Prevention of preterm birth in twins

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Twin deliveries and birth rate in USA


Chauhan et al: Am J Ob Gyn, 2010
High rates of MZ twins (1-5%) among ART births. Blickstein, 1999
Prevention of preterm birth in twins

1. Complications twins vs. singleton
   1. As for pregnant women
   2. As for neonates

2. Tests in asymptomatic twins to prevent preterm birth
   1. U/S measurement of cervical length
   2. Fetal fibronectin

3. Treatment during pregnancy to prevent preterm birth
   1. Tocolytics
   2. Progesterone
   3. Cervical cerclage
   4. Bed rest, home monitoring

4. Treatment of preterm labor in twins
   1. Tocolytics
   2. Cervical pessaries
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Differences in pregnancy according the number of fetuses

<table>
<thead>
<tr>
<th></th>
<th>Initial number of fetuses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Deliveries</td>
<td>7650</td>
</tr>
<tr>
<td>PIH</td>
<td>4,8</td>
</tr>
<tr>
<td>PPROM</td>
<td>3,1</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>12,2</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>26,1</td>
</tr>
</tbody>
</table>

*ESHRE Capri Group, Hum Reprod, 2000*
Risks of twin pregnancies for the woman

- Twin pregnancy increases the risk for
  - Hypertension
  - Premature rapture of membranes

Pregnant woman is in more danger in twin than in singleton pregnancy !!!

- Hospitalization
- Cesarean Section
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Preterm birth in 2006
Twins vs. Singletons

Gestational-age-specific neonatal mortality rates in singletons, twins, and triplets
### Mortality and morbidity in multiples till infancy

<table>
<thead>
<tr>
<th>Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>0</td>
<td>x4</td>
<td>x17</td>
<td></td>
</tr>
<tr>
<td>Infant mortality</td>
<td>0</td>
<td>x7</td>
<td>x20</td>
<td></td>
</tr>
<tr>
<td>Major handicap</td>
<td>0</td>
<td>0</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>NICU admission</td>
<td>&lt;2%</td>
<td>x12</td>
<td>x38</td>
<td>x50</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3500</td>
<td>2347</td>
<td>1687</td>
<td>1309</td>
</tr>
<tr>
<td>Gestational age</td>
<td>39.5</td>
<td>35.5</td>
<td>32.2</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Norwitz, 2005
Risk associated with a twin pregnancy.

Offspring

<table>
<thead>
<tr>
<th>Risk</th>
<th>Twins   vs. Singletons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth rate</td>
<td>14.2 vs. 4.4</td>
</tr>
<tr>
<td>Early neonatal mortality rate</td>
<td>22.8 vs. 2.9</td>
</tr>
<tr>
<td>Late neonatal mortality rate</td>
<td>3.9 vs. 0.8</td>
</tr>
<tr>
<td>Post-natal mortality rate</td>
<td>6.3 vs. 2.4</td>
</tr>
<tr>
<td>Infant mortality rate</td>
<td>33.0 vs. 6.1</td>
</tr>
</tbody>
</table>

Risk of cerebral palsy

Odd ratio: 10.2 compared with singletons

Doyle, 1996

Petridou et al., 1996
Twins complications as for fetuses and neonates

- Increasing of prematurity
  - < 37 & <32 weeks
  - <2500 & <1500 grams

- In twins it is increased:
  - Fetal death
  - Neonatal death
  - Infant death
  - Cerebral palsy
  - Risk of fetal anomalies

- The probability to have a serious illness till the age of 2 is increasing.
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Interventions used to diagnose and prevent preterm birth

- Perinatal care
- Risk scoring
- Cervical cerclage
- Quit of smoking and alcohol using
- Psychological support
- Dietological interventions
- Ca & Mg
- Aspirin
- Progesterone
- Education in preterm labor manifestations
- Home monitoring
- Tocolytic therapies
- Bed rest
- Hydration
- Prenatal examinations for infections
- Antibiotics in premature contractions
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Tests to diagnose preterm birth in asymptomatic twin pregnancies

Routine use of diagnostic tests can ascertain which pregnancy will be delivered prematurely, but should NOT be expected to decrease the preterm birth rate!!!

