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

Short-term morbidity

- *Respiratory distress syndrome*
- *Intraventricular haemorrhage*
- *Necrotizing enterocolitis*
- *Sepsis*
- *Retinopathy of prematurity*

Long-term morbidity

- *Cerebral palsy*
- *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)

→ ***>$26 billion*** → *>$60,000/preterm infant*

TOCOLYSIS

- Goals

  -delay delivery for → 48 hours
  → or more

  -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*

MAGNESIUM SULPHATE

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

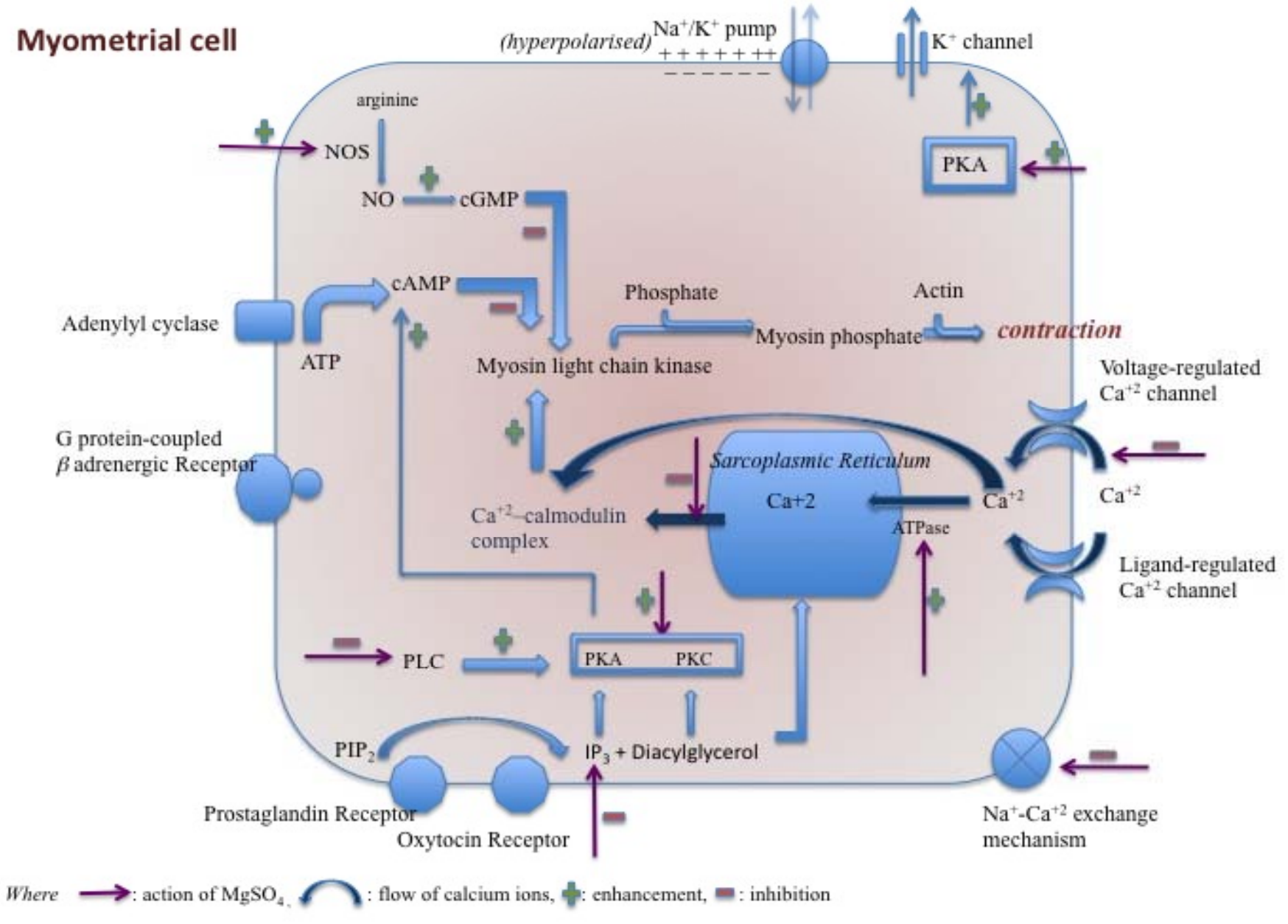
Mg^{+2}: - ↓ Ca^{+2} (intra- and extra-cellularly)

- ✚ 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

→ Cerebral palsy

MAGNESIUM SULPHATE AND NEUROPROTECTION

Magnesium sulphate's action

✖ *NMDA Receptors (N-methyl D-aspartate)*	→	Excitotoxicity, Demyelination
↓ *Oxygen free radicals*	→	Hypoxic damage
↓ *Cytokines*	→	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:

- Hypermagnesaemia
- Motor and Respiratory depression

Central Nervous System depression:

Lethargy,

Hypotonicity,

Depressed Apgar score

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 www.clinicaltrials.gov.

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)

