Preterm Labor: Evaluation & Treatment

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This activity is jointly-provided by SynAptiv and the Colorado Hospital Association

Safe Deliveries Project Partnership

- Colorado Hospital Association
- Anthem Blue Cross and Blue Shield Foundation
- March of Dimes Colorado/Wyoming Chapter
- Colorado Perinatal Care Quality Collaborative

Conflict of Interest Disclosure Statement

I have no financial interest or other relationships with the industry relative to the topics being discussed.

Objectives

At the end of the presentation, the provider will be able to:

- Define preterm labor
- Describe appropriate interventions in the setting of preterm labor to improve outcome
- Describe tocolytic therapies, their uses, mechanism of action, risks and goals of therapy

Presentation Overview

- Definitions
- Evaluation
  - Physical exam
  - Diagnostics
    - Imaging
    - FFN
    - GBS
- Treatment
  - Tocolysis
  - Antibiotics
  - Antenatal steroids
  - $MgSO_4$

Definitions

Preterm Birth and Preterm Labor

- Preterm birth: 20 0/7 – 36 6/7 weeks
- Preterm labor - Clinical criteria:
  - Regular uterine contractions & change in cervical dilation, effacement, or both
    or
  - Initial presentation with regular contractions and cervical dilation of at least 2cm

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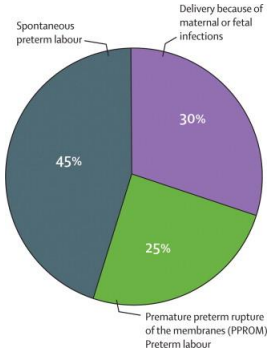
Preterm Birth



Goldenberg et al, Epidemiology and causes of preterm birth Lancet 2008; 371:75-84

Preterm Labor: Outcomes

- 30% resolve
- <10% deliver within 7d
- 50% deliver at term

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Assessments

Initial Evaluation

- Signs/symptoms
  - Change in type of vaginal discharge (watery, mucus, or bloody)
  - Increase in amount of discharge
  - Pelvic or lower abdominal pressure
  - Constant low, dull backache
  - Mild abdominal cramps, with or without diarrhea
  - Regular or frequent contractions or uterine tightening
  - Ruptured membranes
- Fetal monitoring and uterine activity monitoring
- Sterile speculum exam if rupture of membranes suspected
- Physical exam for diagnosis/etiology

Diagnostics

- Imaging
  - Fetal size
  - Amniotic fluid
  - Cervical length
- FFN
- Amniocentesis

Imaging

- Fetal size
- Amniotic fluid
- Cervical length

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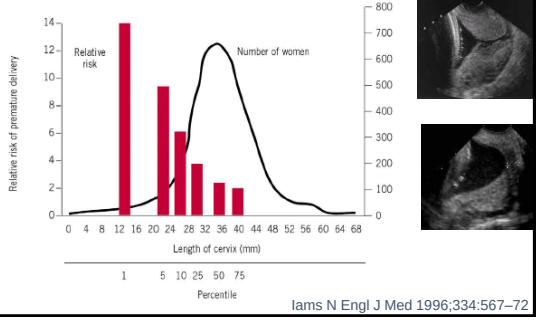
Cervical Length and Risk of PTD



Iams N Engl J Med 1996;334:567–72

Fetal Fibronectin

- A “glue like” protein produced by fetal cells at the interface between the chorion and decidua
- Present in vaginal secretions before 22 weeks and at end of pregnancy
- Generally not detectable between 22-34 weeks
  - Positive test at this time suggests risk of PTB, however false positive results are common
  - Negative test: low likelihood of delivery within 7d

The short-term prediction of preterm birth: a systematic review and diagnostic metaanalysis

Amy B. Boots, DO; Luis Sanchez-Ramos, MD; Dawn M. Bowers, MD; Andrew M. Kaunitz, MD; Javier Zamora, PhD; Peter Schlattmann, MD, PhD

Am J Obstet Gynecol 2014;210:54.e1-10.