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable definition</th>
<th>&lt;28</th>
<th>&lt;30</th>
<th>&lt;32</th>
<th>&lt;34</th>
<th>&lt;37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative fetal fibronectin level: 135 births, %</td>
<td></td>
<td>2.1</td>
<td>2.9</td>
<td>4.5</td>
<td>&lt;11.5</td>
<td>46</td>
</tr>
<tr>
<td>Negative fetal fibronectin level and transvaginal cervical length ≥20 mm: 120 births, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either positive fetal fibronectin level or transvaginal cervical length &lt;20 mm: 24 births, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive fetal fibronectin level and transvaginal cervical length &lt;20 mm: 11 births, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fox NS et al: Am J Ob Gyn, 2009
Cervical length in asymptomatic twin pregnancies as a predictor of PTD

- Cervical shortening between 22 and 27 weeks
- Single cervical length (CL) measurement at 22 weeks

- The performance of cervical shortening for the prediction of preterm delivery of asymptomatic twins before 34 weeks does NOT differ from that of CL measurements at 22 or 27 weeks.

Leveque C: J Matern Fetal Neonatal Med. 2015
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Treatments **during pregnancy** to prevent preterm birth in twins

- **Prophylactic use of oral betamimetics**
  - Birth <37 weeks of gestation (RR, 0.85), <34 weeks of gestation (RR, 0.47)
  - Birthweight <2500 grm (RR, 1.19)
  - Neonatal mortality (RR, 0.80)
  
  *Yamasmit W et al: Cochr, Syst Rev, 2012*

- **Bed rest**
  - Birth <34 weeks of gestation (RR, 1.84)

  *Crowther CA et al: Cohr, Syst Rev, 2001*

- **Home monitoring**
  - Not beneficial in prevention of PTB

  *Colton T et al: Obstet Gynecol, 1995*

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The use of prophylactic tocolysis should not be undertaken to prevent preterm birth in twins !!!

*Combs, Am J Obst Gynecol, 2011*
Progestosterone and risk of preterm delivery in twins with cervical length <30mm and history of PTD

Table 3: Maternal and infant outcomes according to treatment with progesterone (n = 17) or placebo (n = 30) in women with twin pregnancy and cervical length ≤ 30 mm.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone group (n (%)</th>
<th>Placebo group (n (%))</th>
<th>Odds ratio (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>4 (23.5)</td>
<td>5 (16.7)</td>
<td>1.54 (0.35–6.73)</td>
<td>0.57</td>
</tr>
<tr>
<td>&lt; 34 weeks</td>
<td>5 (29.4)</td>
<td>12 (40.0)</td>
<td>0.63 (0.18–2.23)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Table 4: Maternal and infant outcomes according to treatment with progesterone (n = 10) or placebo (n = 18) in women with a history of spontaneous preterm delivery before 34 weeks or miscarriage after 12 weeks.

| Outcome                | Progesterone group (n (%)) | Placebo group (n (%)) | Odds ratio (95% CI) | P†   |
|------------------------|---------------------------|                       |                     |      |
| Gestational age at delivery |                           |                       |                     |      |
| < 32 weeks             | 3 (30.0)                  | 3 (16.7)              | 2.14 (0.34–13.42)   | 0.42 |
| < 34 weeks             | 3 (30.0)                  | 4 (22.2)              | 1.50 (0.26–8.64)    | 0.65 |

Klein K: UOG, 2011
The use of prophylactic Progesterone should NOT be undertaken to prevent preterm birth in twins!!!
Reducing the rate of preterm birth in twins by cervical circlage

- Cervical cerclage used as prophylactic for history indication
  - 😞 Prematurity 45% vs 48% without suture
  - 😞 Neonatal mortality 15% vs. 18% without suture
    - Dor J et al: Gynecol Obstet Invest, 1982

- Cervical cerclage of asymptomatic short cervix
  - 😞 Preterm birth <35 weeks (75% vs. 36% without suture)
    - Berghella et al: Obstet Gynecol, 2005
Cerclage for short cervix in twin pregnancies: Meta-analysis

- Twin pregnancies screened by transvaginal ultrasound in second trimester and where mothers had a short cervical length <25 mm before 24 weeks

Cerclage of asymptomatic short cervix must be avoided for twin gestation!!!

