterogeneity. $Chi^2 = 1.02$,							
Test for overall effect: Z = 0.	29 (P = 0.77)						Envours MaSO Envours control
							ravours myson ravours control

• Periventricular Leucomalacia

	Magnesium Sul	Conti	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Mittendorf (MAGNET) 1997	0	54	0	51		Not estimable	
Schorr 1997	1	43	0	45	100.0%	3.14 [0.13, 74.95]	
Total (95% CI)		97		96	100.0%	3.14 [0.13, 74.95]	
Total events	1		0				
Heterogeneity. Not applicable	1/8 - 0.48)						0.01 0.1 1 10 100
Test for overall effect. $z = 0.7$	I (F = 0.40)						Favours MgSO ₄ Favours control

• Cerebral Palsy

	Magnesium Sul	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Mittendorf (MAGNET) 1997	0	54	3	51	100.0%	0.14 [0.01, 2.55]	
Total (95% CI)		54		51	100.0%	0.14 [0.01, 2.55]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.3	0 4 (P = 0.18)		3				0.01 0.1 1 10 100 Favours MgSO, Favours control

MAGNESIUM SULPHATE VERSUS COMPARISONall trials

TOCOLYTIC OUTCOME

No statistically significant difference in tocolytic effectiveness

Birth<48hours

	Magnesium Su	phate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Borna 2007	7	52	10	52	5.5%	0.70 [0.29, 1.70]	
Chau 1992	2	46	4	52	1.6%	0.57 [0.11, 2.94]	
Cotton 1984	10	16	9	19	11.7%	1.32 [0.72, 2.42]	
Fox 1993	19	45	29	45	26.3%	0.66 [0.44, 0.98]	
Glock 1993	3	41	3	39	1.8%	0.95 [0.20, 4.43]	
Haighighi 1999	12	40	8	34	7.3%	1.27 [0.59, 2.75]	
Larmon 1999	4	65	4	57	2.4%	0.88 [0.23, 3.35]	
Lorzadeh 2007	7	51	5	50	3.7%	1.37 [0.47, 4.04]	
Lyell 2007	7	92	8	100	4.5%	0.95 [0.36, 2.52]	+
McWhorter 2004	10	106	б	101	4.5%	1.59 [0.60, 4.21]	
Morales 1993	8	52	5	49	3.9%	1.51 [0.53, 4.30]	_
Suricharmorn 2001	2	36	3	35	1.4%	0.65 [0.12, 3.65]	
Taherian 2007	31	63	22	57	25.3%	1.27 [0.84, 1.93]	
Total (95% CI)		705		690	100.0%	1.01 [0.82, 1.24]	•
Total events	122		116				
Heterogeneity. Tau ² =	0.00 ; $Chi^2 = 9.8$	8, df = 0	12 (P = 0).63); I ²	= 0%		
Test for overall effect:	Z = 0.08 (P = 0.)	94)	-				Eavours MaSO Eavours control
							ravours myso4 ravours control

Preterm birth (<37weeks)

	Magnesium Su	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chau 1992	12	46	25	52	11.2%	0.54 [0.31, 0.95]	
Cotton 1984	14	16	15	19	6.5%	1.11 [0.82, 1.49]	+
Floyd 1992	18	40	18	50	7.6%	1.25 [0.76, 2.07]	
Glock 1993	24	41	23	39	11.2%	0.99 [0.69, 1.43]	+
Lyell 2007	50	92	52	100	23.8%	1.05 [0.80, 1.36]	+
Miller 1982	б	14	7	15	3.2%	0.92 [0.41, 2.07]	
Schorr 1997	7	43	4	45	1.9%	1.83 [0.58, 5.81]	
Suricharmorn 2001	21	36	20	35	9.7%	1.02 [0.69, 1.52]	+
Taherian 2007	47	57	55	63	24.9%	0.94 [0.81, 1.10]	+
Total (95% CI)		385		418	100.0%	0.99 [0.87, 1.11]	
Total events	199		219				
Heterogeneity. $Chi^2 =$	7.43, df = 8 (P =	0.49); I	² = 0%			0.01 0.1 1 10 100	
rest for overall effect:	z = 0.23 (P = 0.	82)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS COMPARISON*high-quality trials*