RESULTS

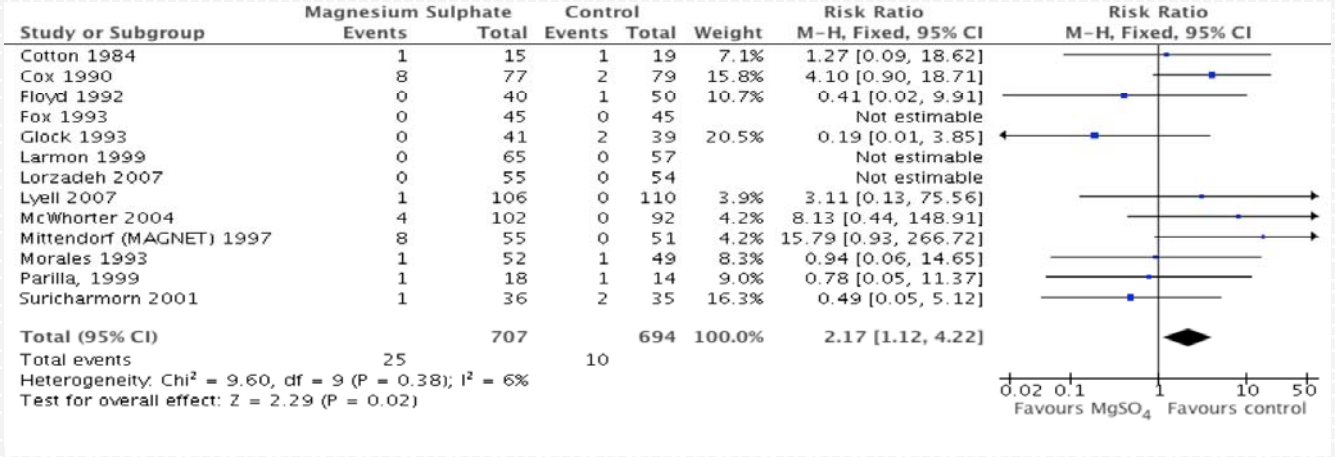
Identified: 41 RCTs

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***

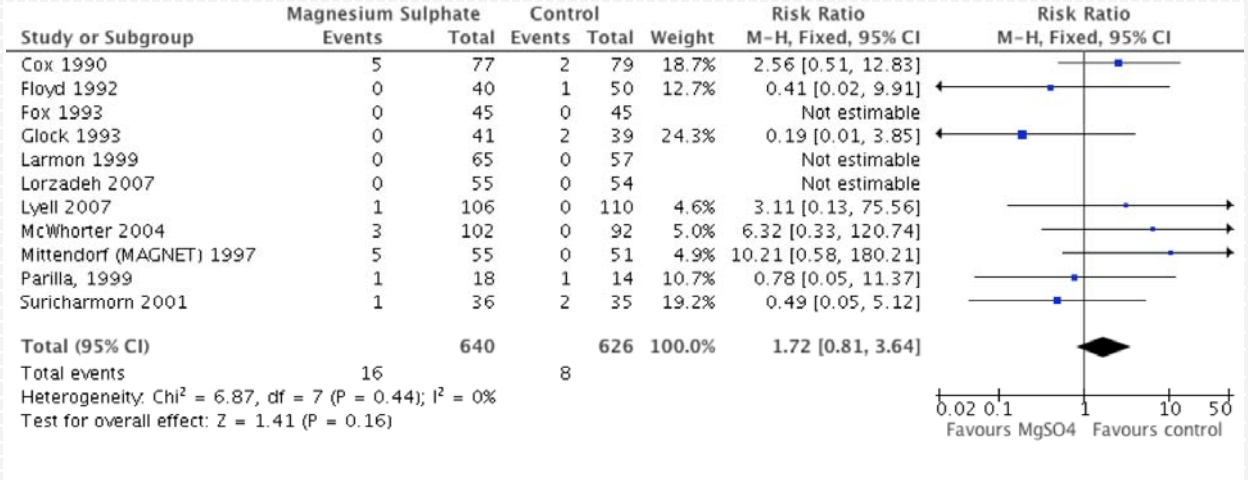


Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cotton 1984	1	15	1	19	7.1%	1.27 [0.09, 18.62]
Cox 1990	8	77	2	79	15.8%	4.10 [0.90, 18.71]
Floyd 1992	0	40	1	50	10.7%	0.41 [0.02, 9.91]
Fox 1993	0	45	0	45		Not estimable
Glock 1993	0	41	2	39	20.5%	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: $Chi^2 = 9.60$, $df = 9$ ($P = 0.38$); $I^2 = 6\%$
Test for overall effect: $Z = 2.29$ ($P = 0.02$)

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.



Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 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]
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]
McWhorter 2004	3	102	0	92	5.0%	6.32 [0.33, 120.74]
Mittendorf (MAGNET) 1997	5	55	0	51	4.9%	10.21 [0.58, 180.21]
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: $Chi^2 = 6.87$, $df = 7$ ($P = 0.44$); $I^2 = 0\%$

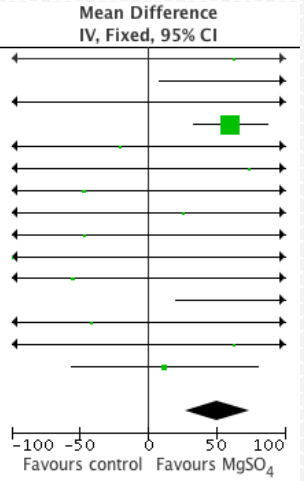
Test for overall effect: $Z = 1.41$ ($P = 0.16$)

MAGNESIUM SULPHATE VERSUS COMPARISON- *all trials*

- ***Increased neonatal birth weight*** *in the magnesium sulphate group*

Study or Subgroup	Magnesium Sulphate Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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); $I^2 = 0\%$
Test for overall effect: Z = 4.18 (P < 0.0001)

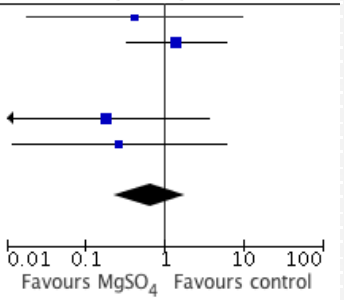


- ***No benefit for magnesium sulphate in improving perinatal outcomes:***

-Necrotising enterocolitis

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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: $Chi^2 = 2.15$, df = 3 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 0.81 (P = 0.42)

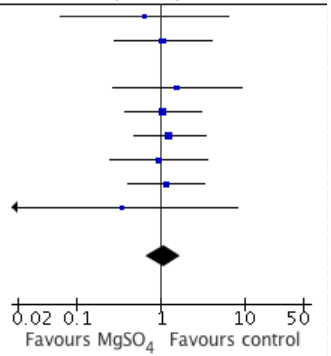


MAGNESIUM SULPHATE VERSUS COMPARISON- *all trials*

- *Intraventricular haemorrhage*

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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	6	92	20.9%	1.05 [0.37, 3.02]
Mittendorf (MAGNET) 1997	8	54	6	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	6	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			

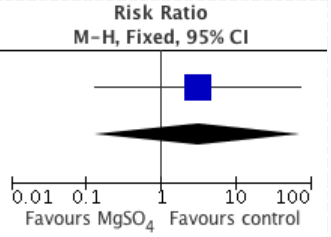
Heterogeneity: $Chi^2 = 1.02$, df = 7 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 0.29 (P = 0.77)



- *Periventricular Leucomalacia*

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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			

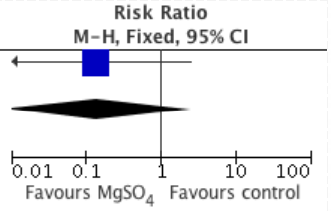
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



- *Cerebral Palsy*

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)



MAGNESIUM SULPHATE VERSUS COMPARISON- *all trials*

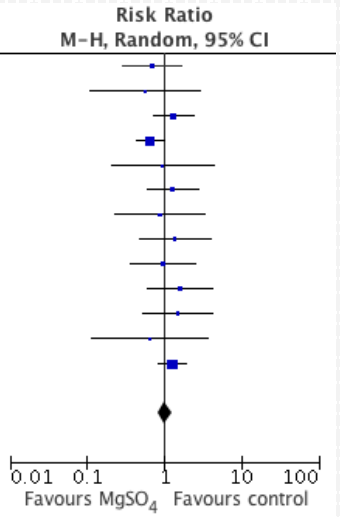
TOCOLYTIC OUTCOME

No statistically significant difference in tocolytic effectiveness

Birth<48hours

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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	6	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			

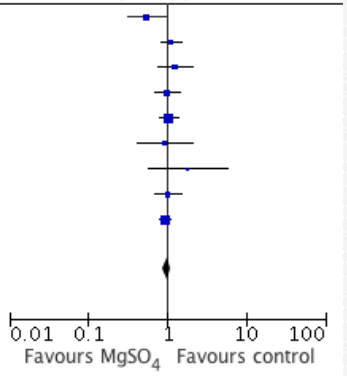
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.88$, df = 12 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 0.08 (P = 0.94)



Preterm birth (<37weeks)

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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	6	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			