- Primary outcomes: preterm birth <34 weeks
- Adjusting for previous preterm birth and gestational age at randomization, there were no statistically significant differences in primary (adjusted odds ratio 1.17, 95% confidence interval 0.23-3.79) and secondary outcomes
- Rates of very low birthweight and of respiratory distress syndrome were significantly higher in the cerclage group than in the control group

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Tocolytics in the treatment of preterm labor in twins

- The use of tocolytics for the treatment of preterm labor has **not** been shown to decrease:
  - Delivery within 7 days
  - Perinatal death
  - Neonatal death
  - Respiratory syndrome
  - Necrotizing enterocolitis

- ACOG comments that tocolytics should be used judiciously once preterm labor in twins is diagnosed!

- **Respiratory syndrome**
- 😞 **Necrotizing enterocolitis**  
  - Anotayanonth S: Coch Syst Rev, 2004

- **Side effects**
- **Risk of maternal pulmonary edema**
### Results of the use of Arabin pessary in twin pregnancy with cervix <25mm

- **Randomized clinical trial (Spain)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Arabin Pessary</th>
<th>Expectant management</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous delivery &lt;28 wks</td>
<td>4/68 (5.9%)</td>
<td>9/68 (13.6%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Spontaneous delivery &lt;34 wks</td>
<td>11/68 (16.2%)</td>
<td>17/68 (25.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td>36.4 (26-38)</td>
<td>35.0 (22-38)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Carreras E: 13<sup>th</sup> WCFM, 2014

- **Randomized clinical trial (FMF)**

No statistical significance in preterm delivery in two groups. Trial was stopped due to the risk of possible adverse clinical effects in pessaries group.
Antenatal corticosteroids (ACS) in preterm labor in twins

- The use of ACS decrease:
  - Neonatal death (RR, 0.69; 95% CI, 0.58-0.81)
  - Respiratory distress (RR, 0.66; 95% CI, 0.43-0.69)
  - Intraventricular hemorrhage (RR, 0.54; 95% CI, 0.43-0.69)
  - Necrotizing enterocolitis (RR, 0.46; 95% CI, 0.29-0.74)
  - Systemic infection (RR, 0.56; 95% CI, 0.38-0.58) Roberts D: Cochr Syst Rev, 2006

- Every 2 weeks from 24 week vs. when in immediate risk for PTL
  - Respiratory distress syndrome: 13% vs. 11% Murphy DJ: AJOOG, 2002

- Single rescue course of ACS must be given if at least 14 days have elapsed and delivery is likely at <33 weeks
  - Neonatal morbidity: 64% vs. 42% (p<.02) GariteTJ: AJOOG, 2009

- A single course of ACS treatment was associated with a decreased rate of RDS only when the ACS-to-delivery interval was between 2 and 7 days Kuk JY: AJOOG, 2013

NIH recommends that all women in preterm labor, regardless the number of fetuses, must be given a course of ACS!!!
Use of tocolytics in twin pregnancies should be limited

- Cervical length <25 mm
- fFN is positive
- Both of the above are present
- 48 hours have elapsed since the first dosage of corticosteroids has been administered
- The patient has been transferred to a tertiary center
IVF success rate transferring more than ONE embryo

- Twin pregnancies must be considered severe complications of ART  
  ESHRE Campus, 2002

- Imposing singleton delivery as the success indicator for IVF treatment  
  Hazekamp et al, 2000

- Calculate success rate as the % of singleton living full term delivery per initiated IVF cycle  
  (BESST: Birth Emphasizing a Successful Singleton Term) to consider MP as failures  
  Min et al, 2004
Summary

- Although there are diagnostic tests to identify preterm birth in twins, they do not decrease the rate of preterm birth.
- There are no known treatments to decrease the rate of preterm birth.
- Tocolytics should be administered when twins are in danger of preterm delivery.
- Prolonged tocolytic use should be avoided.

Thank you very much!!!