



**DISCLAIMER:** Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

**Date:** 14 February 2018

**Sources:** Medline, Embase, DynaMed.

## Magnesium Sulphate Infusion and Preterm Deliveries (23-24 Weeks)

[See full search strategy](#)

### Evidence Summary:

According to the results of a Cochrane review, ([Crowther, C.A. et al, 2014](#)) magnesium sulphate is ineffective at delaying birth or preventing preterm birth and has no apparent advantages for a range of neonatal and maternal outcomes as a tocolytic agent.

Evidence for the administration of peripartum magnesium infusion at the threshold of viability to prevent cerebral palsy is currently lacking. However, although there is no trial data specific to the use of magnesium sulphate in gestations <24 weeks, it has been shown to improve neurologic outcomes without increasing mortality when administered before 30 weeks gestation ([Costantine, MM, 2009](#)). The American College of Obstetricians and Gynecologist consensus guidance ([ACOG, 2017](#)) recommend considering the prophylactic use in periviable deliveries from 23 0/7 weeks if a viable infant is anticipated (please refer to the table below). This recommendation is also endorsed in the RCOG (Feb 2014) Scientific Impact Paper No.41 [Perinatal Management of Pregnant Women at the Threshold of Infant viability](#).

<b>Table 3. General Guidance Regarding Obstetric Interventions for Threatened and Imminent Periviable Birth by Best Estimate of Gestational Age<sup>a</sup></b>					
	<b>20 0/7 weeks to 21 6/7 weeks</b>	<b>22 0/7 weeks to 22 6/7 weeks</b>	<b>23 0/7 weeks to 23 6/7 weeks</b>	<b>24 0/7 weeks to 24 6/7 weeks</b>	<b>25 0/7 weeks to 25 6/7 weeks</b>
Neonatal assessment for resuscitation <sup>*</sup>	Not recommended 1A	Consider 2B	Consider 2B	Recommended 1B	Recommended 1B
Antenatal corticosteroids	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Tocolysis for preterm labor to allow for antenatal corticosteroid administration	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Magnesium sulfate for neuroprotection	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Antibiotics to prolong latency during expectant management of preterm PROM if delivery is not considered imminent	Consider 2C	Consider 2C	Consider 2B	Recommended 1B	Recommended 1B
Intrapartum antibiotics for group B streptococci prophylaxis <sup>†</sup>	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Cesarean delivery for fetal indication <sup>‡</sup>	Not recommended 1A	Not recommended 1A	Consider 2B	Consider 1B	Recommended 1B

Abbreviation: PROM, premature rupture of membranes.

<sup>a</sup>Survival of infants born in the periviable period is dependent on resuscitation and support. Between 22 weeks and 25 weeks of gestation, there may be factors in addition to gestational age that will affect the potential for survival and the determination of viability. Importantly, some families, concordant with their values and preferences, may choose to forgo such resuscitation and support. Many of the other decisions on this table will be linked to decisions regarding resuscitation and support and should be considered in that context.

<sup>†</sup>Group B streptococci carrier, or carrier status unknown

<sup>‡</sup>For example, persistently abnormal fetal heart rate patterns or biophysical testing, malpresentation

**1. Antenatal magnesium sulfate is beneficial or harmful in very preterm and extremely preterm neonates: a new insight.**

**Author(s):** Garg, Bhawan Deep

**Source:** The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Jan 2018 ; p. 1-7

**Publication Date:** Jan 2018

**Publication Type(s):** Journal Article

**PubMedID:** 29301419

**Abstract:**AIM STo evaluate whether antenatal MgSO<sub>4</sub> is beneficial or harmful in very preterm and extremely preterm neonates.MATERIALS AND METHODSWe retrieved published literature through searches of PubMed or Medline, CINAHL, and the Cochrane Library. Results were restricted to systematic reviews, meta-analysis, randomized controlled trials (RCTs), and relevant observational studies.RESULTSEvidence revealed that antenatal MgSO<sub>4</sub> has neuroprotective role in preterm neonates and it decreased the risk of cerebral palsy and gross motor dysfunction. Evidences regarding association of antenatal MgSO<sub>4</sub> with feed intolerance, NEC and SIP were from cohort studies and controversial.CONCLUSIONS We should continue use antenatal MgSO<sub>4</sub> to all eligible patients according to protocol till the more robust evidence will suggest association with gastrointestinal complications. In the meantime, we should have a high index of suspicion of gastrointestinal complications in extremely preterms particularly <26 weeks of gestation.

**Database:** Medline

**2. Is maternal magnesium sulfate administration prior to delivery an independent predictor of survival in neonates who weigh fewer than five hundred grams?**

**Author(s):** Aziz M.M.; Graham B.; Bursac Z.; Goedecke P.; Dhanireddy R.; Mari G.

**Source:** American Journal of Obstetrics and Gynecology; Jan 2018; vol. 218 (no. 1)

**Publication Date:** Jan 2018

**Publication Type(s):** Conference Abstract

**Abstract:**OBJECTIVE: To determine if magnesium sulfate is an independent predictor of survival in neonates whose birth weight is fewer than five hundred grams. STUDY DESIGN: This was a retrospective cohort study of live-born neonates from 2012 to 2015 at an academic tertiary referral center. The primary outcome was survival from 12 hours of life until discharge. Neonates who did not survive the first 12 hours were excluded so that the results would not be confounded by limited intervention. Severe intraventricular hemorrhage (IVH, grade III/IV) was a secondary outcome. Multivariable logistic regression analyses were performed, controlling for potential confounders. RESULTS: Thirty-four deliveries were included; thirty were exposed to magnesium sulfate. Birth weights ranged from 310g to 495g (median: 450g); gestational ages ranged from 22 to 29 weeks (median: 24 weeks). The rate of survival from 12 hours until discharge was 76% (26/34). Maternal magnesium sulfate administration was associated with improved survival (OR= 22.3; 95% CI 1.9-607; p=0.023) while controlling for gender; corticosteroids and surfactant administration were removed due to collinearity with the exposure. Magnesium sulfate did not appear to protect from severe IVH (OR= 0.20; 95% CI 0.01-2.4; p=0.21). CONCLUSION: Maternal magnesium appears to be an independent predictor of survival from 12 hours after birth until discharge among neonates who are born weighing less than 500g. This is the first study that has found a survival benefit in these periviable birth weights.

**Database:** EMBASE

### **3. Optimization of Maternal Magnesium Sulfate Administration for Fetal Neuroprotection: Application of a Prospectively Constructed Pharmacokinetic Model to the BEAM Cohort**

**Author(s):** Brookfield K.F.; Elkomy M.; Su F.; Drover D.R.; Carvalho B.

**Source:** Journal of Clinical Pharmacology; Nov 2017; vol. 57 (no. 11); p. 1419-1424

**Publication Date:** Nov 2017

**Publication Type(s):** Article

Available at [Journal of Clinical Pharmacology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:**The aim of the study was to identify the optimal therapeutic maternal magnesium drug exposure and maternal serum concentration to prevent cerebral palsy in the extremely preterm fetus. We applied a previously constructed pharmacokinetic model adjusted for indication to a large cohort of pregnant women receiving magnesium sulfate to prevent cerebral palsy in their preterm offspring at 20 different US academic centers between December 1997 and May 2004. We simulated the population-based individual maternal serum magnesium concentration at the time of delivery and the total magnesium dose for each woman who received magnesium sulfate to determine the relationship between maternal serum magnesium level at the time of delivery and the development of cerebral palsy. Among 1905 women who met inclusion criteria, the incidence of cerebral palsy in the cohort was 3.6% for women who had received magnesium sulfate and 6.4% for controls. The simulated maternal serum concentration at delivery associated with the lowest probability of delivering an infant with cerebral palsy was 4.1 mg/dL (95%CI 3.7 to 4.4). Our population-based estimates of magnesium disposition suggest that to optimize fetal neuroprotection and prevent cerebral palsy, magnesium sulfate administration should target a maternal serum magnesium level between 3.7 and 4.4 mg/dL at delivery. Copyright © 2017, The American College of Clinical Pharmacology

**Database:** EMBASE

#### **4. Obstetric Care consensus No. 6: Periviable Birth.**

**Author(s):** American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine

**Source:** Obstetrics and gynecology; Oct 2017; vol. 130 (no. 4); p. e187

**Publication Date:** Oct 2017

**Publication Type(s):** Journal Article Consensus Development Conference

**PubMedID:** 28937572

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:** Approximately 0.5% of all births occur before the third trimester of pregnancy, and these very early deliveries result in the majority of neonatal deaths and more than 40% of infant deaths. A recent executive summary of proceedings from a joint workshop defined periviable birth as delivery occurring from 20 0/7 weeks to 25 6/7 weeks of gestation. When delivery is anticipated near the limit of viability, families and health care teams are faced with complex and ethically challenging decisions. Multiple factors have been found to be associated with short-term and long-term outcomes of periviable births in addition to gestational age at birth. These include, but are not limited to, nonmodifiable factors (eg, fetal sex, weight, plurality), potentially modifiable antepartum and intrapartum factors (eg, location of delivery, intent to intervene by cesarean delivery or induction for delivery, administration of antenatal corticosteroids and magnesium sulfate), and postnatal management (eg, starting or withholding and continuing or withdrawing intensive care after birth). Antepartum and intrapartum management options vary depending upon the specific circumstances but may include short-term tocolytic therapy for preterm labor to allow time for administration of antenatal steroids, antibiotics to prolong latency after preterm premature rupture of membranes or for intrapartum group B streptococci prophylaxis, and delivery, including cesarean delivery, for concern regarding fetal well-being or fetal malpresentation. Whenever possible, periviable births for which maternal or neonatal intervention is planned should occur in centers that offer expertise in maternal and neonatal care and the needed infrastructure, including intensive care units, to support such services. This document describes newborn outcomes after periviable birth, provides current evidence and recommendations regarding interventions in this setting, and provides an outline for family counseling with the goal of incorporating informed patient preferences. Its intent is to provide support and guidance regarding decisions, including declining and accepting interventions and therapies, based on individual circumstances and patient values.