Variable	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	DOR (95% CI)	AUC (95% CI)
Delivery within 48 hours						
fFN	0.62 (0.43–0.78)	0.81 (0.74–0.86)	3.3 (2.1–5.0)	0.47 (0.29–0.76)	7 (3–17)	0.74 (0.63–0.83)
FBM	0.75 (0.57–0.87)	0.93 (0.75–0.98)	10.4 (2.8–38.4)	0.27 (0.15–0.49)	37.8 (9–164)	0.83 (0.72–0.90)
TVS CL[a]	0.77 (0.54–0.90)	0.88 (0.84–0.91)	6.4 (4.7–8.7)	0.26 (0.12–0.58)	24 (9–65)	0.90 (0.88–0.93)
Delivery within 7 days						
fFN	0.75 (0.69–0.80)	0.79 (0.76–0.83)	3.6 (3.1–4.3)	0.31 (0.25–0.39)	11.5 (8–16)	0.84 (0.80–0.87)
FBM	0.67 (0.43–0.84)	0.98 (0.83–1.00)	31.6 (4.1–244)	0.34 (0.18–0.64)	93 (15–592)	0.91 (0.88–0.93)
TVS CL[a]	0.74 (0.58–0.85)	0.89 (0.85–0.92)	6.8 (5.1–9.2)	0.29 (0.17–0.49)	23 (12–46)	0.91 (0.67–0.98)

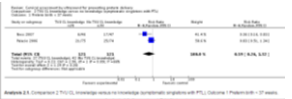
CI, confidence interval; CL, cervical length; DOR, diagnostic odds ratio; FBM, fetal breathing movements; fFN, fetal fibronectin; LR, likelihood ratio; TVS, transvaginal sonographic.

[a] 15 mm cutoff.

In women with signs and symptoms of preterm labor
- Absence of FBM: highest diagnostic accuracy predicting PTB
- fFN and TVS have limited and moderate accuracy, respectively, for the short-term prediction of delivery

Cervical Length: Cochrane Review

- 3 trials singletons with PTL, 290 women
- Insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL.
- Since there is a non-significant association between knowledge of TVU CL results and a lower incidence of PTB at less than 37 weeks in symptomatic women, we encourage further research.



Berghella et al. Cochrane Database 2013

FFN: Cochrane Review

- 5 trials of 474 women
- Although FFN is commonly used in labor and delivery units to help in the management of women with symptoms of preterm labor, currently there is not sufficient evidence to recommend its use.
- Since this review found an association between knowledge of FFN results and a lower incidence of preterm birth before 37 weeks, further research should be encouraged.

Berghella et al. Cochrane Database 2008

Diagnostics

- Imaging
  - Fetal size
  - Amniotic fluid
- Imaging: cervical length
- FFN

•RCTs do not find benefit
•PPV of either is poor and should not direct management

- Amniocentesis

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ACOG Practice Bulletin: FFN, CL

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

▶ The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms.

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Treatment

- Tocolysis
- Antibiotics
- Antenatal steroids
- $MgSO_4$

Tocolysis

Goals of Tocolysis

- Reduce neonatal morbidity and mortality
  - By delaying delivery
  - Allow for administration of corticosteroids
  - Allow for transfer to tertiary care center

Box 1. Contraindications to Tocolysis

- Intrauterine fetal demise
- Lethal fetal anomaly
- Nonreassuring fetal status
- Severe preeclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis
- Preterm premature rupture of membranes*
- Maternal contraindications to tocolysis (agent specific)

*In the absence of maternal infection, tocolytics may be considered for the purposes of maternal transport, steroid administration, or both.

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Tocolytic Therapy

Rationale

- Prevent PTD
- Prolong 48h for corticosteroids
- Improve neonatal outcome

Tocolytic Agents

- β-sympathomimetic agents
- Prostaglandin synthesis inhibitors
- Calcium antagonists
- Oxytocin analogues
- Magnesium sulfate

β-sympathomimetic Agents

- Bind to β-2 receptors in uterus
- Activates adenylate cyclase
- Produces cAMP
- cAMP relaxes smooth muscle

Ritodrine
Terbutaline
Salbutamol
Isoxsuprine

Significant side effects

- Chest pain
- Palpitations
- Tachycardia
- Nausea, vomiting
- Cardiac arrthymias
- Pulmonary edema
- Increase Glc, K
- Headache
- Tremor

Contraindications

- Cardiac disease, hyperthyroidism, unstable DM

β-sympathomimetic Agents

- RCTs
- Meta-analyses:
  - Delay delivery by >48 h, perhaps 7 d
    - Beneficial for corticosteroids
  - Do not reduce PTD < 37 weeks
  - Do not reduce perinatal death/neonatal morbidity

