Updates on Management of Preterm Labor and Premature Rupture of Membranes

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Disclosures
• I have no financial disclosures related to this presentation

Goals
• To discuss recent data on antenatal corticosteroids for both PTL and PPROM
• To discuss recent data on periviability
• To discuss recent data on pessary for PTL/short cervix
• All involve spontaneous PTB (PTL/PPROM) and not iatrogenic/medically indicated PTB (preeclampsia, IUGR, etc.)

The Good
Preterm birth rates

Table E. Distribution of births, by selected gestational age categories: United States, 2007-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Births</th>
<th>37 weeks or more</th>
<th>36-37 weeks</th>
<th>35-36 weeks</th>
<th>34-35 weeks</th>
<th>33-34 weeks</th>
<th>32-33 weeks</th>
<th>31-32 weeks</th>
<th>30-31 weeks</th>
<th>29-30 weeks</th>
<th>28-29 weeks</th>
<th>27-28 weeks</th>
<th>26-27 weeks</th>
<th>25-26 weeks</th>
<th>24 weeks or less</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
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<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
</tr>
<tr>
<td>2014</td>
<td>3,986,079</td>
<td>55.5%</td>
<td>3,867,058</td>
<td>97.2%</td>
<td>119,021</td>
<td>3.0%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>481</td>
<td>0.1%</td>
<td>106</td>
<td>0.0%</td>
<td>104</td>
</tr>
<tr>
<td>2013</td>
<td>3,802,181</td>
<td>55.2%</td>
<td>3,632,490</td>
<td>95.4%</td>
<td>169,691</td>
<td>4.2%</td>
<td>2,042</td>
<td>0.3%</td>
<td>1,024</td>
<td>0.3%</td>
<td>461</td>
<td>0.1%</td>
<td>22</td>
<td>0.0%</td>
<td>21</td>
</tr>
<tr>
<td>2012</td>
<td>3,902,081</td>
<td>55.3%</td>
<td>3,743,990</td>
<td>96.2%</td>
<td>158,091</td>
<td>4.0%</td>
<td>2,042</td>
<td>0.3%</td>
<td>1,024</td>
<td>0.3%</td>
<td>462</td>
<td>0.1%</td>
<td>20</td>
<td>0.0%</td>
<td>18</td>
</tr>
<tr>
<td>2011</td>
<td>3,963,080</td>
<td>55.6%</td>
<td>3,809,870</td>
<td>95.8%</td>
<td>153,210</td>
<td>3.9%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>461</td>
<td>0.1%</td>
<td>17</td>
<td>0.0%</td>
<td>17</td>
</tr>
<tr>
<td>2010</td>
<td>3,898,388</td>
<td>55.3%</td>
<td>3,719,326</td>
<td>95.0%</td>
<td>179,062</td>
<td>4.5%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>462</td>
<td>0.1%</td>
<td>20</td>
<td>0.0%</td>
<td>18</td>
</tr>
<tr>
<td>2009</td>
<td>4,130,883</td>
<td>55.4%</td>
<td>3,924,762</td>
<td>97.6%</td>
<td>206,121</td>
<td>5.0%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>462</td>
<td>0.1%</td>
<td>18</td>
<td>0.0%</td>
<td>18</td>
</tr>
<tr>
<td>2008</td>
<td>4,157,864</td>
<td>55.4%</td>
<td>3,946,898</td>
<td>95.1%</td>
<td>210,966</td>
<td>5.1%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>462</td>
<td>0.1%</td>
<td>18</td>
<td>0.0%</td>
<td>18</td>
</tr>
<tr>
<td>2007</td>
<td>4,214,239</td>
<td>56.0%</td>
<td>4,008,184</td>
<td>95.2%</td>
<td>206,055</td>
<td>4.8%</td>
<td>2,042</td>
<td>0.5%</td>
<td>1,024</td>
<td>0.3%</td>
<td>462</td>
<td>0.1%</td>
<td>18</td>
<td>0.0%</td>
<td>18</td>
</tr>
</tbody>
</table>

Incidence of late PTB – 34-37 weeks

- 6.8% of all births
- Over 70% of all preterm births
- Need to optimize outcomes in this group!
Antenatal corticosteroids 34-37