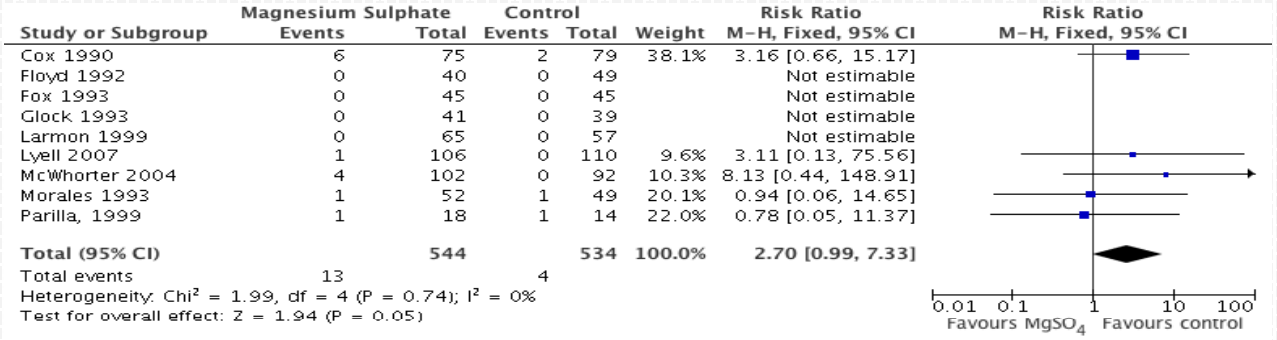
Heterogeneity: $Chi^2 = 7.43$, df = 8 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.23 (P = 0.82)



MAGNESIUM SULPHATE VERSUS COMPARISON- *high-quality trials*

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

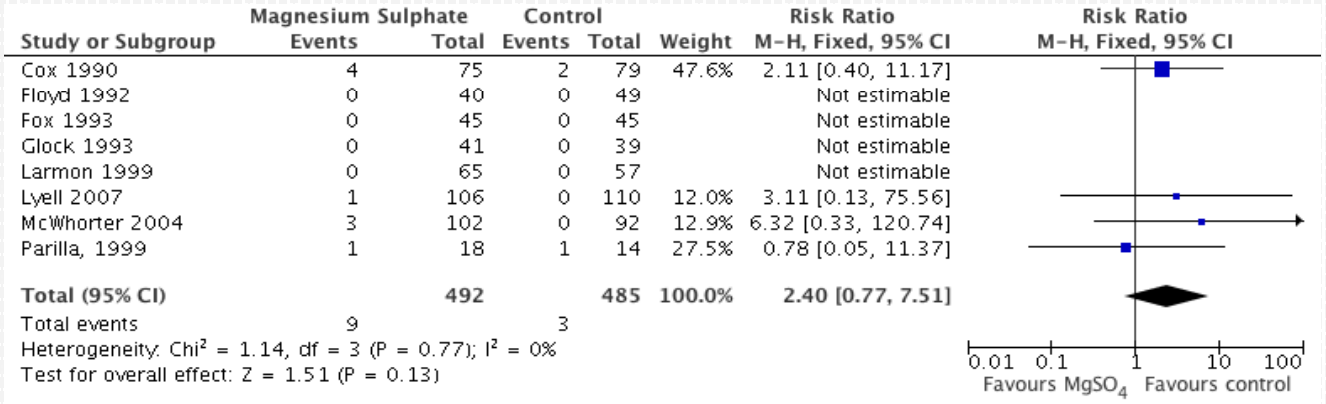
Increased number of neonatal and infant deaths,



Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cox 1990	6	75	2	79	38.1%	3.16 [0.66, 15.17]
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	9.6%	3.11 [0.13, 75.56]
McWhorter 2004	4	102	0	92	10.3%	8.13 [0.44, 148.91]
Morales 1993	1	52	1	49	20.1%	0.94 [0.06, 14.65]
Parilla, 1999	1	18	1	14	22.0%	0.78 [0.05, 11.37]
Total (95% CI)		**544**		**534**	**100.0%**	**2.70 [0.99, 7.33]**
Total events	13		4			

Heterogeneity: Chi² = 1.99, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)

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



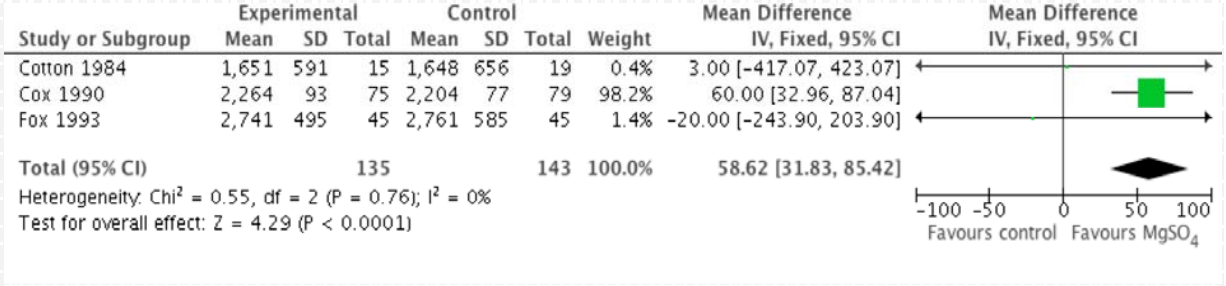
Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cox 1990	4	75	2	79	47.6%	2.11 [0.40, 11.17]
Floyd 1992	0	40	0	49		Not estimable
Fox 1993	0	45	0	45		Not estimable
Glock 1993	0	41	0	39		Not estimable
Larmon 1999	0	65	0	57		Not estimable
Lyell 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: Chi² = 1.14, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

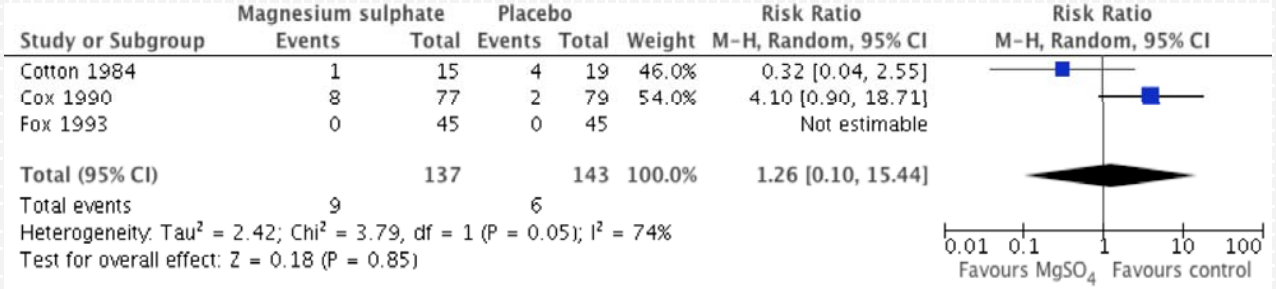
MAGNESIUM SULPHATE VERSUS PLACEBO:

PERINATAL OUTCOME

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



- Similar risk for perinatal mortality

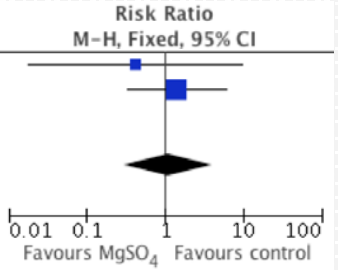


MAGNESIUM SULPHATE VERSUS PLACEBO

- Similar risk for Necrotising Enterocolitis (NEC)

	Magnesium sulphate		Placebo			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				

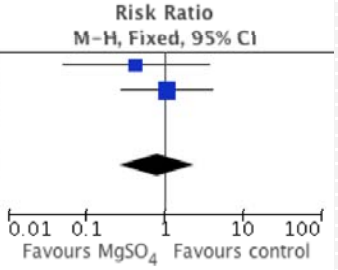
Heterogeneity: $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.14 (P = 0.89)