Terbutaline: Black Box Warning

FDA Drug Safety Communication: New warnings against use of terbutaline to treat preterm labor

Safety Announcement

[02-17-2011] The U.S. Food and Drug Administration (FDA) is warning the public that injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. The agency is requiring the addition of a *Boxed Warning* and *Contraindication* to the terbutaline injection label to warn against this use. In addition, oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns. The agency is requiring the addition of a *Boxed Warning* and *Contraindication* to the terbutaline tablet label to warn against this use.

U.S. Food and Drug Administration

Prostaglandin Synthesis Inhibitors

Indomethacin
Sulindac
Nimesulide
Celecoxib
Rofecoxib

- Blocks cyclo-oxygenase (COX), rate limiting enzyme in the production of PG
- Cox-2 important in labor

Significant side effects

- Premature closure of ductus arteriosus
- Renal failure, Cerebral hemorrhage
- Necrotizing enterocolitis
- GI irritation, altered immune response

Contraindications

- Peptic ulcer disease
- Oligohydramnios
- Hematological, hepatic or renal dysfunction

Prostaglandin Synthesis Inhibitors

- Indomethacin: systematic reviews
  - Delay delivery by >48 h, perhaps 7 d
    - Beneficial for corticosteroids
  - Do not reduce PTD < 37 weeks
  - Do not reduce perinatal death/neonatal morbidity

Calcium Antagonists

Nifedipine

- Block Ca^{2+} channels
- Prevent influx of Ca^{2+} into myometrial cells, prevent myometrial contraction
- Suppresses release of intracellular Ca^{2+} stores

Significant side effects

- Altered cardiac conduction
- Tachycardia
- Hypocalcemia

Contraindications

- Hypotension
- Congestive heart failure
- Aortic stenosis

**concurrent use of Ca-channel blockers and $MgSo_4$ may result in profound hypotension or potentiate neuromuscular blockade

Calcium Antagonists

- RCTs:
  - No placebo-controlled RCTs
  - vs $MgSO_4$: n=3 RCTs
- Meta-analyses:
  - Delay delivery by >48 h, and >34 weeks
    - Beneficial for corticosteroids
  - Do not reduce PTD < 37 weeks
  - Do not reduce perinatal death/neonatal morbidity

Oxytocin Analogues

Atosiban

- Increase in myometrial oxytocin receptor expression
- Oxytocin antagonist: Atosiban

Significant side effects

- Nausea
- Headache
- tachycardia
- Hyperglycemia
- Hypotension
- palpitations

Contraindications

- none

Oxytocin Analogues

- RCTs: 2 vs placebo; 4 vs beta-mimetics
  - No difference in perinatal outcome vs placebo
  - Fewer maternal side-effects than beta-mimetics
  - No benefit in delaying or preventing preterm birth
  - Atosiban was associated with more infant deaths in one placebo controlled trial.

Magnesium Sulfate

- Competition with calcium ions
- Inhibition of uterine smooth muscle contractility
- Increases repolarization time between UCs and decreasing force of contractions

Significant side effects

- Chest pain
- Flushing
- Nausea, vomiting
- Pulmonary edema

Contraindications

- Myasthenia gravis
- Heart block

Magnesium Sulfate

- RCTs
  - $MgSO_4$ vs placebo (n=2)
  - $MgSO_4$ vs B-mimetics (n=4)
  - $MgSO_4$ vs Nifedipine (n=3)
- Systematic review:
  - Does not delay delivery
  - Does not reduce PTD < 37 weeks
  - Does not reduce perinatal death/neonatal morbidity

Tocolytic Therapy

Summation of evidence

- ~~Prevent PTD~~
- Prolong 48h for corticosteroids
- ~~Improve neonatal outcome~~

Tocolytic Rx: Summation of Evidence

- First line: Nifedipine 10-20 mg q 20 min x 3 doses then 10-20 mg q 3-4 hours (max: 120 mg/day)
- Second line: Indocin 25-50 mg q 6 hours (max: 200 mg/day)