10 trials (1171 women) No clear perinatal or tocolytic benefit

Increased number of neonatal and infant deaths,



which was no longer statistically significant when congenital anomalies and twin-

twin transfusion were excluded

	Magnesium Su	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cox 1990	4	75	2	79	47.6%	2.11 [0.40, 11.17]	
Floyd 1992	0	40	0	49		Not estimable	
Fox 1993	0	45	0	45		Not estimable	
Glock 1993	0	41	0	39		Not estimable	
Larmon 1999	0	65	0	57		Not estimable	
Lyell 2007	1	106	0	110	12.0%	3.11 [0.13, 75.56]	
McWhorter 2004	3	102	0	92	12.9%	6.32 [0.33, 120.74]	 >
Parilla, 1999	1	18	1	14	27.5%	0.78 [0.05, 11.37]	
Total (95% CI)		492		485	100.0%	2.40 [0.77, 7.51]	
Total events	9		3				
Heterogeneity. $Chi^2 =$	1.14, df = 3 (P =	• 0.77); İ	² = 0%				
Test for overall effect:	Z = 1.51 (P = 0.5)	13)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS PLACEBO:

PERINATAL OUTCOME

- 3 trials (281 women)
- Increased neonatal birth weight in the magnesium sulphate group



• Similar risk for perinatal mortality

	Magnesium su	Iphate	Place	bo		Risk Ratio	Risk Rat	io
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random	95% CI
Cotton 1984	1	15	4	19	46.0%	0.32 [0.04, 2.55]		•
Cox 1990	8	77	2	79	54.0%	4.10 [0.90, 18.71]	+	-
Fox 1993	0	45	0	45		Not estimable		
Total (95% CI)		137		143	100.0%	1.26 [0.10, 15.44]		
Total events	9		6					
Heterogeneity: Tau ² =	= 2.42; Chi ² = 3. ¹	79, df = 1	1 (P = 0.	05); I ^z -	= 74%			10 1
Test for overall effect	Z = 0.18 (P = 0)	.85)					Envours MaSO En	

MAGNESIUM SULPHATE VERSUS PLACEBO

• Similar risk for Necrotising Enterocolitis (NEC)

	Magnesium sul	phate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	0	15	1	19	31.3%	0.42 [0.02, 9.55]	
Cox 1990	4	75	3	79	68.7%	1.40 [0.33, 6.07]	
Fox 1993	0	45	0	45		Not estimable	
Total (95% CI)		135		143	100.0%	1.09 [0.30, 3.97]	-
Total events	4		4				
Heterogeneity: Chi ² =	0.48, df = 1 (P =	0.49); l	$^{2} = 0\%$				
Test for overall effect:	Z = 0.14 (P = 0.8)	39)					Favours MgSO ₄ Favours control

• Similar risk for Intraventricular Haemorrhage (IVH)

	Magnesium su	Iphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Cotton 1984	1	15	3	19	40.5%	0.42 [0.05, 3.66]	
Cox 1990	4	75	4	79	59.5%	1.05 [0.27, 4.06]	
Fox 1993	0	45	0	45		Not estimable	
Total (95% CI)		135		143	100.0%	0.80 [0.26, 2.45]	-
Total events	5		7				
Heterogeneity. Chi ² =	0.50, df = 1 (P)	= 0.48); ($^{2} = 0\%$				ho1 01 1 10 100
Test for overall effect:	Z = 0.39 (P = 0)	.69)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS PLACEBO:

TOCOLYTIC EFFECT

• Similar risk of birth <48 hours

	Magnesium su	lphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cotton 1984	10	16	9	19	44.6%	1.32 [0.72, 2.42]	
Fox 1993	19	45	29	45	55.4%	0.66 [0.44, 0.98]	-
Total (95% CI)		61		64	100.0%	0.90 [0.45, 1.77]	•
Total events	29		38				
Heterogeneity. Tau ² =	0.18; Chi ² = 3.5	4, df = 1	L (P = 0.0	06); l²	= 72%		0.01 0.1 1 10 100
rescror overall effect.	2 = 0.52 (r = 0.	/ 2)					Favours MgSO ₄ Favours control

• Similar risk of preterm birth (<37 weeks)

	Magnesium su	Iphate	Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	14	16	16	19	100.0%	1.31 [0.19, 9.02]	
Total (95% CI)		16		19	100.0%	1.31 [0.19, 9.02]	
Total events	14		16				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.28 (P = 0)	.78)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

PERINATAL OUTCOME

- 4 trials (324 women)
- Similar risk of perinatal mortality



• Similar risk of Respiratory Distress Syndrome

	Magnesium su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	6	15	4	19	64.6%	1.90 [0.65, 5.53]	
Miller 1982	3	15	2	16	35.4%	1.60 [0.31, 8.29]	
Total (95% CI)		30		35	100.0%	1.79 [0.73, 4.41]	•
Total events	9		б				
Heterogeneity: Chi ² = Test for overall effect:	0.03, df = 1 (P Z = 1.27 (P = 0	= 0.86); I .20)	² = 0%				0.01 0.1 1 10 100 Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