- Similar risk for Intraventricular Haemorrhage (IVH)

	Magnesium sulphate		Placebo			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	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				

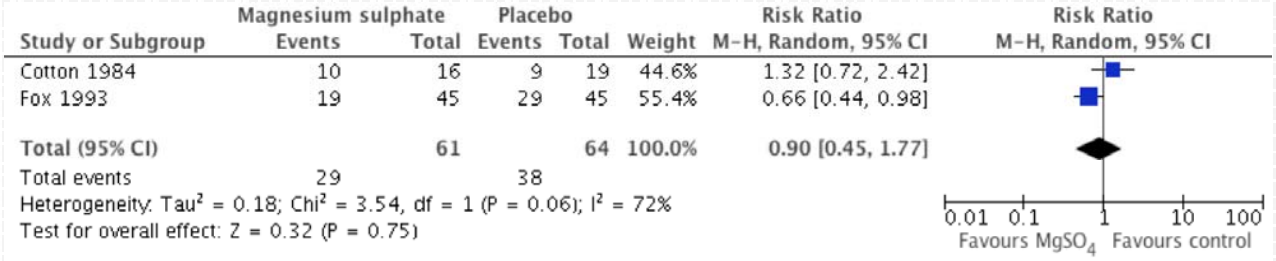
Heterogeneity: $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 0.39 (P = 0.69)



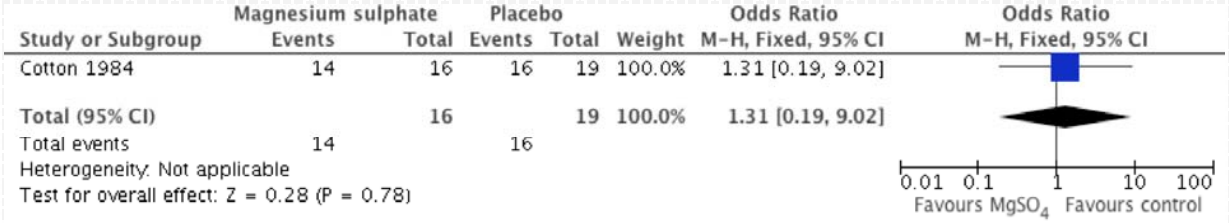
MAGNESIUM SULPHATE VERSUS PLACEBO:

TOCOLYTIC EFFECT

- Similar risk of birth <48 hours



- Similar risk of preterm birth (<37 weeks)

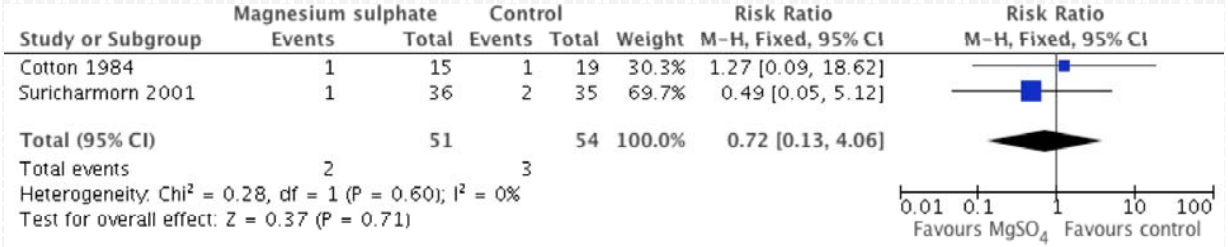


MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

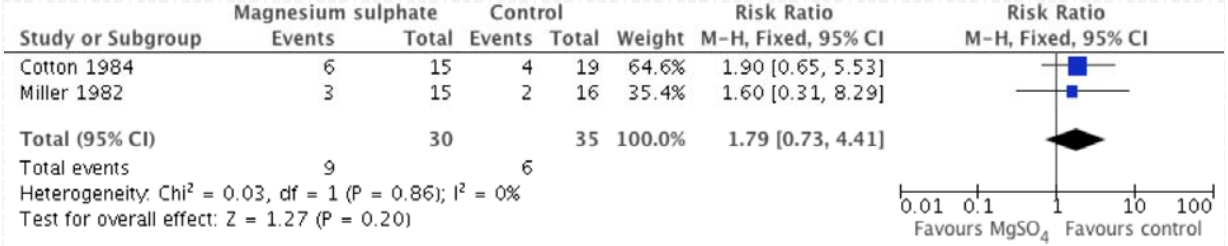
PERINATAL OUTCOME

- *4 trials (324 women)*

- Similar risk of perinatal mortality

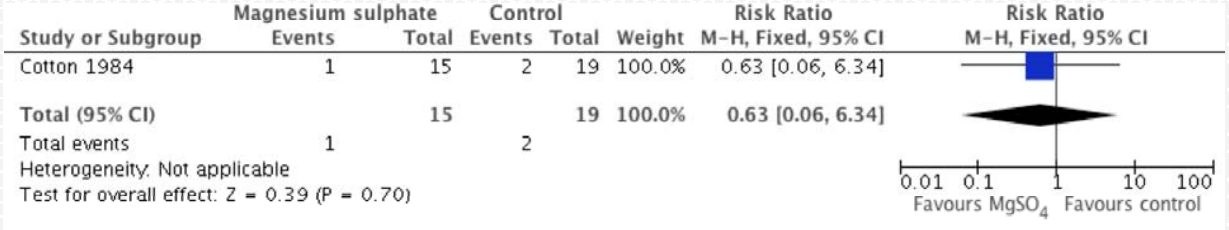


- Similar risk of Respiratory Distress Syndrome

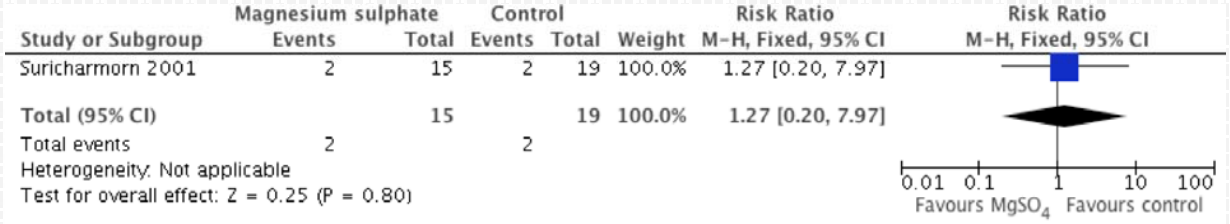


MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

- Similar risk of Necrotising enterocolitis



- Similar risk of Patent ductus arteriosus



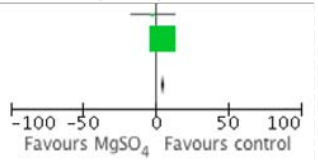
MAGNESIUM SULPHATE VERSUS BETAMIMETICS:

TOCOLYTIC OUTCOME

- ***Increased mean gestational age at delivery***, *in the betamimetics group*

Study or Subgroup	Magnesium Sulphate Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]**

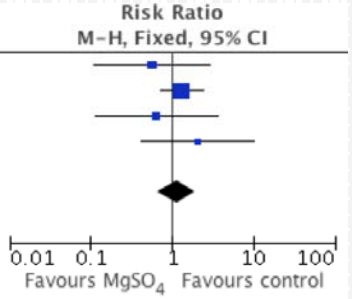
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 7.43 (P < 0.00001)