24-32 weeks:
1. Indomethacin
2. Nifedipine

32-34 weeks
1. Nifedipine
2. Terbutaline

Single agents only
Discontinue 48h after ACS administered

Tocolysis: Timing

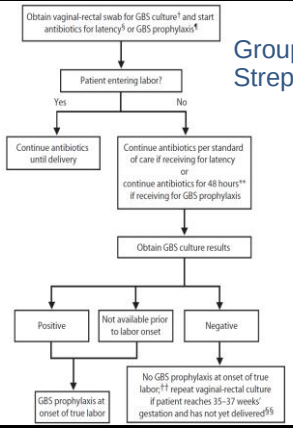
- Lower GA limit:
  - expert opinion; based on clinical scenario (e.g. appendectomy at 20 weeks with contractions)
  - Workshop on periviability: 22 0/7 if steroids being administered
  - ACOG/SMFM: 24 0/7; consider at 23 weeks based on individual circumstances
- Upper GA limit
  - ACOG/SMFM: 34 weeks

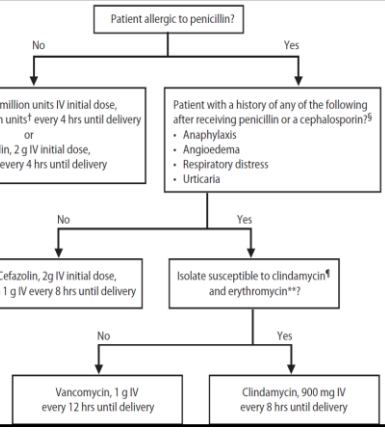
Antibiotics

Group B Streptococcus

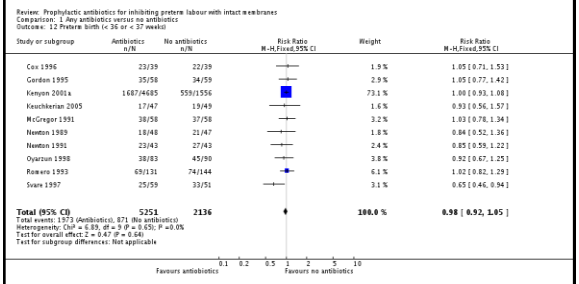
- 25% of pregnant women are asymptomatic carriers
- If untreated 1-2% of babies infected during childbirth (meningitis, pneumonia, sepsis)
  - Higher risk if preterm
- Standard testing at 35-37 weeks
  - Preterm labor – test and initiate treatment

Group B Streptococcus



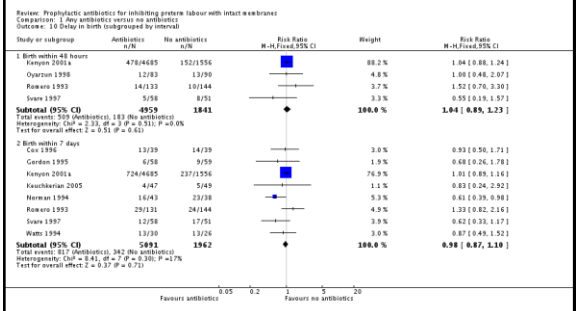


Preterm Birth: Antibiotics in Intact Membranes



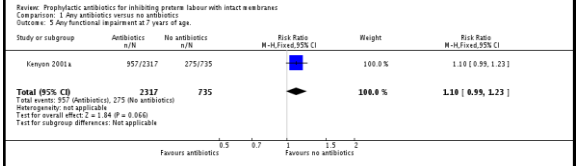
Flenady et al. Cochrane Database of Systematic Reviews 2013(12)

Antibiotics in Intact Membranes: Effect on Delivery <48h or <7d



Flenady et al. Cochrane Database of Systematic Reviews 2013(12)

Antibiotics in Intact Membranes: Long-term Outcome



Flenady et al. Cochrane Database of Systematic Reviews 2013(12)
Kenyon et al. Lancet 2008;372:1319–27

Cochrane Review: Antibiotics

- No benefit in important neonatal outcomes with the use of prophylactic antibiotics for women in preterm labor with intact membranes, although maternal infection may be reduced.
- Of concern, is the finding of short- and longer-term harm for children of mothers exposed to antibiotics.
- The evidence supports not giving antibiotics routinely to women in PTL with intact membranes in the absence of overt signs of infection.