• Similar risk of Necrotising enterocolitis

	Magnesium su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	1	15	2	19	100.0%	0.63 [0.06, 6.34]	
Total (95% CI)		15		19	100.0%	0.63 [0.06, 6.34]	
Total events	1		2				
Heterogeneity. Not ap Test for overall effect	oplicable : Z = 0.39 (P = 0	0.70)					0.01 0.1 1 10 100 Favours MgSO4 Favours control

• Similar risk of Patent ductus arteriosus

	Magnesium su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Suricharmorn 2001	2	15	2	19	100.0%	1.27 [0.20, 7.97]	
Total (95% CI)		15		19	100.0%	1.27 [0.20, 7.97]	
Total events	2		2				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.25 (P = 0	.80)					0.01 0.1 1 10 100 Favours MgSQ, Favours control

MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

TOCOLYTIC OUTCOME

• Increased mean gestational age at delivery, in the betamimetics group

	Magnesi	ium Sulp	hate	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cotton 1984	31	1.9	16	33.1	33.3	19	0.7%	-2.10 [-17.10, 12.90]	
Suricharmorn 2001	36.21	2.76	36	31.26	2.81	35	99.3%	4.95 [3.65, 6.25]	-
Total (95% CI)			52			54	100.0%	4.90 [3.61, 6.19]	
Heterogeneity: Chi ² =	0.84, df =	1(P = 0)	.36); I ²	= 0%					100 to to to 100
Test for overall effect:	Z = 7.43 ((P < 0.00	0001)						Favours MgSO ₄ Favours control

• Similar risk of delivery <48 hours

	Magnesium Su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chau 1992	2	46	4	52	21.8%	0.57 [0.11, 2.94]	
Cotton 1984	10	16	9	19	47.8%	1.32 [0.72, 2.42]	
Suricharmorn 2001	2	36	3	35	17.7%	0.65 [0.12, 3.65]	
Wilkins 1988	5	66	2	54	12.8%	2.05 [0.41, 10.13]	
Total (95% CI)		164		160	100.0%	1.13 [0.66, 1.94]	•
Total events	19		18				
Heterogeneity: Chi ² =	1.85, df = 3 (P =	= 0.60); I	² = 0%				
Test for overall effect:	Z = 0.44 (P = 0.	66)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS:

PERINATAL OUTCOME

6 trials (687 women)

• No benefit for magnesium sulphate over Ca⁺² channel antagonists in improving perinatal outcome

• Perinatal mortality

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	Magnesium Sul	phate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Floyd 1992	0	40	1	50	30.5%	0.41 [0.02, 9.91]	
Glock 1993	0	41	2	39	58.4%	0.19 [0.01, 3.85]	< ■
Larmon 1999	0	65	0	57		Not estimable	
Lyell 2007	1	106	0	110	11.2%	3.11 [0.13, 75.56]	
Total (95% CI)		252		256	100.0%	0.59 [0.13, 2.70]	-
Total events	1		3				
Heterogeneity. Chi ² =	1.64, df = 2 (P =	0.44); I	² = 0%				
Test for overall effect:	Z = 0.69 (P = 0.5)	49)					Favours MgSO ₄ Favours control

Respiratory Distress Syndrome

	Magnesium Su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Floyd 1992	4	40	5	49	17.9%	0.98 [0.28, 3.41]	_
Lyell 2007	24	106	21	110	82.1%	1.19 [0.70, 2.00]	
Total (95% CI)		146		159	100.0%	1.15 [0.71, 1.86]	•
Total events	28		26				
Heterogeneity: Chi ² –	0.08, df - 1 (P -	- 0.78); I	2 - 0%				
Test for overall effect:	Z = 0.57 (P = 0.57)	.57)					Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS

• Intraventricular haemorrhage

	Magnesium Su	lphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lyell 2007	3	106	2	110	100.0%	1.56 [0.27, 9.13]	
Total (95% CI)		106		110	100.0%	1.56 [0.27, 9.13]	
Total events	3		2				
Heterogeneity. Not ap Test for overall effect:	plicable Z = 0.49 (P = 0.	.62)					0.02 0.1 1 10 50 Favours MgSO ₄ Favours control

Admission to the NICU

•

	Magnesium Su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Larmon 1999	11	65	15	57	41.7%	0.64 [0.32, 1.28]	
Lyell 2007	55	106	41	110	58.3%	1.39 [1.03, 1.89]	=
Total (95% CI)		171		167	100.0%	1.01 [0.47, 2.14]	•
Total events	66		56				
Heterogeneity: Tau ² = Test for overall effect:		0.01 0.1 1 10 100 Favours MgSO ₄ Favours control					

MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS:

