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SPECIAL ARTICLE

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FIGO good practice recommendations on magnesium sulfate administration for preterm fetal neuroprotection

Andrew Shennan[1] | Natalie Suff[1] | Bo Jacobsson[2,3,4] | on behalf of the FIGO Working Group for Preterm Birth

[1]Department of Women and Children's Health, King's College, London, UK

[2]Department of Obstetrics and Gynecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Gothenburg, Sweden

[4]Department of Genetics and Bioinformatics, Domain of Health Data and Digitalization, Institute of Public Health, Oslo, Norway

Correspondence
Andrew Shennan, Department of Women and Children's Health, St Thomas' Hospital, London SE1 7EH, UK.
Email: andrew.shennan@kcl.ac.uk

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Abstract

In women at risk of early preterm imminent birth, from viability to 30 weeks of gestation, use of MgSO4 for neuroprotection of the fetus is recommended. In pregnancies below 32–34 weeks of gestation, the use of MgSO4 for neuroprotection of the fetus should be considered. MgSO4 should be administered regardless of the cause for preterm birth and the number of babies in utero. MgSO4 should be administered when early preterm birth is planned or expected within 24 h. When birth is planned, MgSO4 should commence as close as possible to 4 h before birth. If delivery is planned or expected to occur sooner than 4 h, MgSO4 should be administered, as there is still likely to be an advantage from administration within this time. The optimal regimen of MgSO4 for fetal neuroprotection is an intravenous loading dose of 4 g (administered slowly over 20–30 min), followed by a 1 g per hour maintenance dose. This regimen should continue until birth but should be stopped after 24 h if undelivered. When MgSO4 is administered, women should be monitored for clinical signs of magnesium toxicity at least every 4 h by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

KEYWORDS
antenatal, child outcome, magnesium sulfate, neuroprotection

1 | INTRODUCTION

The prevalence of cerebral palsy is increasing, related to an increase in early gestation survival.[1] Twenty-five percent of all cerebral palsy cases occur in babies born before 34 weeks of gestation.[2] Observational data from studies examining the use of magnesium sulfate (MgSO4) for tocolysis and for treating preeclampsia first indicated the potential neuroprotective effects for preterm infants.[3]

Subsequent randomized controlled trials to assess the role of MgSO4 in preterm fetal neuroprotection were analyzed in a Cochrane review in 2009. This meta-analysis concluded that antenatal MgSO4 therapy given to women at risk of early preterm birth (under 34 weeks) reduces the risk of cerebral palsy in their children (RR 0.68, 95% CI 0.54–0.87; five trials, 6145 infants).[4] In addition, in an individual participant data meta-analysis, antenatal MgSO4 reduced the combined risk of death or cerebral palsy (RR 0.86, 95% CI 0.75–0.99) with an NNT of 41 women (to reduce a combination of death and both moderate and severe types of cerebral palsy).[5] MgSO4 is an inexpensive drug; however, setting up and monitoring magnesium sulfate infusions incurs additional medical staff time. Nevertheless, training time should be minimal, as most units have experience with MgSO4 infusion for eclampsia prevention.

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

2 | GESTATIONAL AGE AT WHICH MgSO4 IS GIVEN

All women in the 2009 Cochrane review were given MgSO4 at <34 weeks of gestation, with 68% of women <30 weeks of gestation.[4] Cerebral palsy is inversely related to gestational age; therefore, the absolute risk difference from treatment is likely to be larger at earlier gestations. Correspondingly, numbers needed to treat will be smaller earlier in pregnancies and higher at later gestational ages.

Recommendation: In women at risk of early preterm imminent birth, from viability to 30 weeks of gestation, use of MgSO4 for neuroprotection of the fetus is recommended. In women at risk of early preterm imminent birth, <32–34 weeks of gestation, the use of MgSO4 for neuroprotection of the fetus should be considered.

3 | OPTIMAL TIMING FOR MgSO4 ADMINISTRATION

In two of the four trials included in the Cochrane review, MgSO4 was given when birth was expected or planned within 24 h.[6,7] Subgroup analyses of these trials showed a RR of 0.81 (0.68–0.97) of death or cerebral palsy.[4] The median time from randomization to birth in the MgSO4 group of these two trials was between 1.6 and 3.7 h.