**Database:** Medline

## **5. Antenatal Exposure to Magnesium Sulfate and Spontaneous Intestinal Perforation and Necrotizing Enterocolitis in Extremely Preterm Neonates**

**Author(s):** Shalabi M.; Mohamed A.; Shah P.S.; Lemyre B.; Aziz K.; Faucher D.

**Source:** American Journal of Perinatology; Oct 2017; vol. 34 (no. 12); p. 1227-1233

**Publication Date:** Oct 2017

**Publication Type(s):** Article

**Abstract:**Background There have been recent concerns regarding the higher rates of spontaneous intestinal perforation (SIP) in preterm infants that have been exposed to intrapartum magnesium sulfate (MgSO<sub>4</sub>). Objective To assess the association between intrapartum MgSO<sub>4</sub> exposure and necrotizing enterocolitis (NEC) and/or SIP in extremely preterm neonates. Design A retrospective cohort study was conducted using data from the Canadian Neonatal Network database. Infants born at < 28 weeks' gestation admitted to neonatal units in Canada between 2011 and 2014 were divided into two groups: those exposed antenatally to MgSO<sub>4</sub> and those unexposed. Stratified analyses for infants born between 22 and 25 weeks' gestation and those born between 26 and 27 weeks' gestation were conducted. The primary outcome was intestinal injury, identified as either NEC or SIP. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression. Results We compared 2,300 unexposed infants with 2,055 exposed infants. There was no difference in the odds of NEC (9.88% exposed vs. 9.59% unexposed; aOR: 0.92; 95% CI: 0.75-1.14) or SIP (3.4% exposed vs. 3.39% unexposed; aOR: 1.05; 95% CI: 0.75-1.48) between the two groups. Conclusion Antenatal exposure to MgSO<sub>4</sub> was not associated with NEC or SIP in extremely preterm infants. Copyright © 2017 by Thieme Medical Publishers, Inc.

**Database:** EMBASE

## **6. No. 347-Obstetric Management at Borderline Viability.**

**Author(s):** Ladhani, Noor Niyar N; Chari, Radha S; Dunn, Michael S; Jones, Griffith; Shah, Prakesh; Barrett, Jon F R

**Source:** Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC; Sep 2017; vol. 39 (no. 9); p. 781-791

**Publication Date:** Sep 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28859764

**Abstract:**OBJECTIVEThe primary objective of this guideline was to develop consensus statements to guide clinical practice and recommendations for obstetric management of a pregnancy at borderline viability, currently defined as prior to 25+6 weeks.INTENDED USERSClinicians involved in the obstetric management of women whose fetus is at the borderline of viability.TARGET POPULATIONWomen presenting for possible birth at borderline viability.EVIDENCEThis document presents a summary of the literature and a general consensus on the management of pregnancies at borderline viability, including maternal transfer and consultation, administration of antenatal corticosteroids and magnesium sulfate, fetal heart rate monitoring, and considerations in mode of delivery. Medline, EMBASE, and Cochrane databases were searched using the following keywords: extreme prematurity, borderline viability, preterm, pregnancy, antenatal corticosteroids, mode of delivery. The results were then studied, and relevant articles were reviewed. The references of the reviewed studies were also searched, as were documents citing pertinent studies. The evidence was then presented at a consensus meeting, and statements were developed.VALIDATION METHODSThe content and recommendations were developed by the consensus group from the fields of Maternal-Fetal Medicine, Neonatology, Perinatal Nursing, Patient Advocacy, and Ethics. The quality of evidence was rated using criteria described in the Grading of Recommendations Assessment,

Development and Evaluation methodology framework (reference 1). The Board of the Society of Obstetricians and Gynaecologists of Canada approved the final draft for publication. **METHODS** The quality of evidence was rated using the criteria described in the Grading of Recommendations, Assessment, Development, and Evaluation methodology framework. The interpretation of strong and weak recommendations is described later. The Summary of Findings is available upon request. **BENEFITS, HARMS, AND COSTS** A multidisciplinary approach should be used in counselling women and families at borderline viability. The impact of obstetric interventions in the improvement of neonatal outcomes is suggested in the literature, and if active resuscitation is intended, then active obstetric interventions should be considered. **GUIDELINE UPDATE** Evidence will be reviewed 5 years after publication to decide whether all or part of the guideline should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations. **SPONSORS** This guideline was developed with resources funded by the Society of Obstetricians and Gynaecologists of Canada and the Women and Babies Program at Sunnybrook Health Sciences Centre. **RECOMMENDATIONS**

**Database:** Medline

## **7. Medical and Surgical Interventions Available Before a Periviable Birth.**

**Author(s):** Chien, Edward K; Gibson, Kelly S

**Source:** Clinics in perinatology; Jun 2017; vol. 44 (no. 2); p. 347-360

**Publication Date:** Jun 2017

**Publication Type(s):** Journal Article Review

**PubMedID:** 28477665

**Abstract:** Periviable birth contributes disproportionately to perinatal morbidity and mortality. By analyzing the most relevant outcomes after a preterm birth some information can be provided on the potential benefit of interventions. This article discusses surgical and medical interventions that may offer neonatal benefit including cerclage, amniocentesis, progesterone, antenatal corticosteroids, magnesium sulfate for neuroprotection, and tocolysis. Cervical cerclage has the greatest promise at reducing morbidity and mortality related to periviable birth even though it may not reduce the overall preterm birth rate. The use of antenatal corticosteroids, magnesium sulfate, progesterone, and tocolytics may also improve outcome. Studies specifically evaluating these interventions are needed.

**Database:** Medline

## **8. Neuroprotective benefit of antenatal magnesium sulfate for preterm infants. is it the magnesium or the sulfate?**

**Author(s):** Hurrion E.M.; Kumar S.; Flenady V.J.; Dawson P.A.; Colditz P.B.; Boyd R.N.; Badawi N.; Koorts P.J.

**Source:** Archives of Disease in Childhood; May 2017; vol. 102

**Publication Date:** May 2017

**Publication Type(s):** Conference Abstract

Available at [Archives of Disease in Childhood](#) - from BMJ Journals - NHS

**Abstract:** Aims To determine whether antenatal magnesium sulfate (MgSO<sub>4</sub>) administration correlates with circulating sulfate level in very/extremely preterm infants, and specifically whether nonexposed infants become sulphate deficient. Methods Ion chromatography was used to measure plasma sulfate levels in preterm infants (<32 wk gestation) whose mothers did or did not receive antenatal MgSO<sub>4</sub>. Results Within 24 hours after birth, supra-physiological plasma sulfate levels were measured in infants whose mothers received MgSO<sub>4</sub> (mean+/-SD mmol/L 774+/-397, n=26), whereas sulfate levels in the group without MgSO<sub>4</sub> (257+/-162, n=10) were similar to that found in term cord blood. At 3 days and at 1 and 4 weeks of age, babies without antenatal MgSO<sub>4</sub> had reduced plasma sulfate level (3d: 190+/-96, n=49; 1 wk 118+/-61, n=67; 4 wk 125+/-79, n=6) whereas the group with antenatal MgSO<sub>4</sub> therapy maintained normal levels (3d: 287+/-160, n=68; 1 wk 250+/-125, n=119; 4 wk 228+/-89, n=56). Conclusions These data positively correlate antenatal MgSO<sub>4</sub> administration with neonatal plasma sulfate levels, and suggest that unexposed preterm infants (who lack the capacity to generate sulphate) rapidly become sulphate depleted. Animal models and human studies demonstrate that sulphate is important for modulating brain development. It may be, therefore, that the neuroprotective benefit of antenatal MgSO<sub>4</sub> for preterm infants is attributable to the sulphate rather than the magnesium content. If sulfate neuroprotection is proven, then neonatal sulfate supplementation (in place of antenatal MgSO<sub>4</sub>) may prove a simple and effective, low-cost, low-risk intervention universally available to all preterm infants to improve their chances of a normal neurodevelopmental outcome.