TOCOLYTIC OUTCOME

• Similar tocolytic efficacy,

-birth <48 hours



• Shorter time to uterine quiescence in the Ca⁺² channel antagonists group

	Magnesi	ium Sulp	hate	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Glock 1993	4.2	1.6	41	3.2	1.9	39	42.0%	1.00 [0.23, 1.77]	
Haighighi 1999	4.8	4.23	40	2.98	3.03	43	13.2%	1.82 [0.23, 3.41]	
Larmon 1999	5.3	2.9	65	3.3	2.1	57	34.3%	2.00 [1.11, 2.89]	+
Lyell 2007	8.4	6.5	92	6.1	6.3	100	10.4%	2.30 [0.49, 4.11]	•
Total (95% CI)			238			239	100.0%	1.59 [0.98, 2.20]	
Heterogeneity: Tau ² =	0.08; Chi ²	= 3.70,	df = 3	(P = 0.3)	30); I ²	= 19%			
Test for overall effect:	Z = 5.08 ((P < 0.00	001)						Eavours MoSO - Eavours contr

MAGNESIUM SULPHATE VERSUS COX INHIBITORS :

PERINATAL OUTCOME

5 trials (524 women) -No statistically significant difference

Perinatal mortality

	Magnesium Sul	phate	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
McWhorter 2004	4	102	0	92	19.6%	8.13 [0.44, 148.91]	
Morales 1993	1	52	1	49	38.4%	0.94 [0.06, 14.65]	
Parilla, 1999	1	18	1	14	42.0%	0.78 [0.05, 11.37]	
Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	6 1.75, df = 2 (P = Z = 1.13 (P = 0.2	172 0.42); ľ 26)	2 2 = 0%	155	100.0%	2.28 [0.55, 9.55]	0.02 0.1 1 10 50 Eavours MoSQ. Eavours control
							rated a massa

Intraventricular haemorrhage

	Magnesium Su	lphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
McWhorter 2004	7	102	6	92	38.5%	1.05 [0.37, 3.02]	
Morales 1993	4	52	4	49	25.1%	0.94 [0.25, 3.56]	_
Parilla, 1999	6	18	4	14	27.4%	1.17 [0.41, 3.35]	
Schorr 1997	0	43	1	45	8.9%	0.35 [0.01, 8.33]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		215		200	100.0%	0.99 [0.52, 1.88]	•
Total events	17		15				
Heterogeneity. Chi ² =	0.53, df = 3 (P =	= 0.91); I	² = 0%				
Test for overall effect:	Favours MgSO ₄ Favours control						

Respiratory distress syndrome

	Magnesium Su	lphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
McWhorter 2004	19	102	18	92	59.8%	0.95 [0.53, 1.70]	
Morales 1993	5	52	5	49	16.3%	0.94 [0.29, 3.06]	
Parilla, 1999	5	18	5	14	17.8%	0.78 [0.28, 2.17]	
Schorr 1997	4	43	2	45	6.2%	2.09 [0.40, 10.85]	
Total (95% CI)		215		200	100.0%	0.99 [0.63, 1.55]	•
Total events	33		30				
Heterogeneity: Chi ² =	1.03, df = 3 (P =	0.79); I	² = 0%				
Test for overall effect:	Z = 0.04 (P = 0.04)	96)					Eavours Maso, Eavours control

MAGNESIUM SULPHATE VERSUS COX INHIBITORS :

TOCOLYTIC OUTCOME

• Similar tocolytic efficacy

Birth<48 hours

	Magnesium Su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Borna 2007	7	52	10	52	47.0%	0.70 [0.29, 1.70]	-8-
McWhorter 2004	10	106	6	101	28.9%	1.59 [0.60, 4.21]	
Morales 1993	8	52	5	49	24.2%	1.51 [0.53, 4.30]	
Total (95% CI)		210		202	100.0%	1.15 [0.67, 1.99]	•
Total events	25		21				
Heterogeneity: Chi ² =	1.88, df = 2 (P	= 0.39); I	² = 0%				h 01 01 1 10 100
Test for overall effect:	Z = 0.51 (P = 0)	.61)					Favours MgSO ₄ Favours control

Preterm birth (<37 weeks)

	Magnesium Sul	phate	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Schorr 1997	7	43	4	45	100.0%	1.83 [0.58, 5.81]	-	
Total (95% CI)		43		45	100.0%	1.83 [0.58, 5.81]	•	
Total events	7		4					
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.03 (P = 0.3	30)					0.01 0.1 1 10 Favours MgSO ₄ Favours co	100 ntrol

• Except for a *shorter time to uterine quiescence in the COX-inhibitors subgroup* (but with significant heterogeneity)