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Betamethasone (N=1427)</th>
<th>Placebo (N=1400)</th>
<th>Relative Risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (CPAP or high flow nasal cannula)</td>
<td>165 (11.6%)</td>
<td>202 (14.4%)</td>
<td>0.80 (0.66-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe respiratory complications</td>
<td>111 (8.1%)</td>
<td>169 (12.1%)</td>
<td>0.67 (0.53-0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory distress (RDS)</td>
<td>79 (5.5%)</td>
<td>89 (6.4%)</td>
<td>0.87 (0.56-1.17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Transient tachypnea of the newborn (TTN)</td>
<td>95 (6.7%)</td>
<td>138 (9.9%)</td>
<td>0.68 (0.53-0.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>BPD</td>
<td>2 (0.1%)</td>
<td>9 (0.6%)</td>
<td>0.22 (0.02-0.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Composite of RDS, TTN, or apnea</td>
<td>198 (13.9%)</td>
<td>249 (17.8%)</td>
<td>0.78 (0.66-0.93)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

How to implement

- A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation, including for those with ruptured membranes and multiple gestations.
- A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.
- Do not delay PPROM induction at late preterm gestational ages.
Standard PPROM Management

- Early term and term (>37 0/7 weeks) – deliver!
- Late preterm (34 0/7 – 36 6/7 weeks) – deliver!
- Preterm (24 0/7 – 33 6/7 weeks)
  - Expectant management
  - Antibiotics, ACS
  - Magnesium sulfate between 24 0/7 and 32 0/7 weeks
- Periviable GA (before 24 0/7 weeks)
  - Counseling
  - Antibiotics can be considered as early as 20 0/7 weeks
  - No ACS before viability
  - No tocolysis before viability
  - No magnesium sulfate before viability

ACS and PPROM 34-37 weeks

- Recent data indicate that administration of betamethasone in the late preterm period between 34 0/7 weeks and 36 6/7 weeks reduces respiratory morbidity in newborns.

  “It is assumed that patients with preterm PROM will benefit from betamethasone in the late preterm period, but because the study design excluded patients who had received corticosteroids earlier in the pregnancy, it is unknown whether there is any benefit to a second course of betamethasone in the late preterm period in these patients.”

The Bad

A 30 year old presents at 30 0/7 weeks with PTL. Which tocolytic do you administer?

A. Magnesium sulfate
B. Calcium channel blocker (Nifedipine)
C. COX inhibitor (Indocin)
D. Beta 2 adrenergic agonist (Terbutaline)
E. Oxytocin receptor blocker (Ritodrine)
F. All of the above!
G. No tocolytic!
Tocolytics

Calcium channel blockers (mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth thus, theoretically, allowing time for administration of antenatal corticosteroids and transfer to higher level care.

Calcium channel blockers were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects.

Calcium channel blockers may also have some benefits over ORAs and magnesium sulphate, although ORAs result in fewer maternal adverse effects.

Tocolytics – which one to use?

In this review, no clear benefit for COX inhibitors was shown over placebo or any other tocolytic agents.

While some benefit was demonstrated in terms of postponement of birth for COX inhibitors over placebo and betamimetics and also maternal adverse effects over betamimetcs and MgSO4...there is insufficient evidence on which to base decisions about the role of COX inhibition for women in preterm labour.
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).”

Cochrane data review 2014

**Magnesium sulfate for neuroprotection**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Magnesium (N=1041)</th>
<th>Placebo (N=1095)</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or severe CP or death</td>
<td>118/1041 (11.3%)</td>
<td>128/1095 (11.7%)</td>
<td>0.97 (0.77-1.23)</td>
<td>0.8</td>
</tr>
<tr>
<td>Moderate or severe CP alone</td>
<td>20/1041 (1.9%)</td>
<td>38/1095 (3.5%)</td>
<td>0.55 (0.32-0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death alone</td>
<td>99/1041 (9.5%)</td>
<td>93/1095 (8.5%)</td>
<td>1.12 (0.85-1.47)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Rouse D et al. NEJM 2014

**Magnesium Sulfate**

- 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.
- ACOG and SMFM continue to support the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for 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.

ACOG Committee Opinion 652 2016
Tocolytics vs. MgSO4 for neuroprotection

- Beta-adrenergic agents, calcium channel blockers, NSAIDs can be used for short term (up to 48 hours) to allow corticosteroid administration
- If MgSO4 is used for neuroprotection and patient still experiencing contractions, a different tocolytic can be used for PTL management

Periviability

Periviable delivery - survival

<table>
<thead>
<tr>
<th>Birth period</th>
<th>Gestational age in weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>0/77 (9.0%)</td>
</tr>
</tbody>
</table>
Periviable delivery - Moderate disability