**Database:** EMBASE

## **9. Perinatal neuroprotection update.**

**Author(s):** Jelin, Angie C; Salmeen, Kirsten; Gano, Dawn; Burd, Irina; Thiet, Mari-Paule

**Source:** F1000Research; 2016; vol. 5

**Publication Date:** 2016

**Publication Type(s):** Journal Article Review

**PubMedID:** 27606053

Available at [F1000Research](#) - from Europe PubMed Central - Open Access

Available at [F1000Research](#) - from nih.gov

**Abstract:**Antepartum, intrapartum, and neonatal events can result in a spectrum of long-term neurological sequelae, including cerebral palsy, cognitive delay, schizophrenia, and autism spectrum disorders [1]. Advances in obstetrical and neonatal care have led to survival at earlier gestational ages and consequently increasing numbers of periviable infants who are at significant risk for long-term neurological deficits. Therefore, efforts to decrease and prevent cerebral insults attempt not only to decrease preterm delivery but also to improve neurological outcomes in infants delivered preterm. We recently published a comprehensive review addressing the impacts of magnesium sulfate, therapeutic hypothermia, delayed cord clamping, infections, and prevention of preterm delivery on the modification of neurological risk [2]. In this review, we will briefly provide updates to the aforementioned topics as well as an expansion on avoidance of toxin and infections, specifically the Zika virus.

**Database:** Medline

## **10. Perinatal Neuroprotection for Extremely Preterm Infants.**

**Author(s):** Davis, Alexis S; Berger, Victoria K; Chock, Valerie Y

**Source:** American journal of perinatology; Feb 2016; vol. 33 (no. 3); p. 290-296

**Publication Date:** Feb 2016

**Publication Type(s):** Journal Article Review

**PubMedID:** 26799965

**Abstract:**The preterm brain is vulnerable to injury through multiple mechanisms, from direct cerebral injury through ischemia and hemorrhage, indirect injury through inflammatory processes, and aberrations in growth and development. While prevention of preterm birth is the best neuroprotective strategy, this is not always possible. This article will review various obstetric and neonatal practices that have been shown to confer a neuroprotective effect on the developing brain.

**Database:** Medline

## **11. Committee Opinion No 652: Magnesium Sulfate Use in Obstetrics.**

**Author(s):**

**Source:** Obstetrics and gynecology; Jan 2016; vol. 127 (no. 1); p. e52

**Publication Date:** Jan 2016

**Publication Type(s):** Journal Article

**PubMedID:** 26695587

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**The U.S. Food and Drug Administration advises against the use of magnesium sulfate injections for more than 5-7 days to stop preterm labor in pregnant women. Based on this, the drug classification was changed from Category A to Category D, and the labeling was changed to include this new warning information. However, the U.S. Food and Drug Administration's change in classification addresses an unindicated and nonstandard use of magnesium sulfate in obstetric care. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for appropriate conditions and for appropriate durations of treatment, which includes the prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery, and short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days.

**Database:** Medline

## **12. Tocolysis for inhibiting preterm birth in extremely preterm birth, multiple gestations and in growth-restricted fetuses: a systematic review and meta-analysis**

**Author(s):** Miyazaki C.; Moreno R.G.; Ota E.; Mori R.; Swa T.; Oladapo O.T.

**Source:** Reproductive Health; Jan 2016; vol. 13 (no. 1)

**Publication Date:** Jan 2016

**Publication Type(s):** Review

**PubMedID:** 26762152

Available at [Reproductive Health](#) - from BioMed Central

Available at [Reproductive Health](#) - from Europe PubMed Central - Open Access

nih.gov

**Abstract:** This systematic review was to identify available evidence on the effectiveness of tocolysis in inhibiting preterm delivery for women with threatened extremely preterm birth, multiple gestations, and growth-restricted babies, and their infants' outcomes. A comprehensive search using MEDLINE, Embase, the Cochrane Library, CINAHL, POPLINE and the WHO Global Health Library databases was conducted on 14 February 2014. For selection criteria, randomized controlled trials and non-randomized studies that compared tocolysis treatment to placebo or no treatment were considered. Selection of eligible studies, critical appraisal of the included studies, data collection, meta-analyses, and assessment of evidence quality were performed in accordance with the Cochrane Collaboration's guidance and validated assessment criteria. The search identified seven studies for extremely preterm birth, in which three were randomized controlled trials (RCTs) and four were non-randomized studies (non-RCTs). There were no eligible studies identified for women with multiple pregnancy and growth-restricted fetuses. Meta-analyses indicated no significant difference was found for the relative effectiveness of tocolytics versus placebo for prolonging pregnancy in women with extremely preterm birth (RR 1.04, 95 % CI 0.83 to 1.31) or reducing the rate of perinatal deaths (RR 2.22, 95 % CI 0.26 to 19.24). In summary, there is no evidence to draw conclusions on the effectiveness of tocolytic therapy for women with threatened extremely preterm birth, multiple gestations, and growth-restricted babies. Copyright © 2016 Miyazaki et al.

**Database:** EMBASE

### **13. The use of intravenous magnesium in non-preeclamptic pregnant women: fetal/neonatal neuroprotection**

**Author(s):** Jacquemyn Y.; Zecic A.; Van Laere D.; Roelens K.

**Source:** Archives of Gynecology and Obstetrics; 2015; vol. 291 (no. 5); p. 969-975

**Publication Date:** 2015

**Publication Type(s):** Review

**PubMedID:** 25501980

Available at [Archives of Gynecology and Obstetrics](#) - from SpringerLink

**Abstract:** Purpose: To review the effect of intravenous magnesium in obstetrics on fetal/neonatal neuroprotection. Methods: A systematic review of published studies. Results: Five randomized trials and 4 meta-analyses have shown a significant 32 % reduction of cerebral palsy when administering magnesium sulfate in case of preterm delivery. The pathophysiologic mechanism is not fully unraveled: modulation of the inflammatory process, both in the mother and the fetus, and downregulation of neuronal stimulation seem to be involved. After long-term high-dose intravenous administration of magnesium, maternal and neonatal adverse effects such as maternal and neonatal hypotonia and osteoporosis and specific fetal/neonatal cerebral lesions have been described. In case of administration for less than 48 h at 1 g/h and a loading dose of 4 g, these toxic amounts are not achieved. American, Canadian and Australian guidelines recommend the use of intravenous magnesium in any threatening delivery at less than 32 weeks. The "number needed to treat" to avoid 1 cerebral palsy is between 15 and 35. Conclusions: Intravenous magnesium significantly reduces the risk for cerebral palsy in preterm birth. Open questions remain the optimal dosing schedule, whether or not repeating when delivery has been successfully postponed and a new episode of preterm labor occurs. Some concern has been raised on a too optimistic value for random error which might have led to over-optimistic conclusions in classic meta-analysis. Randomized trials comparing different doses and individual patient data meta-analysis might resolve these issues. Copyright © 2014, Springer-Verlag Berlin Heidelberg.

**Database:** EMBASE

#### **14. Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour.**

**Author(s):** McNamara, Helen C; Crowther, Caroline A; Brown, Julie

**Source:** The Cochrane database of systematic reviews; Dec 2015 (no. 12); p. CD011200

**Publication Date:** Dec 2015

**Publication Type(s):** Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review

**PubMedID:** 26662716

Available at [The Cochrane database of systematic reviews](#) - from Cochrane Collaboration (Wiley)

**Abstract:**BACKGROUND Magnesium sulphate has been used to inhibit preterm labour to prevent preterm birth. There is no consensus as to the safety profile of different treatment regimens with respect to dose, duration, route and timing of administration. OBJECTIVE To assess the efficacy and safety of alternative magnesium sulphate regimens when used as single agent tocolytic therapy during pregnancy. SEARCH METHODS We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2015) and reference lists of retrieved studies. SELECTION CRITERIA Randomised trials comparing different magnesium sulphate treatment regimens when used as single agent tocolytic therapy during pregnancy in women in preterm labour. Quasi-randomised trials were eligible for inclusion but none were identified. Cross-over and cluster trials were not eligible for inclusion. Health outcomes were considered at the level of the mother, the infant/child and the health service. INTERVENTION Intravenous or oral magnesium sulphate given alone for tocolysis. Comparison: alternative dosing regimens of magnesium sulphate given alone for tocolysis. DATA COLLECTION AND ANALYSIS Two review authors independently assessed trial eligibility and quality and extracted data. MAIN RESULTS Three trials including 360 women and their infants were identified as eligible for inclusion in this review. Two trials were rated as low risk of bias for random sequence generation and concealment of allocation. A third trial was assessed as unclear risk of bias for these domains but did not report data for any of the outcomes examined in this review. No trials were rated to be of high quality overall. Intravenous magnesium sulphate was administered according to low-dose regimens (4 g loading dose followed by 2 g/hour continuous infusion and/or increased by 1 g/hour hourly until successful tocolysis or failure of treatment), or high-dose regimens (4 g loading dose followed by 5 g/hour continuous infusion and increased by 1 g/hour hourly until successful tocolysis or failure of treatment, or 6 g loading dose followed by 2 g/hour continuous infusion and increased by 1 g/hour hourly until successful tocolysis or failure of treatment). There were no differences seen between high-dose magnesium sulphate regimens compared with low-dose magnesium sulphate regimens for the primary outcome of fetal, neonatal and infant death (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.12 to 1.56; one trial, 100 infants). Using the GRADE approach, the evidence for fetal, neonatal and infant death was considered to be VERY LOW quality. No data were reported for any of the other primary maternal and infant health outcomes (birth less than 48 hours after trial entry; composite serious infant outcome; composite serious maternal outcome). There were no clear differences seen between high-dose magnesium sulphate regimens compared with low-dose magnesium sulphate regimens for the secondary infant health outcomes of fetal death; neonatal death; and rate of hypocalcaemia, osteopenia or fracture; and secondary maternal health outcomes of rate of caesarean birth; pulmonary oedema; and maternal self-reported adverse effects. Pulmonary oedema was reported in two women given high-dose magnesium sulphate, but not in any of the women given low-dose magnesium sulphate. In a single trial of high and low doses of magnesium sulphate for tocolysis including 100 infants, the risk of respiratory distress syndrome was lower with use of a high-dose regimen compared with a low-dose regimen (RR 0.31, 95% CI 0.11 to 0.88; one trial, 100 infants). Using the GRADE approach, the evidence for respiratory distress syndrome was judged to be LOW quality. No difference was seen in the rate of admission to the neonatal intensive care unit. However, for those babies admitted, a high-dose regimen was associated with a reduction in the