	Magnesi	um Sulp	hate	с	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Borna 2007	2.8	0	52	4.1	1.4	52		Not estimable	
Morales 1993	7.9	2.3	52	б.2	2	49	60.0%	1.70 [0.86, 2.54]	
Schorr 1997	6.22	5.65	43	2.7	2.16	45	40.0%	3.52 [1.72, 5.32]	
Total (95% CI)	-		147		_	146	100.0%	2.43 [0.68, 4.18]	•
Heterogeneity: Tau ² =	1.14; Chi²	= 3.22,	df = 1	(P = 0.0)	07); I ²	= 69%			-100 -50 0 50 100
Test for overall effect:	Z = 2.72 (P = 0.00	6)						Favours MgSO ₄ Favours control

MAGNESIUM SULPHATE VERSUS HCG :

PERINATAL OUTCOME

- 1 trial (91 women) -No statistically significant difference
- No deaths in either group

	Magnesium Su	lphate	HCO	G		Risk Ratio	Risk Ra	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed,	95% CI
Lorzadeh 2007	0	55	0	54		Not estimable		
Total (95% CI)		55		54		Not estimable		
Total events	0		0					
Heterogeneity: Not ap Test for overall effect:	plicable Not applicable						0.01 0.1 1 Favours MgSO ₄ F	10 100 avours control

• Respiratory distress syndrome

	Magnesium Sulphate		HCG		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Lorzadeh 2007	9	55	9	54	100.0%	0.98 [0.42, 2.28]	
Total (95% CI)		55		54	100.0%	0.98 [0.42, 2.28]	+
Total events	9		9				
Heterogeneity: Not ap Test for overall effect:	97)					0.01 0.1 1 10 100 Favours MgSO ₄ Favours control	

MAGNESIUM SULPHATE VERSUS HCG :

TOCOLYTIC OUTCOME

• Similar tocolytic efficacy

• Birth <48 hours

	Magnesium Sul	phate	нсо	G		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lorzadeh 2007	7	51	5	50	100.0%	1.37 [0.47, 4.04]	-
Total (95% CI)		51		50	100.0%	1.37 [0.47, 4.04]	-
Total events	7		5				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.58 (P = 0.5	57)					0.01 0.1 1 10 100 Favours MgSO ₄ Favours control

There was a significantly increased risk of perinatal mortality in the short-term low dose subgroup

Number of total deaths (fetal, neonatal, infant) Magnesium Sulphate Control **Risk Ratio** Risk Ratio Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup Events 1.1.1 Short-term therapy (up to 48 hours), low dose Cotton 1984 1 15 1 19 7.1% 1.27 [0.09, 18.62] Cox 1990 8 77 2 79 15.8% 4.10 [0.90. 18.71] Lorzadeh 2007 0 55 0 54 Not estimable Lyell 2007 1 106 0 110 3.9% 3.11 [0.13, 75.56] Mittendorf (MAGNET) 1997 8 55 0 4.2% 15.79 [0.93, 266,72] 51 Suricharmorn 2001 36 2 35 0.49 [0.05, 5.12] 1 16.3% Subtotal (95% CI) 344 348 47.3% 3.38 [1.36, 8.37] Total events 19 5 Heterogeneity. $Chi^2 = 4.32$, df = 4 (P = 0.36); $I^2 = 7\%$ Test for overall effect: Z = 2.63 (P = 0.009) 1.1.2 Short-term therapy, high dose McWhorter 2004 4 102 0 92 4.2% 8.13 [0.44, 148.91] Morales 1993 1 52 1 49 8.3% 0.94 [0.06, 14.65] Parilla, 1999 1 18 1 14 9.0% 0.78 [0.05, 11.37] Subtotal (95% CI) 172 21.5% 2.28 [0.55, 9.55] 155 Total events б 2 Heterogeneity. $Chi^2 = 1.75$, df = 2 (P = 0.42); $I^2 = 0\%$ Test for overall effect: Z = 1.13 (P = 0.26) 1.1.3 Long-term therapy (until 37th week of gestation) Flovd 1992 0 40 1 50 10.7% 0.41 [0.02, 9.91] Fox 1993 0 45 0 45 Not estimable Glock 1993 0 41 2 39 20.5% 0.19 [0.01, 3.85] Larmon 1999 0 65 0 57 Not estimable 191 Subtotal (95% CI) 191 31.3% 0.27 [0.03, 2.29] Total events 0 З Heterogeneity. $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$ Test for overall effect: Z = 1.20 (P = 0.23) Total (95% CI) 707 694 100.0% 2.17 [1.12, 4.22] Total events 25 10 Heterogeneity. $Chi^2 = 9.60$, df = 9 (P = 0.38); $I^2 = 6\%$ 0.02 0.1 10 50 Test for overall effect: Z = 2.29 (P = 0.02) Favours MgSO₄ Favours control Test for subgroup differences: $Chi^2 = 4.55$, df = 2 (P = 0.10), $I^2 = 56.0\%$