It has been previously shown that antenatal infusions enable the prompt transfer of MgSO4 to the mother (within 30 min) and that neonatal magnesium sulfate concentrations remained elevated up to 24 h. This indicates that MgSO4 crosses the placenta to the fetus promptly after commencing the infusion.

Recommendation: MgSO4 should be administered when early preterm birth is planned or expected within 24 h. When birth is planned, MgSO4 should commence as close as possible to 4 h before birth. If delivery is planned or expected to occur sooner than 4 h MgSO4 should be administered, as there is still likely to be an advantage from administration within this time.

4 | OPTIMAL REGIMEN FOR MgSO4 ADMINISTRATION

The dose of MgSO4 differed between studies, with loading doses varying between 4 g and 6 g, and inconsistency in whether a maintenance dose was administered. A meta-analysis concluded that although the beneficial effect of MgSO4 persisted in the studies using lower overall doses, there is currently insufficient evidence to define a minimum effective dose or optimal regimen for administration.[2] Magnesium toxicity is unlikely at the dose recommended below, and serum magnesium monitoring is not routinely recommended.

Recommendation: In women at risk of early preterm birth, use magnesium sulfate for neuroprotection of the fetus:

- *intravenously with a 4 g loading dose (administered slowly over 20–30 min)*
- *1 g per hour maintenance dose via the intravenous route*
- *continue regimen until birth, but stop after 24 h if undelivered.*

5 | MgSO4 ADVERSE EFFECTS

Magnesium sulfate produces flushing, sweating, and a sensation of warmth due to its peripheral vasodilator effects when infused intravenously. Other reported maternal side effects related to dosage and speed of infusion include nausea, vomiting, headache, palpitations and, rarely, pulmonary edema. Overdose can result in cardiac and neurological adverse events. There is no evidence of any unintended adverse outcomes in the neonate.[8] MgSO4 was initially considered as a tocolytic; however, there is no evidence that delivery is delayed when used.

Recommendation: Where MgSO4 is administered, monitor women for clinical signs of magnesium toxicity at least every 4 h by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

6 | EFFICACY OF MgSO4 IN SUBGROUPS

MgSO4 is beneficial for fetal neuroprotection in spontaneous and iatrogenic preterm births, with no apparent differences in treatment effects among the subgroups (including pre-eclampsia, spontaneous PTB, PPROM, chorioamnionitis, and antepartum hemorrhage).[6] All trials in the Cochrane review included twins, with two of the four trials including high-order multiples, and showed evidence of benefit.[4]

Recommendation: In women at risk of imminent preterm birth, MgSO4 should be used for neuroprotection of the fetus, regardless of the cause for preterm birth and the number of babies in utero.

CONFLICTS OF INTEREST

Andrew Shennan reports payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Manipal India; support for attending meetings and/or travel from Hologic; leadership or fiduciary roles in the HTA Commissioning Board UK and Action on Pre-eclampsia charity. Natalie Suff reports no conflicts of interest. Bo Jacobbson reports research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health; clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expendidures reimbused per patient; clinical probiotic studies with product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study); collaboration in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents to PLGF analyses; coordination of scientific conferences and meetings with commercial partners as such as NNFM 2015, ESPBC 2016 and a Nordic educational meeting about NIPT and preeclampsia

screening. Bo Jacobbson is also Chair of the FIGO Working Group for Preterm Birth and the European Association of Perinatal Medicine's special interest group of preterm delivery; steering group member of Genomic Medicine Sweden; chairs the Genomic Medicine Sweden complex diseases group; and is Swedish representative in the Nordic Society of Precision Medicine.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. AS and NS wrote the first version of the manuscript. BJ and JN revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

Bo Jacobsson (Chair), Joe Leigh Simpson, Jane Norman, William A. Grobman, Ana Bianchi, Stephen Munjanja, Catalina María Valencia González, Ben W. Mol.

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