- *Similar risk of delivery <48 hours*

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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: Chi² = 1.85, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)



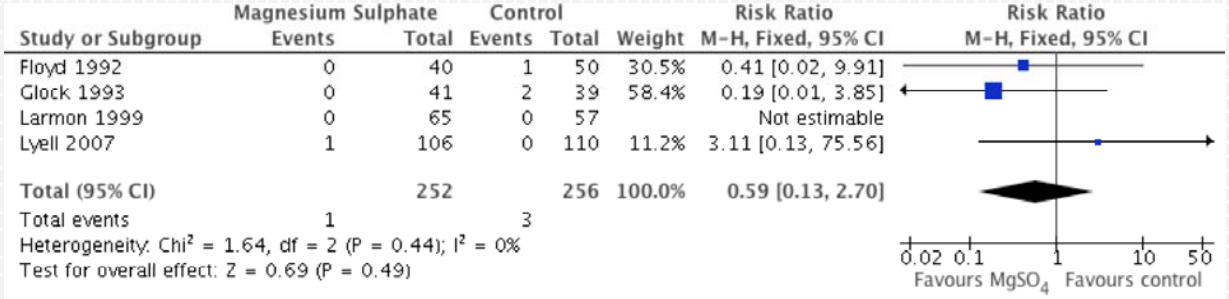
MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS:

PERINATAL OUTCOME

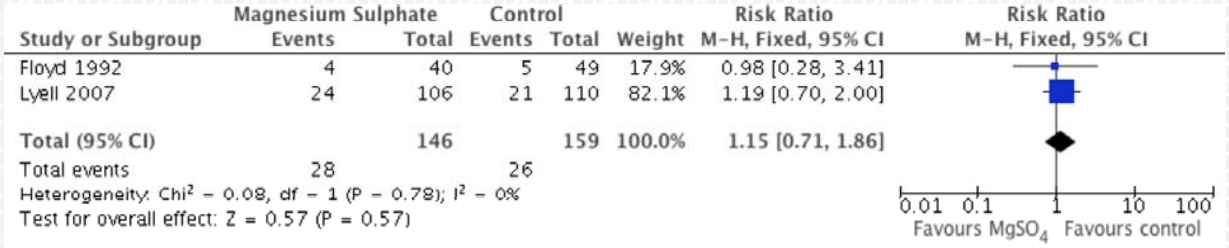
6 trials (687 women)

- ***No benefit for magnesium sulphate over Ca^{+2} channel antagonists in improving perinatal outcome***

- Perinatal mortality



- Respiratory Distress Syndrome

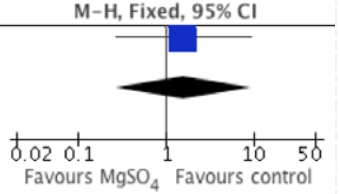


MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS

- Intraventricular haemorrhage

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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			

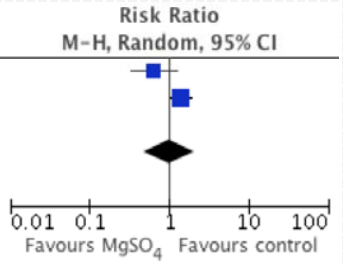
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)



- Admission to the NICU

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.23$; $Chi^2 = 4.09$, df = 1 (P = 0.04); $I^2 = 76\%$
Test for overall effect: Z = 0.02 (P = 0.98)



MAGNESIUM SULPHATE VERSUS CALCIUM CHANNEL ANTAGONISTS:

TOCOLYTIC OUTCOME

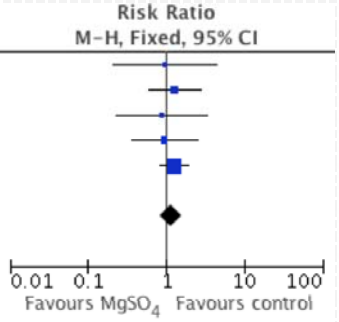
- ***Similar tocolytic efficacy,***

-birth <48 hours

Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Glock 1993	3	41	3	39	6.6%	0.95 [0.20, 4.43]
Haighighi 1999	12	40	8	34	18.5%	1.27 [0.59, 2.75]
Larmon 1999	4	65	4	57	9.1%	0.88 [0.23, 3.35]
Lyell 2007	7	92	8	100	16.4%	0.95 [0.36, 2.52]
Taherian 2007	31	63	22	57	49.4%	1.27 [0.84, 1.93]
Total (95% CI)		**301**		**287**	**100.0%**	**1.16 [0.84, 1.62]**
Total events	57		45			

Heterogeneity: $Chi^2 = 0.64$, $df = 4$ ($P = 0.96$); $I^2 = 0\%$

Test for overall effect: $Z = 0.91$ ($P = 0.36$)

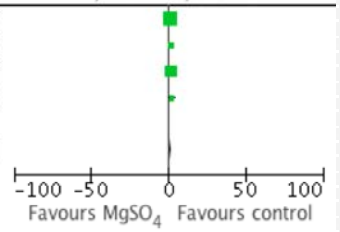


- ***Shorter time to uterine quiescence in the Ca^{+2} channel antagonists group***

Study or Subgroup	Magnesium Sulphate Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
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: $Tau^2 = 0.08$; $Chi^2 = 3.70$, $df = 3$ ($P = 0.30$); $I^2 = 19\%$

Test for overall effect: $Z = 5.08$ ($P < 0.00001$)

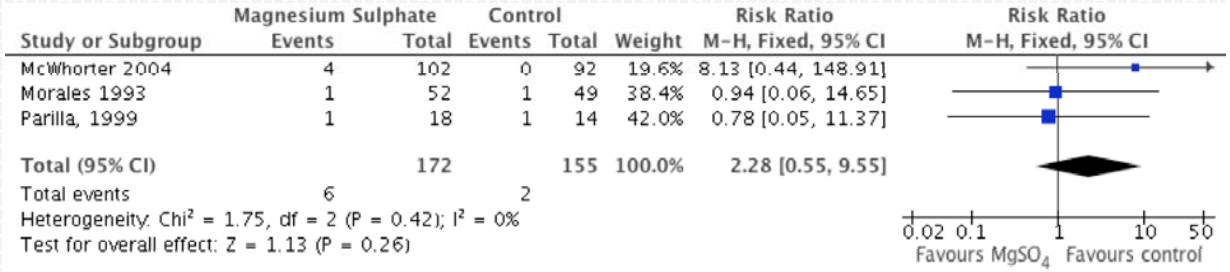


MAGNESIUM SULPHATE VERSUS COX INHIBITORS :