Total deaths - excluding deaths not related to the tocolytic agent (e.g congenital anomalies, severe twin-twin transfusion)

	Magnesium Sulphate		Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.2.1 Short-term therapy, lo	ow dose						
Cox 1990	5	77	2	79	18.7%	2.56 [0.51, 12.83]	
Lorzadeh 2007	0	55	0	54		Not estimable	
Lyell 2007	1	106	0	110	4.6%	3.11 [0.13, 75.56]	· · · · · · · · · · · · · · · · · · ·
Mittendorf (MAGNET) 1997	5	55	0	51	4.9%	10.21 [0.58, 180.21]	
Suricharmorn 2001	1	36	2	35	19.2%	0.49 [0.05, 5.12]	
Subtotal (95% CI)		329		329	47.5%	2.57 [0.93, 7.13]	
Total events	12		4				
Heterogeneity: $Chi^2 = 2.82$, c	f = 3 (P = 0.42);	$ ^2 = 0\%$					
Test for overall effect: Z = 1.8	B1 (P = 0.07)						
1.2.2 Short-term, high dose							
McWhorter 2004	3	102	0	92	5.0%	6.32 [0.33, 120,74]	
Parilla 1999	1	18	1	14	10.7%	0.78 [0.05, 11.37]	
Subtotal (95% CI)	-	120	-	106	15.6%	2.54 [0.42, 15.28]	
Total events	4		1				
Heterogeneity, $Chi^2 = 1.12$, o	f = 1 (P = 0.29)	$l^2 = 109$	6 -				
Test for overall effect: Z = 1.0	O2 (P = 0.31)						
1.2.3 Long-term therapy							
Floyd 1992	0	40	1	50	12.7%	0.41 [0.02, 9.91]	• • • • • • • • • • • • • • • • • • •
Fox 1993	0	45	0	45		Not estimable	
Glock 1993	0	41	2	39	24.3%	0.19 [0.01, 3.85]	• • • • • • • • • • • • • • • • • • •
Larmon 1999	0	65	0	57		Not estimable	
Subtotal (95% CI)		191		191	36.9%	0.27 [0.03, 2.29]	
Total events	0		3				
Heterogeneity: $Chi^2 = 0.12$, d	if = 1 (P = 0.73);	$ ^2 = 0\%$					
Test for overall effect: $Z = 1.2$	20 (P = 0.23)						
Total (95% CI)		640		626	100.0%	1.72 [0.81, 3.64]	-
Total events	16		8				
Heterogeneity. $Chi^2 = 6.87$, c	f = 7 (P = 0.44);	$ ^2 = 0\%$					
Test for overall effect: Z = 1.4	41 (P = 0.16)						Eavours MaSO4 Eavours control
							ravours mysom ravours control

• Pattern towards better oucomes in the short-term, high dose or the long-term treatment subgroups compared to the short-term low dose subgroup.

1. Intraventricular Haemorrhage

	Magnesium Su	Iphate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.10.1 Short-term therapy, I	ow dose						
Cotton 1984	1	15	2	19	12.8%	0.63 [0.06, 6.34]	
Cox 1990	4	75	4	79	28.2%	1.05 [0.27, 4.06]	
Lyell 2007	3	106	2	110	14.2%	1.56 [0.27, 9.13]	
Mittendorf (MAGNET) 1997 Subtotal (95% CI)	8	250	б	51 259	44.7%	1.26 [0.47, 3.38]	
Total opents	16	250	14	235	100.070	1.10 [0.50, 2.52]	
Heterogeneity Chi ² - 0.42 d	f = 2 /P = 0.94)	12 - 0%	14				
Test for overall effect: $7 = 0.42$, d	1 = 3 (P = 0.94)	, 1- = 026					
rescrot overall effect. 2 = 0.4	rs (r = 0.07)						
1.10.2 Short-term therapy, I	high dose						
McWhorter 2004	7	102	б	92	42.3%	1.05 [0.37, 3.02]	
Morales 1993	4	52	4	49	27.6%	0.94 [0.25, 3.56]	
Parilla, 1999	6	18	4	14	30.1%	1.17 [0.41, 3.35]	_
Subtotal (95% CI)		172		155	100.0%	1.06 [0.55, 2.03]	•
Total events	17		14				
Heterogeneity: Chi ² = 0.06, d	f = 2 (P = 0.97)	$; ^2 = 0\%$					
Test for overall effect: Z = 0.1	ьб (P = 0.87)						
1 10 2 Long-term therapy							
LIOS LONG-term therapy	~	45	~	45			
FOX 1993	0	45	0	45	100.00	Not estimable	
Subtotal (95% CI)	0	43	T	45	100.0%	0.35 [0.01, 8.33]	
	~	00	1	90	100.0%	0.33 [0.01, 8.33]	
lotal events	Ų		1				
Heterogeneity. Not applicable	E (D 0 E 2)						
Test for overall effect: $Z = 0.6$	(P = 0.52)						
							0.02 0.1 1 10 50