- ACOG/SMFM Consensus 2016

**Are all “disability the same”?**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>GA</td>
<td>22-27/6/7 wk EGA</td>
<td>22-26/6/7 wk EGA</td>
<td>&lt;27 wk EGA</td>
<td>22-25 wk EGA</td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>2 years</td>
<td>3 years</td>
<td>2.5 years</td>
<td>36-42 months</td>
</tr>
<tr>
<td>% Follow-up of eligible survivors</td>
<td>163 (95%)</td>
<td>576 (55%)</td>
<td>415 (90%)</td>
<td>562 (72%)</td>
</tr>
<tr>
<td>Blind</td>
<td>0</td>
<td>1%</td>
<td>0.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Developmental impairment</td>
<td>None/&lt;1SD: 52%</td>
<td>1-2SD: 12%</td>
<td>2-3SD: 12%</td>
<td>3SD: 4%</td>
</tr>
<tr>
<td>Cerebral palsy (CP) or motor delay</td>
<td>Any CP: 9.8%</td>
<td>Any CP: 14%</td>
<td>Moderate motor: 3%</td>
<td>Severe motor: 5%</td>
</tr>
<tr>
<td>Overall disability or impairment</td>
<td>None: 51%</td>
<td>Mild: 29%</td>
<td>Moderate: 16%</td>
<td>Severe: 4%</td>
</tr>
</tbody>
</table>

**What is the earliest GA you administer corticosteroids for PTL/PPROM?**

- A. 22 0/7 weeks
- B. 22 5/7 weeks
- C. 23 0/7 weeks
- D. 23 5/7 weeks
- E. 24 0/7 weeks
- F. 25 0/7 weeks

**What is the earliest GA you administer tocolytics?**

- A. 22 0/7 weeks
- B. 22 5/7 weeks
- C. 23 0/7 weeks
- D. 23 5/7 weeks
- E. 24 0/7 weeks
- F. 25 0/7 weeks
What is the earliest GA you perform a cesarean delivery for fetal indications?

A. 22 0/7 weeks
B. 22 5/7 weeks
C. 23 0/7 weeks
D. 23 5/7 weeks
E. 24 0/7 weeks
F. 25 0/7 weeks

Unanswered questions

- When to administer ACS – 22 5/7 or 23 0/7 or 23 5/7 or 24 0/7?
- When to initiate tocolysis and which one is the best?
- When to transport to tertiary care center?

Opportunities for transport – CA data

- “To facilitate needed transfers, hospitals without the optimal resources for maternal, fetal, and neonatal care needed for periviable birth should have policies and procedures in place to facilitate timely transport to a receiving hospital.”
- Of 1,508,143 births in the study population 13,919 were VLBW births (<1500 gm.)
- 14.9% of VLBW births occurred in non-Level III centers – 8.4% in Level I and 6.5% in Level II centers.
- The median % of VLBW births at Level I hospitals was 0.26% annually, while the median % at Level II hospitals was 0.47% annually.
Opportunities for transport

<table>
<thead>
<tr>
<th>Table 1. Antimortem length of stay for very low birth weight (VLBW) infant births, 2008 to 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>vLBW births, n</td>
</tr>
<tr>
<td>Statistics</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Mode</td>
</tr>
<tr>
<td>Std.</td>
</tr>
<tr>
<td>Interquartile</td>
</tr>
<tr>
<td>range (25-75th)</td>
</tr>
<tr>
<td>Total range</td>
</tr>
</tbody>
</table>

Robles et al J Perinatology 2016

The Ugly

Why do we care about the cervix?

- Placental Abruption/bleeding
- Cervical problem (Cone biopsy/insufficiency)
- Hormonal changes
- Uterine Over-distension (twins/polyhydramnios)
- Infection/Inflammation
- Genetics
- Short Cervix
- PPROM/PTL
- PTB
- Uterine contractions

How do we assess the cervix today?

Figure 2. Photograph of the silicone cervical cap
(A) inner diameter, (B) outer diameter, (C) lateral view
How do we assess the cervix today?

Cervical measurement at 16-24 weeks can predict PTB

Can we do something about it?

- Women with *no history of preterm birth*:
  - *Vaginal progesterone* can reduce PTB before 34 weeks by 45% (34.4% to 19.2%) and PTB before 35 weeks by 38% (23.3% to 14.5%)
- Women with *history of preterm birth*:
  - Weekly 17P irrespective of cervical length
  - *Cerclage* in women with a short cervix can reduce PTB before 35 weeks by 30%

What are the limitations of our current knowledge?