length of stay in the neonatal intensive care unit compared with a low-dose regimen (mean difference -3.10 days, 95% confidence interval -5.48 to -0.72). We found no data for the majority of our secondary outcomes. **AUTHORS' CONCLUSION** There are limited data available (three studies, with data from only two studies) comparing different dosing regimens of magnesium sulphate given as single agent tocolytic therapy for the prevention of preterm birth. There is no evidence examining duration of therapy, timing of therapy and the role for repeat dosing. Downgrading decisions for our primary outcome of fetal, neonatal and infant death were based on wide confidence intervals (crossing the line of no effect), lack of blinding and a limited number of studies. No data were available for any of our other important outcomes: birth less than 48 hours after trial entry; composite serious infant outcome; composite serious maternal outcome. The data are limited by volume and the outcomes reported. Only eight of our 45 pre-specified primary and secondary maternal and infant health outcomes were reported on in the included studies. No long-term outcomes were reported. Downgrading decisions for the evidence on the risk of respiratory distress were based on wide confidence intervals (crossing the line of no effect) and lack of blinding. There is some evidence from a single study suggesting a reduction in the length of stay in the neonatal intensive care unit and a reduced risk of respiratory distress syndrome where a high-dose regimen of magnesium sulphate has been used compared with a low-dose regimen. However, given that evidence has been drawn from a single study (with a small sample size), these data should be interpreted with caution. Magnesium sulphate has been shown to be of benefit in a wide range of obstetric settings, although it has not been recommended for tocolysis. In clinical settings where health benefits are established, further trials are needed to address the lack of evidence regarding the optimal dose (loading dose and maintenance dose), duration of therapy, timing of therapy and role for repeat dosing in terms of efficacy and safety for mothers and their children. Ongoing examination of different regimens with respect to important health outcomes is required.

**Database:** Medline

### 15. Tocolysis for women with early spontaneous preterm labor and advanced cervical dilation

**Author(s):** Manuck T.A.; Herrera C.A.; Kent Korgenski E.; Jackson M.; Stoddard G.J.; Flint Porter T.; Varner M.W.

**Source:** Obstetrics and Gynecology; Oct 2015; vol. 126 (no. 5); p. 954-961

**Publication Date:** Oct 2015

**Publication Type(s):** Article

**PubMedID:** 26444115

Available at [Obstetrics and Gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**Objective: To characterize tocolytic use and examine perinatal outcomes among women presenting very preterm with spontaneous labor and cervical dilation 4 cm or greater. Methods: This was a retrospective cohort study. Data from January 2000 to June 2011 in a single health care system were reviewed. Women with singleton, nonanomalous fetuses and preterm labor with intact membranes between 23 and 32 weeks of gestation who had cervical dilation 4 cm or greater and less than 8 cm at admission were included. Women receiving one or more tocolytics (magnesium sulfate, indomethacin, or nifedipine) were compared with those who did not receive tocolysis. The primary outcome was composite major neonatal morbidity. Results: Two hundred ninety-seven women were included; 233 (78.5%) received at least one tocolytic. Women receiving tocolysis were slightly less dilated (median 5 compared with 6 cm,  $P<0.01$ ) at presentation and were more likely to receive at least a partial course of corticosteroids (88.4% compared with 56.3%,  $P=0.01$ ). Initial composite severe neonatal morbidity rates were similar (41.6% compared with 43.8%,  $P=0.761$ ) regardless of tocolytic administration. Those receiving tocolysis were significantly more likely to be pregnant at least 48 hours after admission (23.6% compared with 7.8%,  $P=0.05$ ), but a similar proportion delivered within 7 days of admission (94.8% compared with 95.3%,  $P=0.99$ ), and delivery gestational ages were similar (28.9 compared with 29.2 weeks,  $P=0.408$ ). The incidence of chorioamnionitis and postpartum endometritis was similar between groups. **CONCLUSION:** The majority of women presenting very preterm with advanced cervical dilation received tocolysis. Although tocolysis administration increased the likelihood of achieving at least 48 hours of latency, initial neonatal outcomes were similar. Copyright © 2015 by The American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

**Database:** EMBASE

## 16. Magnesium sulphate for preventing preterm birth in threatened preterm labour

**Author(s):** Crowther C.A.; Brown J.; McKinlay C.J.; Middleton P.

**Source:** The Cochrane database of systematic reviews; 2014; vol. 8

**Publication Date:** 2014

**Publication Type(s):** Review

**PubMedID:** 25126773

Available at [The Cochrane database of systematic reviews](#) - from Cochrane Collaboration (Wiley)

**Abstract:** Magnesium sulphate has been used in some settings as a tocolytic agent to inhibit uterine activity in women in preterm labour with the aim of preventing preterm birth. To assess the effects of magnesium sulphate therapy given to women in threatened preterm labour with the aim of preventing preterm birth and its sequelae. We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (last searched 31 January 2014). Randomised controlled trials of magnesium sulphate as the only tocolytic, administered by any route, compared with either placebo, no treatment or alternative tocolytic therapy (not magnesium sulphate) to women considered to be in preterm labour. At least two review authors assessed trial eligibility and risk of bias and undertook data extraction independently. The 37 included trials (total of 3571 women and over 3600 babies) were generally of moderate to high risk of bias. Antenatal magnesium sulphate was compared with either placebo, no treatment, or a range of alternative tocolytic agents. For the primary outcome of giving birth within 48 hours after trial entry, no significant differences were seen between women who received magnesium sulphate and women who did not (whether placebo/no alternative tocolytic drug, betamimetics, calcium channel blockers, cox inhibitors, prostaglandin inhibitors, or human chorionic gonadotropin) (19 trials, 1913 women). Similarly for the primary outcome of serious infant outcome, there were no significant differences between the infants exposed to magnesium sulphate and those not (whether placebo/no alternative tocolytic drug, betamimetics, calcium channel blockers, cox inhibitors, prostaglandin inhibitors, human chorionic gonadotropin or various tocolytic drugs) (18 trials; 2187 babies). No trials reported the outcome of extremely preterm birth. In the seven trials that reported serious maternal outcomes, no events were recorded. In the group treated with magnesium sulphate compared with women receiving antenatal placebo or no alternative tocolytic drug, a borderline increased risk of total death (fetal, neonatal, infant) was seen (risk ratio (RR) 4.56, 95% confidence interval (CI) 1.00 to 20.86; two trials, 257 babies); none of the comparisons between magnesium sulphate and other classes of tocolytic drugs showed differences for this outcome (10 trials, 991 babies). The outcomes of neonatal and/or infant deaths and of fetal deaths did not show differences between magnesium sulphate and no magnesium sulphate, whether compared with placebo/no alternative tocolytic drug, or any specific class of tocolytic drug. For most of the other secondary outcomes, there were no significant differences between magnesium sulphate and the control groups for risk of preterm birth (except for a significantly lower risk with magnesium sulphate when compared with barbiturates in one trial of 65 women), gestational age at birth, interval between trial entry and birth, other neonatal morbidities, or neurodevelopmental outcomes. Duration of neonatal intensive care unit stay was significantly increased in the magnesium sulphate group compared with the calcium channel blocker group, but not when compared with cox inhibitors or prostaglandin inhibitors. No maternal deaths were reported in the four trials reporting this outcome. Significant differences between magnesium sulphate and controls were not seen for maternal adverse events severe enough to stop treatment, except for a significant benefit of magnesium sulphate compared with betamimetics in a single trial. Magnesium sulphate is ineffective at delaying birth or preventing preterm birth, has no apparent advantages for a range of neonatal and maternal outcomes as a tocolytic agent and its use for this indication may be associated with an increased risk of total fetal, neonatal or infant mortality (in contrast to its use in appropriate groups of women for maternal, fetal, neonatal and infant neuroprotection where beneficial effects have been demonstrated).