Flenady et al. Cochrane Database 2013

Antibiotics & PTL Summary

Thus, antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes. This recommendation is distinct from recommendations for antibiotic use for preterm premature rupture of membranes and group B streptococci carrier status.

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Antenatal Steroids

Antenatal Corticosteroids

- Improves outcome for infants born preterm
  - Reduces respiratory distress syndrome
  - Intraventricular hemorrhage
  - Necrotizing enterocolitis
- Effect lasts 7 days

Antenatal Corticosteroids

The most beneficial intervention for improvement of neonatal outcomes among patients who give birth preterm is the administration of antenatal corticosteroids. A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation, and may be considered for pregnant women starting at 23 weeks of gestation, who are at risk of preterm delivery within 7 days (35, 36). A Cochrane meta-analysis reinforces the beneficial effect of this therapy regardless of membrane status and concludes that a single course of antenatal corticosteroids should be considered routine for all preterm deliveries (37).

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Antenatal Corticosteroids: Benefits

• Reduced	(RR, 95% CI)
• Neonatal morbidity and mortality	
• RDS	(0.66, 0.59-0.73)
• Intracranial hemorrhage	(0.54, 0.43-0.69)
• Necrotizing enterocolitis	(0.46, 0.29-0.74)
• Death	(0.69, 0.58-0.81)

Antenatal Corticosteroids: Dosing

- Two 12mg doses betamethosone IM 24h apart
- Four 6-mg doses dexamethasone IM q12h

*no benefit with accelerated dosing, even if delivery appears imminent

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Antenatal Corticosteroids: Dosing

cian to be likely to give birth within the next week. A single repeat course of antenatal corticosteriods should be considered in women whose prior course of antenatal corticosteroids was administered at least 7 days previously and who remain at risk of preterm birth before 34 weeks of gestation (41). However, regularly scheduled repeat courses or multiple courses (more than two) are not currently recommended.

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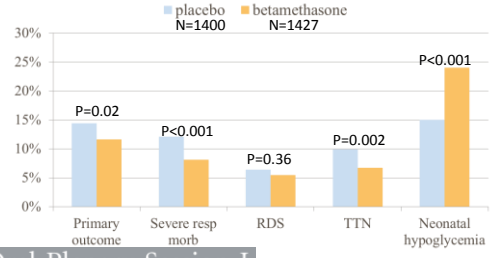
ALPS: Antenatal Late Preterm Steroids

- **Design:** Double-masked placebo-controlled trial of antenatal corticosteroids vs placebo in late preterm period (34-37 weeks)
- **Aim:** To determine if ACS between 340 - 366 weeks with anticipated delivery reduces need for neonatal respiratory support
- **Sample size:** 2,800 women

ACS for women at risk for late PTB(34 0/7 – 36 6/7) associated with decreased respiratory morbidity

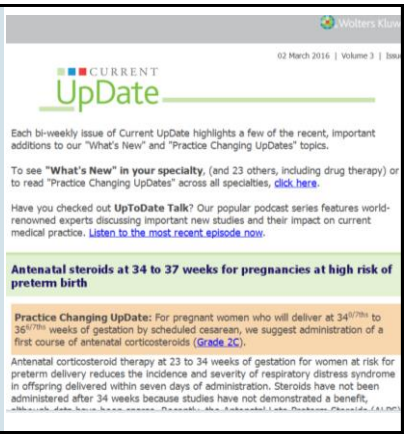


Oral Plenary Session I

Thursday, February 4, 2016 • 8:00 AM – 1(

Gyamfi-Bannerman et al NEJM 2016

Practice Guidance



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CURRENT UpDate

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Antenatal steroids at 34 to 37 weeks for pregnancies at high risk of preterm birth

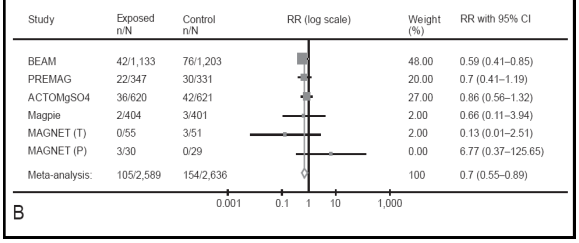
Practice Changing UpDate: For pregnant women who will deliver at $34^{0/7ths}$ to $36^{6/7ths}$ weeks of gestation by scheduled cesarean, we suggest administration of a first course of antenatal corticosteroids (Grade 2C).

