“Magnesium Sulfate for Preterm Labor and Preterm Birth”
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1. How are women in preterm labor treated at your institution? Do you employ a clinical pathway for preterm labor? If so, what are the essential treatment components?

Response from Drs. Brian M. Mercer and Amy A. Merlino:

Our institution does not have a uniform protocol for treatment of preterm labor. Because of this, there is some variability in practice. Tocolysis is typically administered to women in preterm labor between 23 and 34 weeks of gestation who demonstrate cervical change or advanced dilatation on admission. Magnesium sulfate has been our usual first-line tocolytic agent. It is administered concurrent to antenatal corticosteroid treatment and is discontinued with cessation of progressive labor. In general, tocolysis is discouraged once corticosteroid therapy has been completed unless there is a potentially reversible cause. Because twin and multifetal gestations have a further increase in intravascular volume and cardiac output, indomethacin is often used for preterm labor to reduce fluid volume administration in these women. Prophylactic oral tocolytic agents are not generally administered.
2. ACOG Practice Bulletin No. 43, “Management of Preterm Labor” (Obstet Gynecol 2003; 101:1039–47), states that the choice and use of a tocolytic, including magnesium sulfate, should be determined by “clinical circumstances and physician preferences....” Why do so many U.S. physicians prefer to use magnesium sulfate?

Response from Drs. Brian M. Mercer and Amy A. Merlino:

Because many medications used in pregnancy have not been reviewed and approved by the Food and Drug Administration (FDA), and because many lack thorough study regarding optimal dosing, efficacy, and safety in pregnancy, obstetricians are often faced with prescribing treatments based on studies of lesser quality and without specific guidance. Tocolytic treatments are not an exception. Although the intravenous ritodrine received FDA approval for its evident benefit in reducing the risk of delivery within the first week, its use was not associated with significant improvements in neonatal outcomes. Side effects were not uncommon and its use in clinical practice waned. The popularity of magnesium sulfate as a tocolytic agent likely stems from the fact that its effects on myometrial contractility have been known for many years and it is useful for prevention of seizures in the setting of preeclampsia. Because of its widespread use in preeclampsia, caregivers are comfortable with its administration and monitoring for complications of therapy.
3. You suggest that magnesium sulfate and other tocolytics should be evaluated in trials with a placebo control group. What would you consider to be the critical argument or evidence to present to an institutional review board (IRB) justifying a placebo control group given the prevailing use of magnesium sulfate in most communities? Also, what would be your projections for recruitment to a study that has a placebo control group in light of the potential neuroprotective effects of magnesium sulfate?

Response from Drs. Brian M. Mercer and Amy A. Merlino:

Other than within isolated studies, tocolytic therapy has not been consistently shown to improve newborn outcomes when administered for preterm labor. Because reduction of newborn complications through pregnancy prolongation is the primary reason to administer tocolytic therapy, current evidence does not support the contention that magnesium or other tocolytic agents are better than placebo or no treatment. Since the FDA approval of ritodrine, numerous trials of tocolytic therapy have been undertaken. In general, these have compared different tocolytic regimens and have largely been underpowered to assess latency or newborn morbidities. Despite this, efficacy has been inferred when no differences between treatments were identified. Although tocolytics are commonly administered to enhance the potential for antenatal corticosteroid administration through brief pregnancy prolongation, evidence for a reduction in respiratory distress with this approach is lacking. Most women participating in the published randomized controlled trials of tocolytics remain pregnant for 24-48 hours despite receiving control or no therapy and will have adequate time for antenatal corticosteroid administration regardless of treatment. Failure to perform appropriately designed studies of adequate sample size has resulted in introduction of a series of tocolytic agents into clinical practice despite a lack of compelling
evidence as to their efficacy in reducing newborn complications. Millions of women have been treated with these tocolytic agents. Whether or not such treatment accomplishes its primary goal of improving newborn outcomes needs to be resolved in properly designed and conducted clinical trials.

The approaches to administration of magnesium sulfate for tocolysis and for neuroprotection should not be confused. The suggested benefit of tocolytic treatment is through pregnancy prolongation. The potential benefit of magnesium sulfate neuroprotection is through a direct effect on the fetus that is independent of pregnancy prolongation. Administration of magnesium sulfate for neuroprotection when preterm birth is inevitable is not inconsistent with a placebo-controlled study of tocolytic therapy with magnesium sulfate or other agents for pregnancy prolongation. If magnesium sulfate tocolysis does not prolong pregnancy adequately to improve acute newborn outcomes, it should not be given as a tocolytic simply because of its potential neuroprotective effects. This could divert attention away from other potentially effective treatments for preterm labor. Magnesium sulfate for neuroprotection after failed tocolysis is unlikely to impact significant short-term newborn outcomes, and could be administered to both study groups once a determination has been made that tocolysis has failed and delivery is inevitable.
4. In the routine, non-investigational care of women in preterm labor at your institution, what information is presented to patients regarding the possible neuroprotective effects of magnesium sulfate?

Response from Drs. Brian M. Mercer and Amy A. Merlino:

Like many centers around the country, we are currently considering the available literature regarding magnesium sulfate for neuroprotection and have not yet decided how to best incorporate this treatment into practice. The current literature is encouraging, and recently published meta-analyses have provided additional insights. However, the optimal targets for treatment, regimen, and timing have not yet been determined. If further studies of adequate size are done to address these issues, it will be years before their results are published. It is possible that individual patient-level meta-analysis can shed further light on the optimal approach to this intervention, but national discussion is needed in the meantime.

5. It has been well established that magnesium sulfate in combination with calcium channel blockers or beta-adrenergic agonists is not safe, but do you believe that there may be some value in the future investigation of the concurrent use of multiple tocolytics for the treatment of preterm labor?

Response from Drs. Brian M. Mercer and Amy A. Merlino:

Tocolysis is simply an attempt to cause uterine contractions to stop in the hope that the underlying process will correct itself. Absent a reversible/treatable cause of preterm labor, it is unlikely that substantial gains will be obtained with this approach. Optimally, individual regimens that are effective in
prolonging pregnancy adequately to reduce infant morbidity should be identified before these are studied in combination. Studies of combined treatments should be preceded by in-vitro studies that demonstrate synergistic effects, potentially by tocolytic agents that act through different mechanisms. Because there are a number of biological pathways that can lead to preterm labor, it may be that no single agent will be effective in all circumstances. If this is the case, it may be appropriate to consider progressive treatments with efficacious agents if the first does not work in a given clinical setting.

The above discussion with Drs. Mercer and Merlino reflects the authors’ opinions based on currently available information and does not reflect or represent the views of the Society for Maternal-Fetal Medicine. Practice will reasonably vary depending on location, resources, and individual patient characteristics.