**Database:** EMBASE

**17. Combination of tocolytic agents for inhibiting preterm labour.**

**Author(s):** Vogel, Joshua P; Nardin, Juan Manuel; Dowswell, Therese; West, Helen M; Oladapo, Olufemi T

**Source:** The Cochrane database of systematic reviews; Jul 2014 (no. 7); p. CD006169

**Publication Date:** Jul 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review

**PubMedID:** 25010869

Available at [The Cochrane database of systematic reviews](#) - from Cochrane Collaboration (Wiley)

**Abstract:**BACKGROUND Preterm birth represents the single largest cause of mortality and morbidity for newborns and a major cause of morbidity for pregnant women. Tocolytic agents include a wide range of drugs that can inhibit labour to prolong pregnancy. This may gain time to allow the fetus to mature further before being born, permit antenatal corticosteroid administration for lung maturation, and allow time for intra-uterine transfer to a hospital with neonatal intensive care facilities. However, some tocolytic drugs are associated with severe side effects. Combinations of tocolytic drugs may be more effective over single tocolytic agents or no intervention, without adversely affecting the mother or neonate. OBJECTIVES To assess the effects on maternal, fetal and neonatal outcomes of any combination of tocolytic drugs for the treatment of preterm labour when compared with any other treatment, no treatment or placebo. SEARCH METHODS We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2014) and reference lists of retrieved studies. SELECTION CRITERIA We included randomised controlled trials comparing a combination of tocolytic agents, administered by any route or any dose, for inhibiting preterm labour versus any other treatment (including other combinations of tocolytics or single tocolytics), no intervention or placebo. DATA COLLECTION AND ANALYSIS Two review authors independently assessed study reports for eligibility, carried out data extraction and assessed risk of bias. MAIN RESULTS Eleven studies met our inclusion criteria. Two studies did not report any outcome data relevant to the review, so the results of the review are based on nine trials that contributed data. Primary outcomes were perinatal mortality, serious maternal or infant outcomes, adverse drug reactions, birth before 48 hours of trial entry, birth before 34 weeks' gestation and preterm neonates delivered without a full course of antenatal steroids completed 24 hours before birth. The quality of evidence in included trials was mixed; only three of the trials were placebo controlled. The included trials examined seven different comparisons: intravenous (IV) ritodrine plus oral or IV magnesium (sulphate or gluconate) versus IV ritodrine alone (three trials, 231 women); IV ritodrine plus indomethacin suppositories versus IV ritodrine alone (one trial, 208 women); IV ritodrine plus vaginal progesterone versus IV ritodrine alone (one trial, 83 women); IV hexoprenaline sulphate plus IV magnesium hydrochloride versus IV hexoprenaline sulphate alone (one trial, 24 women); IV fenoterol plus oral naproxen versus IV fenoterol alone (one trial, 72 women); oral pentoxifylline plus IV magnesium sulphate plus IV fenoterol versus IV magnesium sulphate plus IV fenoterol (one trial, 125 women); and, IV terbutaline plus oral metoprolol versus IV terbutaline alone (one trial, 17 women). Few studies with small numbers of women were available for each comparison, hence very little data were pooled in meta-analysis. In all trials, not many of the primary outcomes were reported. Three trials examined intravenous (IV) ritodrine plus IV or oral magnesium (sulphate or gluconate) compared with IV ritodrine alone. One study, with 41 women, reported more adverse drug reactions in the group receiving the combined tocolytics (risk ratio (RR) 7.79, 95% confidence interval (CI) 1.11 to 54.80). Two trials reported discontinuation of therapy due to severe side effects (results were not combined due to high statistical heterogeneity,  $I^2 = 83\%$ ); one trial reported increased severe side effects in the group receiving IV ritodrine alone (RR 7.79, 95% CI 1.11 to 54.80,

41 women); in the other trial there was no clear difference between groups (RR 0.23, 95% CI 0.03 to 1.97, 107 women). Other primary outcomes were not reported. One trial assessed IV ritodrine plus indomethacin suppositories versus IV ritodrine alone. There were no significant differences between groups for perinatal mortality or serious neonatal morbidity. Results for other primary outcomes were not reported. There were no significant differences between groups receiving IV ritodrine plus vaginal progesterone compared with IV ritodrine alone for most outcomes reported, although the latency period (time from recruitment to delivery) was increased in the group receiving the combination of tocolytics. For other combinations of tocolytic agents, primary outcomes were rarely reported and for secondary outcomes results did not demonstrate differences between groups. **AUTHORS' CONCLUSIONS** It is unclear whether a combination of tocolytic drugs for preterm labour is more advantageous for women and/or newborns due to a lack of large, well-designed trials including the outcomes of interest. There are no trials of combination regimens using widely used tocolytic agents, such as calcium channel blockers (nifedipine) and/or oxytocin receptor antagonists (atosiban). Further trials are needed before specific conclusions on use of combination tocolytic therapy for preterm labour can be made.

**Database:** Medline

## **18. Evaluation of the clinical use of magnesium sulfate for cerebral palsy prevention**

**Author(s):** Jeanneteau P.; Bouet P-E.; Baisson A-L.; Courtay V.; Gillard P.; Descamps P.; Sentilhes L.; Gascoin-Lachambre G.; Lasocki S.

**Source:** Journal of Maternal-Fetal and Neonatal Medicine; Jun 2014; vol. 27 ; p. 377-378

**Publication Date:** Jun 2014

**Publication Type(s):** Conference Abstract

**Abstract:** Brief Introduction: The aim of this study is to evaluate the implementation of a clinical protocol for the use of magnesium for cerebral palsy prevention, focusing on uptake, indications and safety. Materials & Methods: This retrospective and unicentred study included all women with fetuses of gestational age < 33 weeks whose birth was planned or expected within 24 hours from September 2011 (starting of implementation of magnesium sulfate in our department) to December 2012. We assigned women to receive magnesium sulfate, administered intravenously as a 4g bolus followed by a constant infusion of 1g per hour. If delivery had not occurred after 12 hours and was no longer considered imminent, the infusion was discontinued. The primary study outcome was to assess the rate of predelivery administration of magnesium sulfate over this time period. Clinical Cases or Summary Results: Among the 5610 patients who delivered during the study period, 119 were eligible for the protocol. 68.1% of eligible gravidas received magnesium sulfate before delivery. In 2011, at the beginning of magnesium sulfate implementation, 76% of eligible gravidas received magnesium before delivery. The mean gestational age of the protocol's implementation was 30 weeks +/- 2 days. The mean duration of magnesium sulfate treatment was 289 +/- 398 minutes. Bolus and constant infusion were respectively administered during 33 +/- 12 minutes and 335 +/- 425 minutes. Four patients (4.9%) received magnesium sulfate during more than 12 hours. The mean dose administered was 7.99 +/- 6.73 g. No major maternal side effects were observed. The use of magnesium sulfate improved neonatal adaptation with a decrease of the rate of Apgar score less than 7 at 5 minute (p = 0.03), pH less than 7.10 (p = 0.03), need for closed cardiac massage (p = 0.003) and use of Adrenaline (p = 0.01). There was no difference either on birth weight or on neonatal morbi-mortality. Conclusions: It is feasible to implement a magnesium sulfate cerebral palsy prevention protocol into clinical practice. (Table presented).

**Database:** EMBASE

### **19. A moving line in the sand: a review of obstetric management surrounding periviability.**

**Author(s):** Arora, Kavita S; Miller, Emily S

**Source:** Obstetrical & gynecological survey; Jun 2014; vol. 69 (no. 6); p. 359-368

**Publication Date:** Jun 2014

**Publication Type(s):** Journal Article Review

**PubMedID:** 25101845

Available at [Obstetrical & gynecological survey](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**Periviable birth poses numerous clinical and ethical challenges for the practicing clinician. We review the data surrounding the administration of corticosteroids for fetal lung maturity, antibiotics in the case of preterm premature rupture of membranes, magnesium sulfate for cerebral palsy prophylaxis, fetal monitoring, and cesarean delivery. The ethical complexities of patient counseling are also reviewed with a recommendation toward shared decision making between patient and physician.

**Database:** Medline

### **20. Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial (MAGENTA)--study protocol.**

**Author(s):** Crowther, Caroline A; Middleton, Philippa F; Wilkinson, Dominic; Ashwood, Pat; Haslam, Ross; MAGENTA Study Group

**Source:** BMC pregnancy and childbirth; Apr 2013; vol. 13 ; p. 91

**Publication Date:** Apr 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article

**PubMedID:** 23570677

Available at [BMC pregnancy and childbirth](#) - from Europe PubMed Central - Open Access

Available at [BMC pregnancy and childbirth](#) - from ProQuest (Hospital Premium Collection) - NHS  
Version Available at [BMC pregnancy and childbirth](#) - from nih.gov

**Abstract:**BACKGROUND Magnesium sulphate is currently recommended for neuroprotection of preterm infants for women at risk of preterm birth at less than 30 weeks' gestation, based on high quality evidence of benefit. However there remains uncertainty as to whether these benefits apply at higher gestational ages. The aim of this randomised controlled trial is to assess whether giving magnesium sulphate compared with placebo to women immediately prior to preterm birth between 30 and 34 weeks' gestation reduces the risk of death or cerebral palsy in their children at two years' corrected age. METHODS/DESIGN Randomised, multicentre, placebo controlled trial. INCLUSION CRITERIA Women, giving informed consent, at risk of preterm birth between 30 to 34 weeks' gestation, where birth is planned or definitely expected within 24 hours, with a singleton or twin pregnancy and no contraindications to the use of magnesium sulphate. Trial entry & randomisation: Eligible women will be randomly allocated to receive either magnesium sulphate or placebo. Treatment groups: Women in the magnesium sulphate group will be administered 50 ml of a 100 ml infusion bag containing 8 g magnesium sulphate heptahydrate [16 mmol magnesium ions]. Women in the placebo group will be administered 50 ml of a 100 ml infusion bag containing isotonic sodium chloride solution (0.9%). Both treatments will be administered through a dedicated IV infusion line over 30 minutes. Primary study outcome: Death or cerebral palsy measured in children at two years' corrected age. SAMPLE SIZE 1676 children are required to detect a decrease in the combined outcome of death or cerebral palsy, from 9.6% with placebo to 5.4% with magnesium sulphate (two-sided alpha 0.05, 80% power, 5% loss to follow up, design effect

1.2).DISCUSSIONGiven the magnitude of the protective effect in the systematic review, the ongoing uncertainty about benefits at later gestational ages, the serious health and cost consequences of cerebral palsy for the child, family and society, a trial of magnesium sulphate for women at risk of preterm birth between 30 to 34 weeks' gestation is both important and relevant for clinical practice globally.TRIAL REGISTRATIONAustralian New Zealand Clinical Trials Registry - ACTRN12611000491965.