2. Necrotising enterocolitis

3. Admission to the NICU

	Magnesium S	ulphate	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cotton 1984	rapy, low dos	15		10	15 60	0 42 10 02 0 551	
Cox 1990	4	75	3	79	34.1%	1.40 [0.33, 6.07]	
Lyell 2007	0	106	0	110		Not estimable	
Subtotal (95% CI)		196	_	208	49.7%	1.09 [0.30, 3.97]	
Total events Hotorogonoity Chil - O	4	0.40× ii	4				
Test for overall effect: Z	148, df = 1 (P 1 = 0.14 (P =	0.89)	= 0%				
1.18.2 Short-term the	rapy, high do	se					
McWhorter 2004	0	102	2	92	30.7%	0.18 [0.01, 3.71]	← ■
Parilla, 1999 Subtatal (95% CI)	Ô	18	1	14	19.6%	0.26 [0.01, 6.01]	
Total compte	0	120	2	100	50.5%	0.21 [0.02, 1.87]	
Heterogeneity: Chi ² = 0	.03. df = 1.(P	= 0.861; l ³	' = 0%				
Test for overall effect: Z	= 1.40 (P =	0.16)	- 070				
1.18.3 Long-term the	rapy						
Fox 1993	0	45	0	45		Not estimable	
Subtotal (95% CI)		45	-	45		Not estimable	
i otal events Heterogeneity: Not appl	0 licable		0				
Test for overall effect: N	lot applicable						
Total (95% CI)		361		359	100.0%	0.65 [0.23, 1.84]	-
Total events	4		7				
Heterogeneity: Chi² = 2 Test for overall effect: Z	.15, df = 3 (F : = 0.81 (P =	' = 0.54); l' 0.42)	= 0%				0.01 0.1 1 10 10 Favours MgSQ, Favours control
To at four such success sliffers	rences: Not an	plicable					
lest for subdroub differ							
rest for subaroup airter							
Test for subaroub differ	Favours Mg	50 ₄ C	ontrol			Risk Ratio	Risk Ratio
Study or Subgroup	Favours Mgs Events	50 ₄ C Total Eve	ontrol nts Tota	al We	ight M-	Risk Ratio H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
Study or Subgroup 1.26.1 Short-term the	Favours Mgs Events grapy, low do	50 ₄ C Total Even se	ontrol nts Tot	al We	ight M-	Risk Ratio H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Study or Subgroup 1.26.1 Short-term the Cox 1990	Favours Mgs Events rapy, low do 5	60 ₄ C Total Eve se 75	ontrol nts Tota 12 7	<u>al We</u> 9 1:	<u>ight M-</u> 1.3%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup 1.26.1 Short-term the Cox 1990 Lorzadeh 2007	Favours Mgs Events erapy, low do 5 9	60 ₄ C Total Even se 75 55	ontrol nts Tota 12 7 9 5	al We 9 1: 4 14	<u>ight M-</u> 1.3% 4.2%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup 1.26.1 Short-term the Cox 1990 Lorzadeh 2007 Lyell 2007	Favours Mgs Events erapy, low do 5 9 55	50 ₄ C Total Even se 75 55 106 226	ontrol nts Tot 12 7 9 5 41 11	al We 9 1: 4 14 0 3:	<u>ight M-</u> 1.3% 4.2% 3.3%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89]	Risk Ratio M-H, Random, 95% Cl
Study or Subgroup 1.26.1 Short-term the Cox 1990 Lorzadeh 2007 Lyell 2007 Subtotal (95% CI)	Favours Mgs Events rapy, low do 5 9 55	50 ₄ C Total Even se 75 55 106 236	ontrol nts Tota 12 7 9 5 41 11 24	al We 9 1: 4 14 0 3: 3 5:	ight M- 1.3% 4.2% 3.3% 8.8%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89] 0.96 [0.50, 1.84]	Risk Ratio M-H, Random, 95% Cl
Study or Subgroup 1.26.1 Short-term the Cox 1990 Lorzadeh 2007 Lyell 2007 Subtotal (95% CI) Total events	Favours Mg Events rapy, low do 5 9 55 69	50 ₄ C Total Even se 75 55 106 236	ontrol <u>nts Tot</u> 12 7 9 5 41 11 24 62 2 (8 - 0	ul We 9 1: 4 14 0 3: 3 5:	ight M- 1.3% 4.2% 3.3% 8.8%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89] 0.96 [0.50, 1.84]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup 1.26.1 Short-term the Cox 1990 Lorzadeh 2007 Lyell 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	Favours Mg Events Prapy, low do 5 55 69 0.20; Chi ² = 1 Z = 0.13 (P =	50 ₄ C Total Even se 75 55 106 236 5.27, df = 0.90)	ontrol <u>12</u> 7 <u>9</u> 5 41 11 <u>24</u> 62 2 (P = 0	al We 9 1: 4 14 0 3: 3 5: 07); I ²	ight M- 1.3% 4.2% 3.3% 8.8%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89] 0.96 [0.50, 1.84]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup difference of the standard o	Favours Mg Events Prapy, low do 5 9 55 69 0.20; Chi ² = 1 Z = 0.13 (P = Prapy, high do	50 ₄ C Total Even se 75 55 106 236 5.27, df = 0.90) ose	ontrol nts Tota 9 5 41 11 24 62 2 (P = 0	al We 9 1: 4 14 0 3: 3 54 07); I ²	ight M- 1.3% 4.2% 3.3% 8.8% ² = 62%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89] 0.96 [0.50, 1.84]	Risk Ratio M-H, Random, 95% CI
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Study or Subdroub differ 1.26.1 Short-term the Cox 1990 Lorzadeh 2007 Lyell 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1.26.2 Short-term the McWhorter 2004 Subtotal (95% CI) Total events Heterogeneity. Not app Test for overall effect: 2 1.26.3 Long-term the Larmon 1999 Subtotal (95% CI) Total events	Favours Mg Events Prapy, low do 5 9 55 0.20; Chi ² = 2 2 = 0.13 (P = Prapy, high do 24 24 24 24 24 24 24 24 21 21 21 21 21 21 21 21 21 21	50 ₄ C Total Ever 55 106 236 5.27, df = 0.90) 058 102 102 0.50) 65 65	ontrol <u>nts Tot</u> 12 7 9 5 41 11 24 62 2 (P = 0 18 9 18 15 5 15	I We 9 1: 4 1: 0 3: 3: 5: 0: 07); 2: 2: 2: 2: 7: 14 7: 14	ight M- 1.3% 4.2% 3.3% 8.8% 2 = 62% 3.1% 3.1% 8.1%	Risk Ratio H, Random, 95% CI 0.44 [0.16, 1.19] 0.98 [0.42, 2.28] 1.39 [1.03, 1.89] 0.96 [0.50, 1.84] 1.20 [0.70, 2.07] 1.20 [0.70, 2.07] 1.20 [0.70, 2.07]	Risk Ratio M-H, Random, 95% CI
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But...the opposite pattern was observed with regard to patent ductus arteriosus (PDA); greater risk in the long-term treatment subgroup