- Cervical length by itself is limited
- May be over-treating some women (recurrent PTB rate is only 30%)
- May be under-diagnosing!
- What is happening in the cervical stroma?
- Gap in knowledge about changes within the cervical stroma, and about appropriate tools to assess those changes
Cervical changes during pregnancy and delivery

- Softening
- Shortening
- Dilation
- Recovery

Collagen remodeling

Tissue hydration

New(ish) imaging modalities

- Cervical attenuation
- Shear wave imaging
- Cervical consistency index
- Cervical elastography

McFarlin BL et al. Ultrasound Obstet Gynecol 2014
Feltovich H et al. AJOG 2012
Carlson LC et al. Ultrasound Obstet Gynecol 2014
McFarlin BL et al. Ultrasound in Med and Biol 2015

Cervical pessary

- Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial

- Cervical pessary use could prevent preterm birth in a population of appropriately selected at-risk women previously screened for cervical length assessment at the midtrimester scan.

Goya M et al Lancet 2012

More recent data

- A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth

- Among girls and women with singleton pregnancies who had a short cervix, a cervical pessary did not result in a lower rate of spontaneous early preterm delivery than the rate with expectant management.

Nicolaides KH et al NEJM 2016
Pessary in all twins

Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial

Sophie Clem, Edvard Schuit, Hendrik Hageman, Jelle Weel, Koen de Beer, Katja Bloemenkamp, Josine Bruins, Hans Duvekot, Bax Meijerink, Maureen Franseman, Ingrid Gaugel, Irene de Graaf, Martijn Goudsblom, Dimitri Papalexopulos, Paulien Perret, Martine Peraard, Lodeth Schepers, Marie Slikker, Jan Spiering, Harry Visser, Willem van Wyllengaarden, Malburga Weiskir, MarieAnne van Peppene, Ben Williams, Dilshad Dadabhoy

- In unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.

Liem S et al Lancet 2013

Pessary in twins with short cervix

Cervical Pessary and Vaginal Progesterone in Twin Pregnancies With a Short Cervix

Nathana S. Fox, MD, Simi Gupta, MD, Jennifer Lam-Rochlin, MD, Andre Reherber, MD, Chad K. Klaus, MD, and Daniel H. Saltzman, MD

- For twin pregnancies with a short cervix, the addition of a cervical pessary to vaginal progesterone is associated with prolonged pregnancy and reduced risk of adverse neonatal outcomes.

Fox NS et al Obstet Gynecol 2016

Pessary in twins with short cervix

Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PCEP-Twins)

Maria Goya, MD, PhD; Maria de la Calle, MD, PhD; Laura Pratcorona, MD; Carme Mercado, MD; Carola Rock, MD; Begoña Muñoz, MD, PhD; Miquel Juan, MD; Ariana Serrano, MD, Elisa Llurba, MD, PhD; Teresa Higuera, MD, PhD; Elena Carrera, MD, PhD; Luis Cabero, MD, PhD, on behalf of the PCEP-Twins Trial Group

- The insertion of a cervical pessary was associated with a significant reduction in the SPB rate. We propose the use of a cervical pessary for preventing preterm birth in twin pregnancies of mothers with a short cervix.

The pessary storm

Management in women with a history of preterm birth

Prior PTB and 2nd trimester loss risk
What about more than one PTB?

Iams J et al Am J Obstet Gynecol 2010

GA of prior PTB

- Women whose prior pregnancy ended between 16 and 20 weeks have a risk of recurrent preterm birth that equals or exceeds the recurrence risk for women whose prior preterm birth occurred after 20 weeks.
- Thus, any woman with a prior birth between 16 0/7 and 36 6/7 weeks should be evaluated as possibly having had a preterm birth, whether the fetus was born alive or stillborn.

Iams J et al Am J Obstet Gynecol 2010

Management of women with prior PTB

- Evaluate medical, obstetrical, or fetal causes thoroughly.
- Obstructed or preexisting/new placenta.
- Medical causes: hypertension, lupus, other.
- Fetal causes: aneuploidy, polyhydramnios, fetal death.

Iams J et al Am J Obstet Gynecol 2010

Not all progesterone is the same

Iams J et al Am J Obstet Gynecol 2010

Conclusion

- Antenatal corticosteroids should now be administered between 34 0/7 and 37 0/7 weeks in women expected to deliver before 37 0/7 weeks who have not previously received ACS
- Work with your local institution and neonatology team to implement periviability algorithm
- Pessary may be effective in twin gestations with short cervix – need more data
- Screen women with a history of PTB with serial cervical length exams between 16 and 24 weeks, and don’t forget 17P!
- Vaginal progesterone and 17P are different medications and should be used for different indications

Thank you