**Database:** Medline

## **21. Magnesium sulphate for women at term for neuroprotection of the fetus.**

**Author(s):** Nguyen, Thuy-My N; Crowther, Caroline A; Wilkinson, Dominic; Bain, Emily

**Source:** The Cochrane database of systematic reviews; Feb 2013 (no. 2); p. CD009395

**Publication Date:** Feb 2013

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article Review

**PubMedID:** 23450601

Available at [The Cochrane database of systematic reviews](#) - from Cochrane Collaboration (Wiley)

**Abstract:**BACKGROUNDMagnesium sulphate is extensively used in obstetrics for the treatment and prevention of eclampsia. A recent meta-analysis has shown that magnesium sulphate is an effective fetal neuroprotective agent when given antenatally to women at risk of very preterm birth. Term infants account for more than half of all cases of cerebral palsy, and the incidence has remained fairly constant. It is important to assess if antenatal administration of magnesium sulphate to women at term protects the fetus from brain injury, and associated neurosensory disabilities including cerebral palsy.OBJECTIVESTo assess the effectiveness of magnesium sulphate given to women at term as a neuroprotective agent for the fetus.SEARCH METHODSWe searched the Cochrane Pregnancy and Childbirth Group's Trial Register (31 July 2012) and the reference lists of other Cochrane reviews assessing magnesium sulphate in pregnancy.SELECTION

CRITERIARandomised controlled trials comparing antenatally administered magnesium sulphate to women at term with placebo, no treatment or a different fetal neuroprotective agent. We also planned to include cluster-randomised trials, and exclude cross-over trials and quasi-randomised trials. We planned to exclude studies reported as abstracts only.DATA COLLECTION AND ANALYSISTwo review authors independently assessed trials for eligibility and for risk of bias. Two authors independently extracted data. Data were checked for accuracy.MAIN RESULTWe included one trial (involving 135 women with mild pre-eclampsia at term). An additional six studies are awaiting further assessment.The included trial compared magnesium sulphate with a placebo and was at a low risk of bias. The trial did not report any of this review's prespecified primary outcomes. There was no significant difference between magnesium sulphate and placebo in Apgar score less than seven at five minutes (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.05 to 5.46; 135 infants), nor gestational age at birth (mean difference (MD) -0.20 weeks; 95% CI -0.62 to 0.22; 135 infants).There were significantly more maternal side effects (feeling warm and flushed) in the magnesium sulphate group than in the placebo group (RR 3.81; 95% CI 2.22 to 6.53; 135 women). However, no significant difference in adverse effects severe enough to cease treatment was observed (RR 3.04; 95% CI 0.13 to 73.42; 135 women). There were no significant differences seen between groups in the rates of postpartum haemorrhage (RR 4.06; 95% CI 0.47 to 35.38; 135 women) and caesarean section (RR 0.80; 95% CI 0.39 to 1.63; 135 women).AUTHORS' CONCLUSIONSThere is currently insufficient evidence to assess the efficacy and safety of magnesium sulphate when administered to women for neuroprotection of the term fetus. As there has been recent evidence for the use of magnesium sulphate for neuroprotection of the preterm fetus, high-quality randomised controlled trials are needed to determine the safety profile and neurological

outcomes for the term fetus. Strategies to reduce maternal side effects during treatment also require evaluation.

**Database:** Medline

**22. Randomized controlled trial of magnesium sulfate in women at risk of preterm deliveryneonatal cardiovascular effects**

**Author(s):** Paradisis M.; Kluckow M.; Osborn D.A.; Evans N.

**Source:** Journal of Perinatology; Sep 2012; vol. 32 (no. 9); p. 665-670

**Publication Date:** Sep 2012

**Publication Type(s):** Article

**PubMedID:** 22094492

Available at [Journal of Perinatology](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**Objective: Use of antenatal magnesium sulfate (MgSO<sub>4</sub>) may reduce cerebral palsy in infants born very preterm. Low systemic blood flow in the first day in very preterm infants has been associated with cerebral injury and adverse motor outcome. The aim was to determine the effect of MgSO<sub>4</sub> on systemic blood flow in preterm infants. Study Design: Randomized trial of MgSO<sub>4</sub> versus saline placebo given to mothers at risk of delivery before 30 weeks gestation. Echocardiographic monitoring performed at 3 to 5, 10 to 12 and 24 h. Result: A total of 48 infants were exposed to MgSO<sub>4</sub> and 39 to placebo. Infants exposed to MgSO<sub>4</sub> were significantly more likely to receive volume expansion (42% versus 21%). Inotrope use did not differ significantly (40% versus 26%). There was no significant difference in mean lowest superior vena cava (SVC) flow or right ventricular output (RVO), or incidence of low SVC flow or RVO in the first 24 h. Infants exposed to MgSO<sub>4</sub> had a significantly higher heart rate and were more likely to have low SVC flow at 10 to 12 h but not other times. Conclusion: Antenatal MgSO<sub>4</sub> produced no consistent cardiovascular effects in the infant in the first 24 h. There is no evidence from this study to suggest the mechanism by which antenatal MgSO<sub>4</sub> prevents cerebral palsy is through a cardiovascular effect in the newborn. © 2012 Nature America, Inc. All rights reserved.

**Database:** EMBASE

### **23. Treatment with magnesium sulphate in pre-term birth: A systematic review and meta-analysis of observational studies**

**Author(s):** Wolf H.T.; Hegaard H.K.; Greisen G.; Huusom L.; Hedegaard M.

**Source:** Journal of Obstetrics and Gynaecology; Feb 2012; vol. 32 (no. 2); p. 135-140

**Publication Date:** Feb 2012

**Publication Type(s):** Review

**PubMedID:** 22296422

**Abstract:** Premature birth increases a child's risk of cerebral palsy and death. The aim of this work is to investigate the association between treatment with magnesium sulphate during premature deliveries and infants' cerebral palsy and mortality through a meta-analysis of observational studies. A comprehensive search of the Cochrane Library, EMBASE and the PubMed database from their inceptions to 1 October, 2010 using the keywords 'magnesium sulphate, children/infant/pre-term/premature and cerebral palsy/mortality/morbidity/ adverse effects/outcome' identified 11 reports of observational studies. Two authors working independently extracted the data. A meta-analysis of the data found an association between magnesium sulphate treatment and a significantly reduced risk of mortality (RR 0.73; 95% CI 0.61-0.89) and cerebral palsy (OR 0.64; 95% CI 0.47-0.89). Antenatal treatment with magnesium sulphate during premature deliveries seems to be associated with health benefits for the infants. The effective dose and timing, however, is not defined and given the lack of mechanistic understanding of the effect of MgSO<sub>4</sub>, a reasonable alternative is a large-scale pragmatic clinical trial. © 2012 Informa UK, Ltd.

**Database:** EMBASE

### **24. Antenatal magnesium sulfate and the postnatal response of the ductus arteriosus to indomethacin in extremely preterm neonates.**

**Author(s):** Katayama, Y; Minami, H; Enomoto, M; Takano, T; Hayashi, S; Lee, Y K

**Source:** Journal of perinatology : official journal of the California Perinatal Association; Jan 2011; vol. 31 (no. 1); p. 21-24

**Publication Date:** Jan 2011

**Publication Type(s):** Comparative Study Journal Article

**PubMedID:** 20505743

Available at [Journal of perinatology : official journal of the California Perinatal Association](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** **OBJECTIVE** The aim of this study is to evaluate the influence of antenatal magnesium sulfate (MgSO<sub>4</sub>) treatment on the clinical responsiveness of the ductus arteriosus to indomethacin prophylaxis and on that of symptomatic patent ductus arteriosus (sPDA) to indomethacin treatment in premature neonates. **STUDY DESIGN** This is a retrospective study of 160 consecutively admitted neonates with a gestational age of <28 weeks (41 MgSO<sub>4</sub> exposed and 119 controls) who received indomethacin prophylaxis. **RESULT** Incidence of early closure of the ductus arteriosus was lower in the MgSO<sub>4</sub>-exposed neonates than in the control group (59 vs 84%, respectively; P=0.002), whereas incidence of an sPDA was higher (46 vs 24%, respectively; P=0.006). Response to indomethacin treatment was similar between the two groups. Logistic regression analysis indicated increased risk of failure of early ductus arteriosus closure following antenatal MgSO<sub>4</sub> treatment (odds ratio, 4.03; P=0.002). **CONCLUSION** In extremely preterm neonates, antenatal MgSO<sub>4</sub> treatment reduces clinical responsiveness of the ductus arteriosus to indomethacin prophylaxis but not that of sPDA to indomethacin treatment.

