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Is the end of an era here for magnesium sulfate tocolysis?

It's time for us to limit or stop this ineffective—and potentially harmful—regimen

Preterm labor and preterm delivery are major obstetric challenges, with an increasing incidence. Approximately 12% of all births in the United States occur preterm, with significant adverse sequelae for the newborn.

Treatments that have been tested for preterm labor include hydration, magnesium sulfate, atosiban, antibiotics, nitroglycerine, indomethacin, nifedipine, and betamimetics[1–6] (**TABLE**). Of these, Cochrane systematic reviews of the literature resulted in the conclusion that hydration, magnesium sulfate, and atosiban are not more effective than control treatments.[1–3] Both nifedipine and betamimetics were reported to be effective, compared with controls, in achieving short-term goals such as preventing delivery before 48 hours after initiation of treatment.[7,8]

There are no wonder drugs

It is unfortunate that there are no "wonder drugs" to prevent or treat preterm labor. It is likely that, until treatments target the underlying initiating mechanisms of preterm labor, our focus on treating contractions will be only marginally successful. A major problem is that most clinical trials that examine tocolysis have significant flaws, which limits the strength of the findings. Clinicians are left in the unenviable position of choosing among medications that are only marginally effective, such as calcium-channel blockers and betamimetics. However, clinicians can strive to avoid using tocolytics that have *no* clearly proven efficacy—such as magnesium sulfate.

I confess that I have prescribed magnesium sulfate tocolysis to dozens of women. I also am committed to changing my practice pattern in regard to this agent.

The long story of magnesium tocolysis

In the 1950s and 1960s, magnesium sulfate was not widely used as a tocolytic agent. In his single-author 1962 work, *A Textbook of Obstetrics,* Duncan E. Reid, MD, does not mention magnesium as a tocolytic agent.[9] Magnesium is discussed in the book as an effective agent for seizure prophylaxis and treatment in women with preeclampsia/eclampsia. In the 1985 (17th) edition of *Williams Obstetrics*, the authors were not enthusiastic about the use of magnesium tocolysis and cited a small trial that concluded that magnesium tocolysis was not superior to placebo.[10]

- **In the 1970s and 1980s, betamimetics were the most widely used tocolytic.** One betamimetic, ritodrine, achieved FDA approval as a tocolytic agent, but is no longer manufactured.

Many clinical trials reported that betamimetics significantly decreased the number of women with preterm labor delivering within 48 hours of initiation of treatment. However, both concern over the many troublesome adverse effects of betamimetics and the marginal efficacy of these agents guided obstetricians to begin using magnesium because it appeared to have fewer adverse effects.

- **Obstetricians were familiar with magnesium because of its marked efficacy in**

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***FAST** TRACK*

For tocolysis of preterm labor, say "No" to:

- magnesium sulfate
- atosiban
- hydration
- antibiotics

READ MORE

For more on magnesium sulfate tocolysis, see "Medical Verdicts" **on page 75**

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TABLE

Only 2 tocolytics pass muster in Cochrane reviews

AGENT (COCHRANE REFERENCE)	TRIALS AND SUBJECTS	IS THE AGENT AN EFFECTIVE TOCOLYTIC?	COCHRANE REVIEW ADVICE OR CONCLUSION
INEFFECTIVE			
Hydration[1]	2 trials, 228 subjects	Not superior to bed rest alone	No advantage over bed rest unless the woman is dehydrated
Magnesium[2]	23 trials, 2,036 subjects	Not superior to control treatments	Magnesium is ineffective at delaying birth or preventing preterm birth, compared with control treatments; its use is associated with increased morbidity for the infant
Atosiban[3]	11 trials, 1,695 subjects	Not superior to placebo	Caution against use
Antibiotics with intact membranes[4]	11 trials, 7,428 subjects	Reduced maternal infection, but no improvement in newborn outcomes; may increase complexity of neonatal infections	Not recommended for routine practice
MAY BE INEFFECTIVE			
Nitric oxide donors (nitroglycerine)[5]	5 trials, 466 subjects	Reduced risk of delivery before 37 weeks, but not 32 or 34 weeks; headache is a common side effect	Insufficient evidence to support use
Cyclooxygenase inhibitors (indomethacin)[6]	13 trials, 713 subjects	Reduction in delivery before 37 weeks compared with controls	Estimates are imprecise and should be interpreted with caution
EFFECTIVE COMPARED WITH CONTROLS			
Calcium-channel blockers[7]	12 trials, 1,029 subjects	Reduction in birth within 7 days of treatment and prior to 34 weeks' gestation; reduced likelihood of termination of therapy because of adverse effects compared with betamimetics	Calcium-channel blockers are preferable to other tocolytic agents; nifedipine* not evaluated against placebo; control groups typically received a betamimetic
Betamimetics[8]	17 trials, 1,320 subjects	Reduced risk of delivery within 48 hours; many adverse effects reported	Betamimetics delay delivery, allowing for completion of a course of glucocorticoids; multiple adverse effects occur