	Magnesium Sulph	ate	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.19.1 Short-term th	erapy						
Cotton 1984 Subtotal (95% CI)	2	15 15	2	19 19	64.4% 64.4%	1.27 [0.20, 7.97] 1.27 [0.20, 7.97]	
Total events Heterogeneity: Not app	2 plicable		2				
Test for overall effect:	Z = 0.25 (P = 0.80))					
1.19.2 Long-term the	erapy						
Schorr 1997 Subtotal (95% CI)	3	43 43	1	45 45	35.6% 35.6%	3.14 [0.34, 29.03] 3.14 [0.34, 29.03]	
Total events Heterogeneity: Not ap Test for overall effect:	3 plicable Z = 1.01 (P = 0.31	1	1				
Total (95% CI)		58		64	100.0%	1.93 [0.48, 7,78]	
Total events Heterogeneity: Chi ² = Test for overall effect:	5 0.39, df = 1 (P = 0 Z = 0.93 (P = 0.35	.53); I)	² = 0%	04	200.070	1.55 [0.40, 7.70]	0.01 0.1 1 10 2 Eavours MgSQ, Eavours cont

Ρ



No association of magnesium sulphate to perinatal mortality

No evidence of neuroprotection

No clear clinical benefit in terms of either perinatal outcomes or tocolytic outcomes, in any of the comparisons.

Magnesium sulphate is not superior nor inferior to any of the tocolytic agents assessed ...nor to placebo! Further high quality RCTs comparing magnesium sulphate to placebo would be essential in order to establish:

whether MgSO₄ can prolong pregnancy for at least 48 hours, in women at high risk of spontaneous birth,

whether it exerts a neuroprotective effect, especially by reducing the risk of cerebral palsy. All currently used tocolytic agents, including magnesium sulphate, wish to prevent preterm labour, by inhibiting uterine contractions, but as this is the result and not the cause,... is that goal reachable?

Thank you for your attention



Christina Ammari