**Database:** Medline

## **25. Magnesium sulfate for preterm labor and preterm birth.**

**Author(s):** Mercer, Brian M; Merlino, Amy A; Society for Maternal-Fetal Medicine

**Source:** Obstetrics and gynecology; Sep 2009; vol. 114 (no. 3); p. 650-668

**Publication Date:** Sep 2009

**Publication Type(s):** Journal Article Review

**PubMedID:** 19701047

Available at [Obstetrics and gynecology](#) - from Ovid (Journals @ Ovid)

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:** Approximately half of the more than 500,000 preterm births each year result from preterm labor. Tocolytic therapy continues to be the focus of treatment of these women. Although a variety of tocolytics are used in clinical practice, magnesium sulfate remains one of the most commonly used agents. Magnesium sulfate has also been the focus of recent research for its potential neuroprotective effects for neonates born preterm. Evaluation of 19 randomized clinical trials reveals that magnesium sulfate tocolysis does not reduce the frequencies of delivery within 48 hours, 7 days, or early/late preterm birth, and is not associated with improvements in newborn morbidities or mortality. No other tocolytic class resulted in improved newborn outcomes when compared with magnesium sulfate tocolysis. We conclude that it is appropriate to withhold tocolysis with magnesium sulfate or other agents from women presenting in preterm labor as newborn benefit has not been demonstrated with such treatment. If initiated to achieve time for antenatal corticosteroid administration, or for other acute reasons, treatment can be discontinued once these goals have been achieved or if labor subsides before then. Because brief pregnancy prolongation is unlikely to improve newborn outcomes after corticosteroid administration has been completed, it is appropriate to withhold magnesium sulfate tocolysis from women with recurrent preterm labor thereafter. If magnesium sulfate is given for neuroprotection, a protocol from one of the three major trials that have demonstrated benefits should be used.

**Database:** Medline

**26. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis.**

**Author(s):** Conde-Agudelo, Agustín; Romero, Roberto

**Source:** American journal of obstetrics and gynecology; Jun 2009; vol. 200 (no. 6); p. 595-609

**Publication Date:** Jun 2009

**Publication Type(s):** Meta-analysis Research Support, N.i.h., Intramural Journal Article Review

**PubMedID:** 19482113

Available at [American journal of obstetrics and gynecology](#) - from nih.gov

**Abstract:**We conducted a systematic review and metaanalysis of randomized controlled trials to determine whether magnesium sulfate administered to women at risk of preterm delivery before 34 weeks of gestation may reduce the risk of cerebral palsy in their children. Six trials involving 4796 women and 5357 infants were included. Antenatal magnesium sulfate was associated with a significant reduction in the risk of cerebral palsy (relative risk [RR], 0.69; 95% confidence interval [CI], 0.55-0.88), moderate or severe cerebral palsy (RR, 0.64; 95% CI, 0.44-0.92), and substantial gross motor dysfunction (RR, 0.60; 95% CI, 0.43-0.83). There was no overall difference in the risk of total pediatric mortality (RR, 1.01; 95% CI, 0.89-1.14). Minor side effects were more frequent among women receiving magnesium sulfate. In conclusion, magnesium sulfate administered to women at risk of delivery before 34 weeks of gestation reduces the risk of cerebral palsy.

**Database:** Medline

**27. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis.**

**Author(s):** Costantine, Maged M; Weiner, Steven J; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

**Source:** Obstetrics and gynecology; Aug 2009; vol. 114 (no. 2); p. 354-364

**Publication Date:** Aug 2009

**Publication Type(s):** Research Support, N.i.h., Extramural Meta-analysis Comparative Study Journal Article

**PubMedID:** 19622997

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**OBJECTIVETo review the evidence regarding neuroprotective effects of antenatal exposure to magnesium sulfate.DATA SOURCESWe conducted database searches of MEDLINE, the Cochrane Library and Controlled Trials Register, as well as the ClinicalTrials.gov and International Clinical Trials Register websites. Bibliographies of all relevant articles were reviewed.METHODS OF STUDY SELECTIONRandomized controlled trials comparing magnesium sulfate with placebo/other treatment in patients at risk of preterm delivery were evaluated for inclusion and methodological quality. The primary outcome was death or cerebral palsy by 18-24 months corrected age. Secondary outcomes were death, cerebral palsy, moderate-severe cerebral palsy, and death or moderate-severe cerebral palsy. Separate analyses were performed according to the gestational age (GA) at randomization (less than 32 to 34 weeks and less than 30 weeks) and for studies in which magnesium sulfate was used exclusively for fetal neuroprotection.TABULATION, INTEGRATION, AND RESULTSFive randomized controlled trials were included (5,235 fetuses/infants). When analyzed by GA at randomization, in utero exposure to magnesium sulfate at less than 32-34 weeks did not reduce the rate of death or cerebral palsy (relative risk [RR] 0.92, 95% confidence interval [CI] 0.83-1.03). However, cerebral palsy (RR 0.70, 95% CI 0.55-0.89), moderate-severe cerebral palsy (RR 0.60,

95% CI 0.43-0.84), and death or moderate-severe cerebral palsy were significantly reduced, without an evident increase in the risk of death (RR 1.01, 95% CI 0.89-1.14). Similar results were obtained when the GA at randomization was less than 30 weeks. When only neuroprotection trials (four trials, 4,324 fetuses/infants) are analyzed, in utero exposure to magnesium sulfate additionally reduced the primary outcome of death or cerebral palsy. The number needed to treat to prevent one case of cerebral palsy among those who survive until age 18-24 months is 46 (95% CI 26-187) in infants exposed to magnesium sulfate in utero before 30 weeks, and 56 (95% CI 34-164) in infants exposed to magnesium sulfate in utero before 32 to 34 weeks. **CONCLUSION** Fetal exposure to magnesium sulfate in women at risk of preterm delivery significantly reduces the risk of cerebral palsy without increasing the risk of death.

**Database:** Medline

## **28. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial\*.**

**Author(s):** Marret, S; Marpeau, L; Zupan-Simunek, V; Eurin, D; Lévêque, C; Hellot, M-F; Bénichou, J; PREMAG trial group

**Source:** BJOG : an international journal of obstetrics and gynaecology; Mar 2007; vol. 114 (no. 3); p. 310-318

**Publication Date:** Mar 2007

**Publication Type(s):** Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 17169012

Available at [BJOG : an international journal of obstetrics and gynaecology](#) - from Wiley Online Library Science , Technology and Medicine Collection 2017

**Abstract:** **OBJECTIVE** To evaluate whether magnesium sulphate (MgSO<sub>4</sub>) given to women at risk of very-preterm birth would be neuroprotective in preterm newborns and would prevent neonatal mortality and severe white-matter injury (WMI). **DESIGN** A randomised study. **SETTING** Eighteen French tertiary hospitals. **Population** Women with fetuses of gestational age < 33 weeks whose birth was planned or expected within 24 hours were enrolled from July 1997 to July 2003 with follow up of infants until hospital discharge. **METHODS** Five hundred and seventy-three mothers were randomly assigned to receive a single 40-ml infusion of 0.1 g/ml of MgSO<sub>4</sub> (4 g) solution or isotonic 0.9% saline (placebo) over 30 minutes. This study is registered as an International Standard Randomised Controlled Trial, number 00120588. **MAIN OUTCOME MEASURE** The primary endpoints were rates of severe WMI or total mortality before hospital discharge, and their combined outcome. Analyses were based on intention to treat. **RESULTS** After 6 years of enrolment, the trial was stopped. Data from 688 infants were analysed. Comparing infants who received MgSO<sub>4</sub> or placebo, respectively, total mortality (9.4 versus 10.4%; OR: 0.79, 95% CI 0.44-1.44), severe WMI (10.0 versus 11.7%; OR: 0.78, 95% CI 0.47-1.31) and their combined outcomes (16.5 versus 17.9%; OR: 0.86, 95% CI 0.55-1.34) were less frequent for the former, but these differences were not statistically significant. No major maternal adverse effects were observed in the MgSO<sub>4</sub> group. **CONCLUSION** Although our results are inconclusive, improvements of neonatal outcome obtained with MgSO<sub>4</sub> are of potential clinical significance. More research is needed to assess the protective effect of MgSO<sub>4</sub> alone or in combination with other neuroprotective molecules.