*Nifedipine is not approved by the FDA for treating preterm labor.

preventing eclamptic seizures. In vitro studies demonstrated that magnesium inhibited myometrial contractility by competing with calcium at the plasma membrane channels and by interfering with calcium activation of myosin light-chain kinase. In addition, there was the theoretical supposition that magnesium might be neuroprotective for the newborn (later proved incorrect). Given obstetricians' familiarity with magnesium for preeclampsia, it is easy to see how we embraced this treatment for preterm labor.

Safety, efficacy are questionable

Data from trials never clearly demonstrated that magnesium has a clinically significant tocolytic effect compared with "control" treatments. In a Cochrane review of magnesium tocolysis, neither improvement in the risk of delivery before 48 hours nor reduction in risk of birth before 34 or 37 weeks was observed, compared with control treatments. More recent data also suggest that magnesium may increase the risk of adverse neonatal outcomes, including death, especially at the upper end of the magnesium dose range.[2]

In the absence of demonstrated clinical efficacy and a concern over potentially negative neonatal effects, obstetricians should consider strictly limiting their use of magnesium for tocolysis.[11]

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INSTANT POLL

What is your opinion?

The tocolytic agent that you use most often to treat preterm labor is:

- ❑ Magnesium
- ❑ Terbutaline
- ❑ Nifedipine
- ❑ Indomethacin
- ❑ Hydration

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If not magnesium, what?

Cochrane analyses indicate that data reliably support the superiority of two tocolytics over controls: *calcium-channel blockers* and *betamimetics* (**TABLE**). The calcium-channel blocker *nifedipine* has been demonstrated to reduce the risk of birth within 7 days of initiating treatment and of birth prior to 34 weeks' gestation, compared with betamimetics. Women in preterm labor who are receiving a calcium-channel blocker are less likely to require discontinuation of the treatment due to adverse effects compared with women treated with a betamimetic. Given the demonstrated clinical efficacy of calcium-channel blockers and their few adverse side effects, these agents should be more widely used as tocolytics.

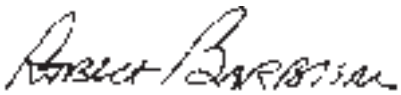
Nifedipine. This calcium-channel blocker has the longest and widest use as a tocolytic. A typical regimen is to administer nifedipine, 10 mg orally, every 20 minutes up to 4 doses as needed to reduce contractions and avoid hypotension. Maintenance treatment is nifedipine, 20 mg orally, every 4 to 8 hours. The maximum daily dosage is in the range of 120 to 180 mg. Nifedipine inhibits voltage-dependent L-type calcium channels, which leads to vascular and other smooth-muscle relaxation and negative inotropic and chronotropic effects on the heart.

Not surprisingly, nifedipine has been reported to be associated with many adverse cardiovascular side effects, including acute pulmonary edema,[12] arrhythmias,[13] and hypotension. Caution is advised when using nifedipine in multiple-gestation pregnancy and maternal cardiac disease.[14,15] Many authorities strongly caution against the use of nifedipine with magnesium or betamimetics because of additive adverse effects on the cardiovascular system.

If the goal of therapy is to complete a course of betamethasone, then nifedipine may be discontinued after 48 hours. Alternatively, the medication can be continued to achieve another endpoint, such as prolonging pregnancy up to 34 weeks when a condition such as polyhydramnios is present.

We need research

Preterm delivery is a major public health problem, and more research is required to identify the fundamental biologic causes of preterm labor. In the near future, basic science discoveries will be translated from the bench to the bedside, resulting in new treatments for the real causes of preterm labor that will be far superior to available tocolytics.



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