Antenatal corticosteroid therapy at 23 to 34 weeks of gestation for women at risk for preterm delivery reduces the incidence and severity of respiratory distress syndrome in offspring delivered within seven days of administration. Steroids have not been administered after 34 weeks because studies have not demonstrated a benefit,

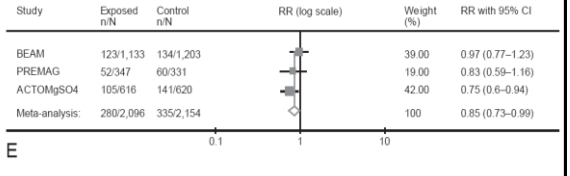
Magnesium for Fetal Neuroprotection

- Observational studies suggested association between prenatal $MgSO_4$ and reduced neurologic morbidities
- Several RCTs evaluated role in neuroprotection

Meta-analysis of all RCT
Any CP
Costantine et al. Obstet Gynecol 2009;114:354–64



Meta-analysis of all RCT
Death or Moderate-Severe CP
Costantine et al. Obstet Gynecol 2009;114:354–64



$MgSO_4$ Considerations

- To prevent one case of cerebral palsy
  - Treat 56 (overall)
  - Treat 46 (<30 weeks)
- To prevent one eclamptic convulsion
  - Treat 71 with severe disease
  - Treat 400 with mild disease

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Patient Safety Checklist ✓ Number 7 • August 2012

MAGNESIUM SULFATE BEFORE ANTICIPATED PRETERM BIRTH FOR NEUROPROTECTION

Date_____ Patient _____ Date of birth_____ MR # _____
Physician or certified nurse–midwife Last menstrual period

Criteria (1):

❑ Gestational age less than or equal to 31 6/7 weeks

and

❑ Singleton or multiple pregnancy at risk for delivery within the next 30 minutes to 24 hours

and either

❑ Active preterm labor with cervix 4–8 cm dilated or preterm premature rupture of membranes if rupture occurred later than 22 weeks

or

❑ Indicated preterm birth within the next 24 hours. (If the planned delivery is for severe preeclampsia or hemolysis, elevated liver enzymes, and low platelet count [HELLP], the full antiseizure magnesium sulfate regimen should be administered as minimal therapy.)

COMMITTEE OPINION

Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection

COMMITTEE OPINION

Conclusions

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 include the following:

- Prevention and treatment of seizures in women with preeclampsia or eclampsia.
- Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery.

Historical Therapies / Interventions

- Bed rest
- Hydration

No evidence to support
Bedrest – some evidence of harm

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Level A Recommendations:

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation, and may be considered for pregnant women starting at 23 weeks of gestation, who are at risk of preterm delivery within 7 days.
- Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.
- The evidence supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.
- Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose.
- Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes.

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Level B Recommendations:

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

- A single repeat course of antenatal corticosteroids should be considered in women whose prior course of antenatal corticosteroids was administered at least 7 days previously and who remain at risk of preterm birth before 34 weeks of gestation.
- Bed rest and hydration have not been shown to be effective for the prevention of preterm birth and should not be routinely recommended.
- The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms.

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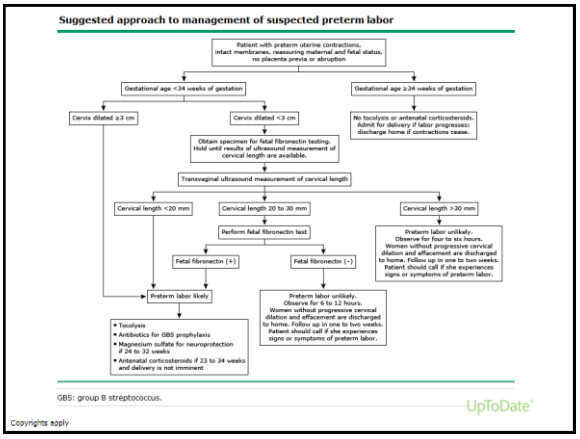

Preterm Labor Evaluation & Treatment

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  - Physical exam
  - Diagnostics
    - Imaging
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- Treatment
  - Tocolysis
  - Antibiotics
  - Antenatal steroids
  - $MgSO_4$

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Questions?