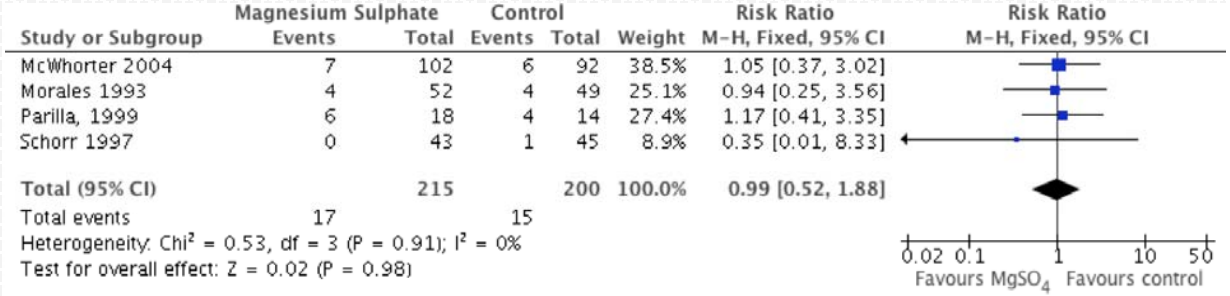
PERINATAL OUTCOME

5 trials (524 women) ***-No statistically significant difference***

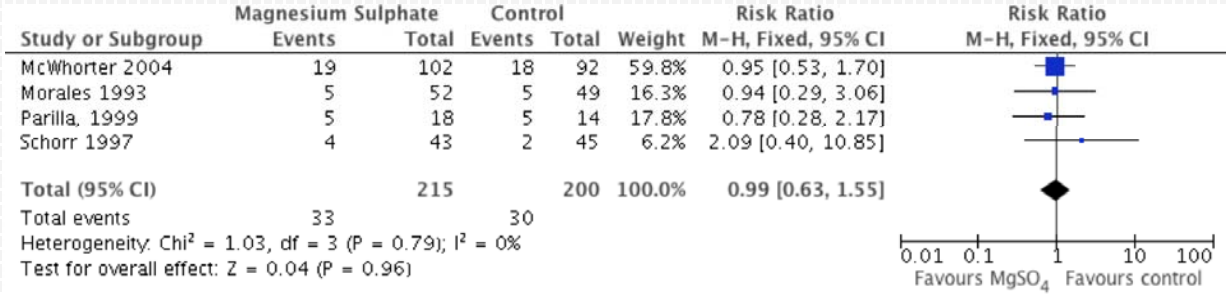
- Perinatal mortality



- Intraventricular haemorrhage



- Respiratory distress syndrome

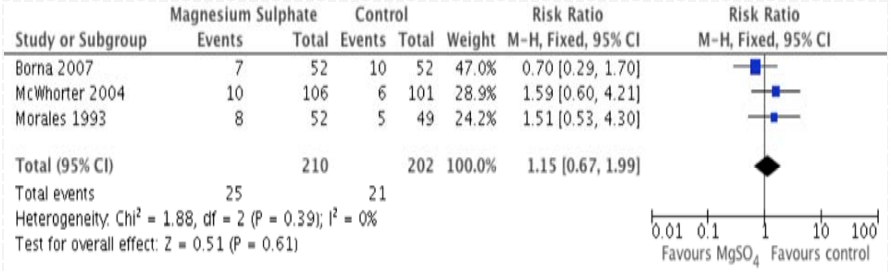


MAGNESIUM SULPHATE VERSUS COX INHIBITORS :

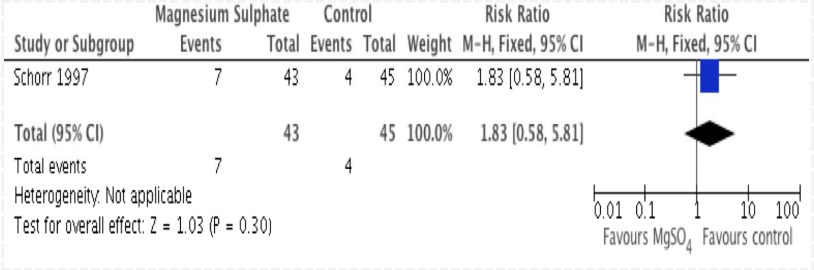
TOCOLYTIC OUTCOME

- ***Similar tocolytic efficacy***

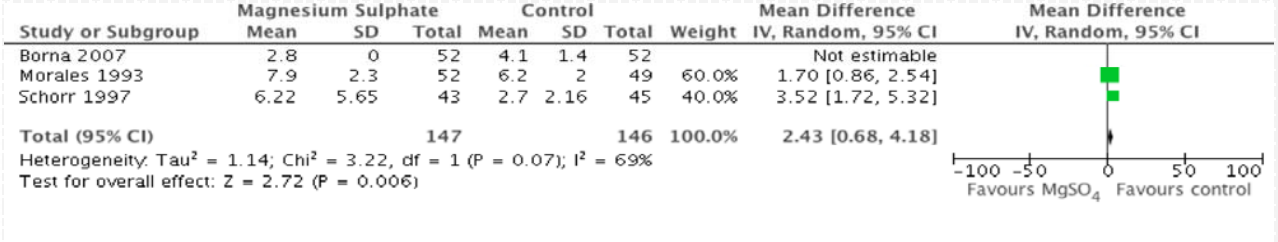
Birth<48 hours



Preterm birth (<37 weeks)



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



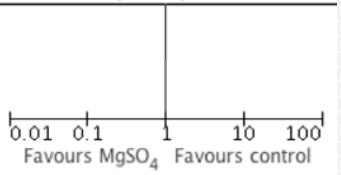
MAGNESIUM SULPHATE VERSUS HCG :

PERINATAL OUTCOME

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

Study or Subgroup	Magnesium Sulphate Events	Total	HCG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lorzadeh 2007	0	55	0	54		Not estimable
Total (95% CI)		55		54		**Not estimable**
Total events	0		0			

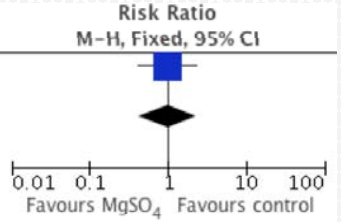
Heterogeneity: Not applicable
Test for overall effect: Not applicable



- Respiratory distress syndrome

Study or Subgroup	Magnesium Sulphate Events	Total	HCG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 0.04 (P = 0.97)



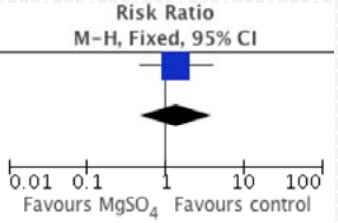
MAGNESIUM SULPHATE VERSUS HCG :

TOCOLYTIC OUTCOME

- ***Similar tocolytic efficacy***

- Birth <48 hours

Study or Subgroup	Magnesium Sulphate Events	Total	HCG Events	Total	Weight	Risk Ratio 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 applicable						
Test for overall effect: Z = 0.58 (P = 0.57)						

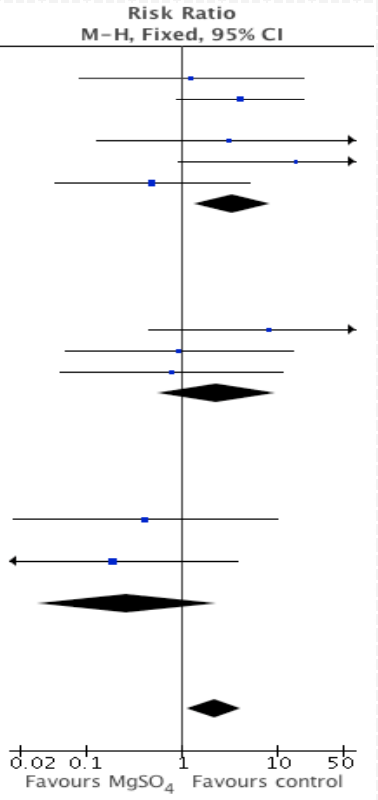


DOSE EXPOSURE & PERINATAL OUTCOME

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

Number of total deaths (fetal,neonatal,infant)