**Database:** Medline

## **29. Rofecoxib versus magnesium sulfate to arrest preterm labor: a randomized trial.**

**Author(s):** McWhorter, Jeannie; Carlan, S J; OLeary, Timothy D; Richichi, Kris; OBrien, W F

**Source:** Obstetrics and gynecology; May 2004; vol. 103 (no. 5); p. 923-930

**Publication Date:** May 2004

**Publication Type(s):** Comparative Study Randomized Controlled Trial Clinical Trial Journal Article

**PubMedID:** 15121566

Available at [Obstetrics and gynecology](#) - from Ovid (LWW Total Access Collection 2015 - Q1 with Neurology)

**Abstract:**OBJECTIVETo compare oral rofecoxib with intravenous magnesium sulfate as a tocolytic.METHODSThis was a randomized study of patients who were between 22 and 34 weeks of gestation with preterm labor. Patients were randomly assigned to receive either daily oral rofecoxib (50 mg) or intravenous magnesium sulfate for a maximum of 48 hours. Outcome variables included delay of delivery for 48 hours and the incidence of side effects. Data were analyzed by using the Student t test, Mann-Whitney U test, chi(2) test, and repeated-measures analysis of variance. Sample size calculations were based on previous studies of tocolytic efficacy.RESULTSTwo hundred fourteen patients were randomly assigned (105 received rofecoxib and 109 received magnesium sulfate). Delivery was delayed for 48 hours in 95 (90.4%) and 96 (88%) of the patients in the rofecoxib and magnesium sulfate groups, respectively (relative risk 0.97; 95% confidence interval 0.89, 1.06). To show a statistically significant benefit in delay of delivery past 48 hours, a total of 2,686 patients would be required in each group. There was no difference between the groups over the course of the study in cervical dilatation, amniotic fluid index, or cervical length by vaginal ultrasonography. The median hospital days on the original admission were also similar at 2 for both groups (P =.10). There was a higher reported incidence of maternal side effects in the magnesium sulfate group (relative risk 1.81; 95% confidence interval 1.07, 3.06). There was no difference in the incidence of neonatal side effects.CONCLUSION There was no difference between oral rofecoxib and intravenous magnesium sulfate in arresting preterm labor.

**Database:** Medline

**30. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial.**

**Author(s):** Crowther, Caroline A; Hiller, Janet E; Doyle, Lex W; Haslam, Ross R; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group

**Source:** JAMA; Nov 2003; vol. 290 (no. 20); p. 2669-2676

**Publication Date:** Nov 2003

**Publication Type(s):** Research Support, Non-u.s. Gov't Randomized Controlled Trial Clinical Trial Multicenter Study Journal Article

**PubMedID:** 14645308

Available at [JAMA](#) - from Patricia Bowen Library & Knowledge Service West Middlesex University Hospital NHS Trust (lib302631) Local Print Collection [location] : Patricia Bowen Library and Knowledge Service West Middlesex university Hospital.

**Abstract:**CONTEXT Prenatal magnesium sulfate may reduce the risk of cerebral palsy or death in very preterm infants. OBJECTIVE To determine the effectiveness of magnesium sulfate given for neuroprotection to women at risk of preterm birth before 30 weeks' gestation in preventing pediatric mortality and cerebral palsy. DESIGN, SETTING, AND PATIENTS Randomized controlled trial at 16 tertiary hospitals in Australia and New Zealand with stratification by center and multiple pregnancy. A total of 1062 women with fetuses younger than 30 weeks' gestation for whom birth was planned or expected within 24 hours were enrolled from February 1996 to September 2000 with follow-up of surviving children at a corrected age of 2 years. INTERVENTIONS Women were randomly assigned to receive a loading infusion of 8 mL (4 g [16 mmol] of 0.5 g/mL of magnesium sulfate solution or isotonic sodium chloride solution [0.9%]) for 20 minutes followed by a maintenance infusion of 2 mL/h for up to 24 hours. MAIN OUTCOME MEASURES Rates of total pediatric mortality, cerebral palsy, and the combined outcome of death or cerebral palsy at a corrected age of 2 years. RESULTS Data were analyzed for 1047 (99%) 2-year survivors. Total pediatric mortality (13.8% vs 17.1%; relative risk [RR], 0.83; 95% confidence interval [CI], 0.64-1.09), cerebral palsy in survivors (6.8% vs 8.2%; RR, 0.83; 95% CI, 0.54-1.27), and combined death or cerebral palsy (19.8% vs 24.0%; RR, 0.83; 95% CI, 0.66-1.03) were less frequent for infants exposed to magnesium sulfate, but none of the differences were statistically significant. Substantial gross motor dysfunction (3.4% vs 6.6%; RR, 0.51; 95% CI, 0.29-0.91) and combined death or substantial gross motor dysfunction (17.0% vs 22.7%; RR, 0.75; 95% CI, 0.59-0.96) were significantly reduced in the magnesium group. CONCLUSIONS Magnesium sulfate given to women immediately before very preterm birth may improve important pediatric outcomes. No serious harmful effects were seen.

**Database:** Medline

## Strategy 370259

#	Database	Search term	Results
1	Medline	("magnesium sulphate").ti,ab	1445
2	Medline	("magnesium sulfate").ti,ab	3273
3	Medline	exp "MAGNESIUM SULFATE"/	4824
4	Medline	(1 OR 2 OR 3)	6759
5	Medline	(IV OR intravenous* OR infusion*).ti,ab	752570
6	Medline	exp "INFUSIONS, INTRAVENOUS"/	52152
7	Medline	(5 OR 6)	763149
8	Medline	((preterm OR "pre term" OR premature) ADJ2 (labor OR labour)).ti,ab	10278
9	Medline	("OBSTETRIC LABOR, PREMATURE").ti,ab,af	12841
10	Medline	(8 OR 9)	17726
11	Medline	((32 OR "thirty two") ADJ2 (gestation OR weeks OR wks)).ti,ab,af	13615
12	Medline	("third trimester").ti,ab,af	14053
13	Medline	exp "PREGNANCY TRIMESTER, THIRD"/	13574
14	Medline	(11 OR 12 OR 13)	36247
15	Medline	(4 AND 7 AND 10 AND 14)	23
16	Medline	(MgSO4).ti,ab,af	2107
17	Medline	(7 AND 10 AND 14 AND 16)	3

18	Medline	(late* ADJ2 pregnanc*).ti,ab,af	11935
19	Medline	(4 AND 7 AND 10 AND 18)	1
20	Medline	(16 AND 18)	2
21	Medline	(4 AND 18)	20
22	Medline	(4 AND 14)	151
23	EMBASE	exp "MAGNESIUM SULFATE"/iv	2414
24	EMBASE	exp "MAGNESIUM SULFATE"/	14899
25	EMBASE	("magnesium sulphate").ti,ab	2161
26	EMBASE	("magnesium sulfate").ti,ab	4264
27	EMBASE	(24 OR 25 OR 26)	15729
28	EMBASE	(IV OR intravenous* OR infusion*).ti,ab	1064818
29	EMBASE	exp "INFUSIONS, INTRAVENOUS"/	368442
30	EMBASE	(28 OR 29)	1275414
31	EMBASE	((preterm OR "pre term" OR premature) ADJ2 (labor OR labour)).ti,ab	13662
32	EMBASE	exp "PREMATURE LABOR"/	40054
33	EMBASE	(31 OR 32)	43487
34	EMBASE	((32 OR "thirty two") ADJ2 (gestation OR weeks OR wks)).ti,ab,af	17251
35	EMBASE	exp "PREGNANCY TRIMESTER, THIRD"/	23292
36	EMBASE	(34 OR 35)	39906

37	EMBASE	(23 AND 33 AND 36)	17
38	EMBASE	(27 AND 30 AND 33 AND 36)	29
39	EMBASE	(37 OR 38)	38
40	EMBASE	(late* ADJ2 pregnanc*).ti,ab,af	14009
41	EMBASE	(27 AND 40)	66
42	Medline	exp "TIME FACTORS"/	1111996
43	Medline	(4 AND 7 AND 10 AND 42)	18
44	Medline	((34 OR "thirty four") ADJ2 (weeks OR wks)).ti,ab	9950
45	Medline	(4 AND 44)	107
46	Medline	exp "GESTATIONAL AGE"/	74213
47	Medline	("gestational age").ti,ab	58019
48	Medline	(46 OR 47)	110228
49	Medline	(4 AND 48)	416
50	EMBASE	(late*1 ADJ2 gestation*).ti,ab	8550
51	EMBASE	(27 AND 50)	21
52	EMBASE	*"GESTATIONAL AGE"/	10026
53	EMBASE	(27 AND 52)	38
54	EMBASE	((34 OR "thirty four") ADJ2 (weeks OR wks)).ti,ab	13030
55	EMBASE	(27 AND 54)	223
56	EMBASE	(term ADJ2 pregnanc*).ti,ab	8764
57	EMBASE	(27 AND 56)	36

59	Medline	(4 AND 7 AND 10)	159
60	EMBASE	**"MAGNESIUM SULFATE"/	5796
61	EMBASE	**"PREMATURE LABOR"/	14779
62	EMBASE	(60 AND 61)	325
63	Medline	(periviab*).ti,ab	119
64	Medline	(4 AND 63)	15
65	Medline	("limit of viability").ti,ab	117
66	Medline	(4 AND 65)	8
67	Medline	(64 OR 66)	15
68	Medline	exp "INFANT, EXTREMELY PREMATURE"/	1420
69	Medline	(4 AND 68)	21
70	Medline	(extreme* ADJ2 (preterm OR prematur*)).ti,ab	3417
71	Medline	(4 AND 70)	18
72	EMBASE	(periviab*).ti,ab	177
73	EMBASE	("limit of viability").ti,ab	197
74	EMBASE	(extreme* ADJ2 (preterm OR prematur*)).ti,ab	4646
75	EMBASE	(72 OR 73 OR 74)	4935
76	EMBASE	(27 AND 75)	72