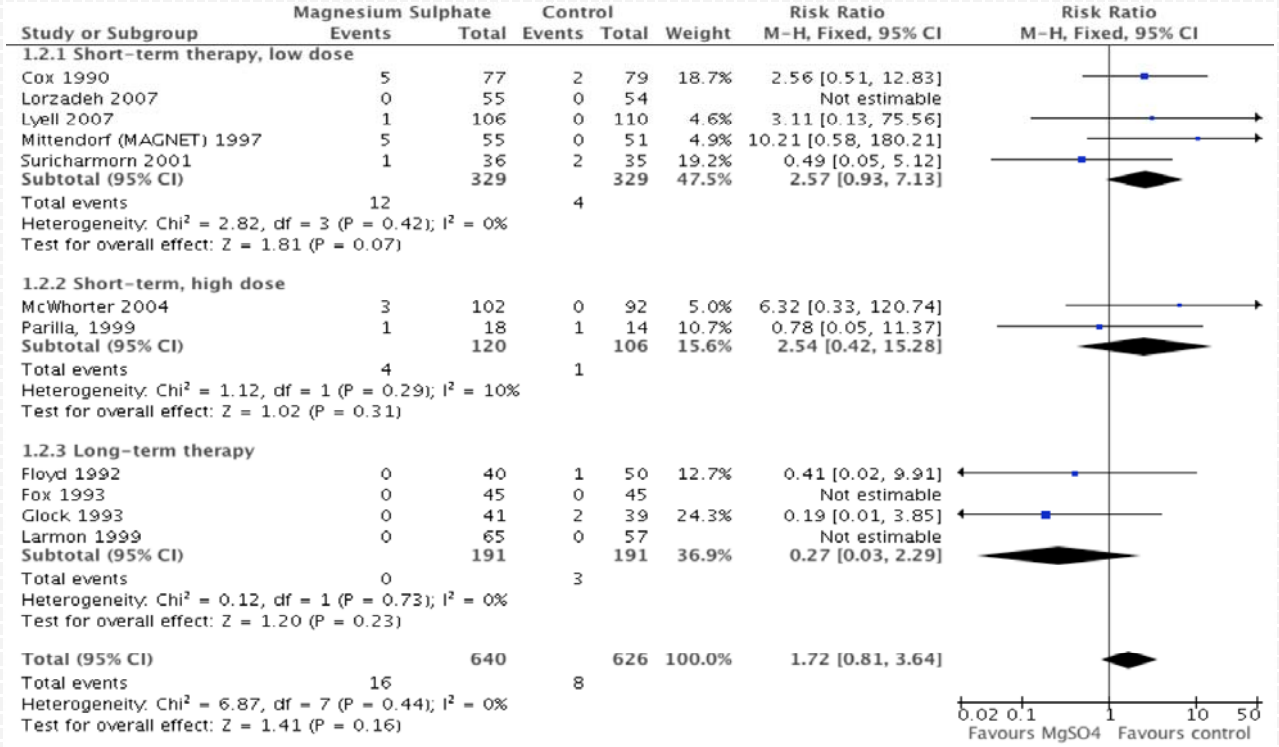
Study or Subgroup	Magnesium Sulphate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Short-term therapy (up to 48 hours), low dose						
Cotton 1984	1	15	1	19	7.1%	1.27 [0.09, 18.62]
Cox 1990	8	77	2	79	15.8%	4.10 [0.90, 18.71]
Lorzadeh 2007	0	55	0	54		Not estimable
Lyell 2007	1	106	0	110	3.9%	3.11 [0.13, 75.56]
Mittendorf (MAGNET) 1997	8	55	0	51	4.2%	15.79 [0.93, 266.72]
Suricharmorn 2001	1	36	2	35	16.3%	0.49 [0.05, 5.12]
Subtotal (95% CI)		**344**		**348**	**47.3%**	**3.38 [1.36, 8.37]**
Total events	19		5			
Heterogeneity: Chi² = 4.32, df = 4 (P = 0.36); I² = 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**		**155**	**21.5%**	**2.28 [0.55, 9.55]**
Total events	6		2			
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.1.3 Long-term therapy (until 37th week of gestation)						
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
Subtotal (95% CI)		**191**		**191**	**31.3%**	**0.27 [0.03, 2.29]**
Total events	0		3			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 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: Chi² = 9.60, df = 9 (P = 0.38); I² = 6%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Test for subgroup differences: Chi² = 4.55, df = 2 (P = 0.10), I² = 56.0%						



DOSE EXPOSURE AND PERINATAL OUTCOME

Total deaths - excluding deaths not related to the tocolytic agent

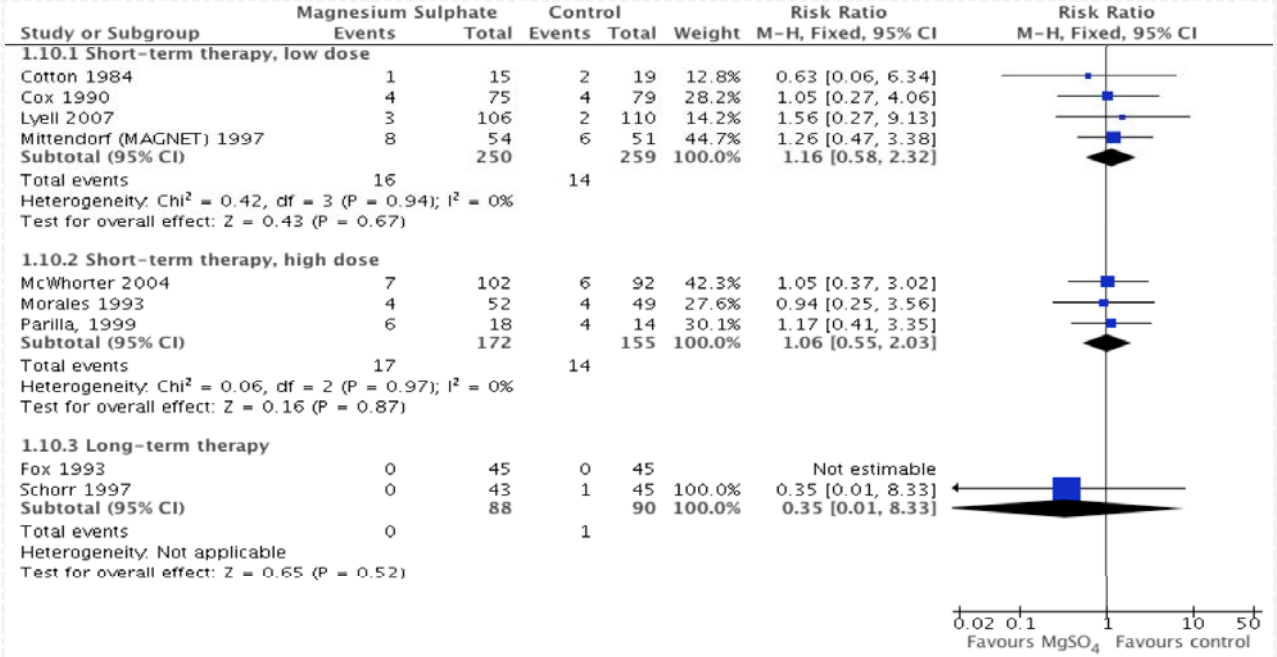
(e.g congenital anomalies, severe twin-twin transfusion)



DOSE EXPOSURE & PERINATAL OUTCOME

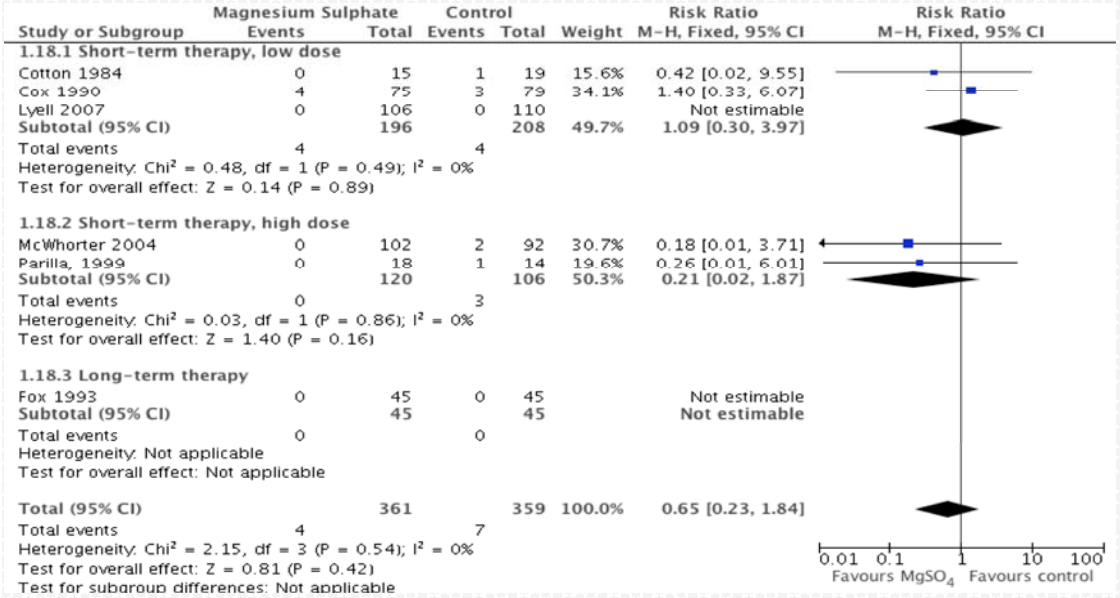
- *Pattern towards better oucomes in the short-term, high dose or the long-term treatment subgroups compared to the short-term low dose subgroup.*

1. Intraventricular Haemorrhage

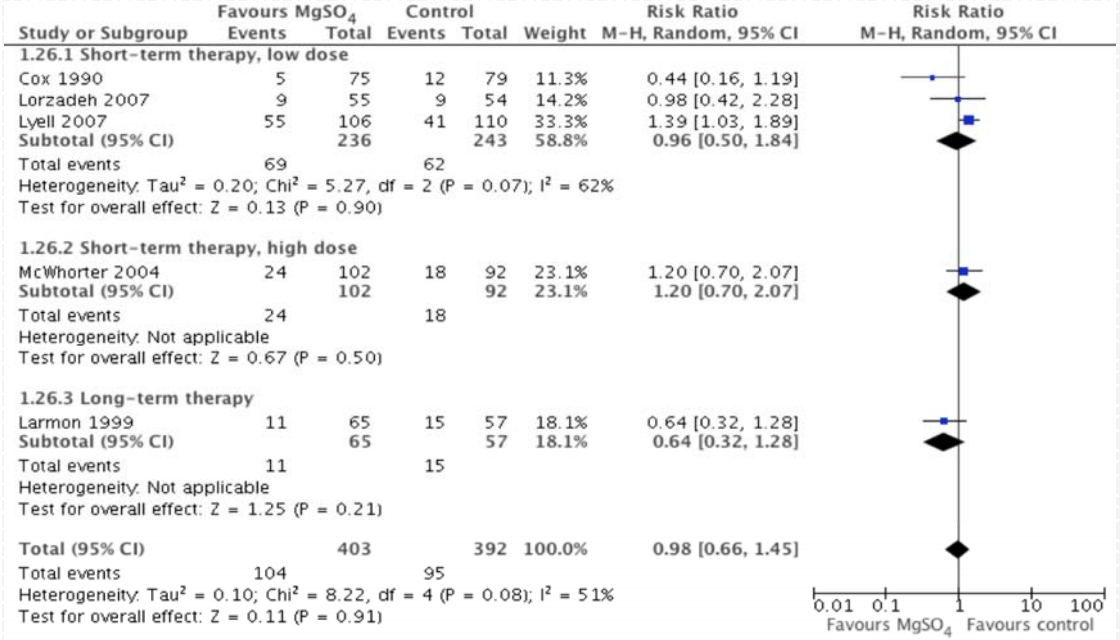


DOSE EXPOSURE & PERINATAL OUTCOME

2. Necrotising enterocolitis



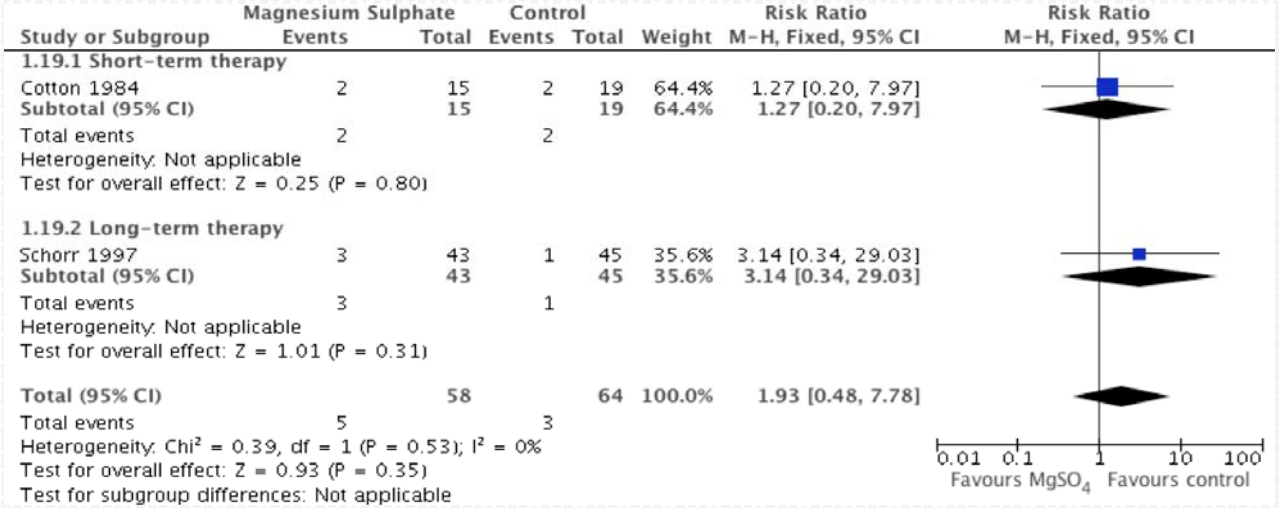
3. Admission to the NICU



DOSE EXPOSURE & PERINATAL OUTCOME

But…the opposite pattern was observed with regard to
patent ductus arteriosus (PDA); *greater risk in the long-term treatment subgroup*

PDA



CONCLUSION

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!

CONCLUSION

Further high quality RCTs comparing magnesium sulphate to placebo would be essential in order to establish:

- whether $MgSO_4$ 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