Preterm delivery in multiples
Outline
• Epidemiology & Etiology
• Prediction
  – cervical length, fFN
• Prophylactic Prevention
  – bed rest, progesterone, cerclage, pessary
• Acute Prevention
  – tocolysis, antibiotics
• Fetal / Neonatal Protection
  – corticosteroids, MgSO\textsubscript{4}

Twin Pregnancy and Preterm Birth

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םותם טובים שניים עם האחד?

Preterm delivery in multiples

The magnitude of the problem

~ 3% of all births in the US:
  - 10% of all preterm deliveries in the US
  - 23% of all births <32 weeks
  - >70% d/t spontaneous preterm birth
  - >50% of all neonatal deaths from multiple pregnancies are attributed to preterm birth
  - 15% of all infants death occur in multiple gestations

Average gestational age at delivery

<table>
<thead>
<tr>
<th></th>
<th>Singleton</th>
<th>Twins</th>
<th>Triplets</th>
<th>Quadruplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight (gr)</td>
<td>3.296</td>
<td>2.336</td>
<td>1.860</td>
<td>1.291</td>
</tr>
<tr>
<td>Mean GA (weeks)</td>
<td>38.7</td>
<td>35.3</td>
<td>31.9</td>
<td>29.5</td>
</tr>
<tr>
<td>% &lt; 32 weeks</td>
<td>1.6</td>
<td>11.4</td>
<td>36.8</td>
<td>64.5</td>
</tr>
<tr>
<td>% &lt; 37 weeks</td>
<td>10.4</td>
<td>58.8</td>
<td>94.4</td>
<td>96.3</td>
</tr>
<tr>
<td>Rate of CP (per 1,000 live births)</td>
<td>1.6</td>
<td>7</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Infant mortality rate (per 1,000 live births)</td>
<td>5.4</td>
<td>23.6</td>
<td>52.5</td>
<td>96.3</td>
</tr>
</tbody>
</table>


Average gestational age at delivery

The number of live births in twin deliveries per 1,000 live births

http://www.cdc.gov

Twin Birth Rate - USA

Average gestational age at delivery
Proposed Mechanisms for increased rate of PTB in multiples

- Uterine / myometrial stretch $\Rightarrow$ increased production of pro-inflammatory cytokines
- Increased placental production of CRH (corticotrophin-releasing hormone) $\Rightarrow$ shown to decrease progesterone production in vitro
- m/p multifactorial – fetal stress signals, infection, placental dysfunction and cervical insufficiency

Preterm delivery in multiples

- Epidemiology & Etiology
- Prediction
- Prophylactic Prevention
- Acute Prevention
- Fetal/Neonatal Protection

Women at risk for PTB

- Prior preterm delivery
- History of cervical surgery / uterine anomalies / instrumentations
- Vaginal bleeding
- Infections – UTI, genital tract
- Periodontal disease
- Behavioral – Low BMI, smoking, substance abuse
- Multiple pregnancy
- etc...

Prediction of PTB in asymptomatic twin pregnancies

- Risk factors
- Chorionicity
- Cervical length
- Fetal Fibronectin
- Home uterine activity monitoring

The preterm prediction study: Risk factors in twin gestations

- Prospectively screened 147 women with twins at 24 and 28 weeks
- > 50 potential risk factors for spontaneous PTB
- Cervical length, bacterial vaginosis and fetal fibronectin
- Results:
  - Only a short cervix ($\leq 25$ mm) was consistently associated with spontaneous PTB
  - A positive fetal fibronectin result was significantly associated with spontaneous PTB at $\leq 32$ weeks
- Conclusion:
  - Most known risk factors for spontaneous PTB in singletons were not significantly associated with spontaneous PTB of twins
  - At 24 weeks, cervical length $\leq 25$ mm was the best predictor of spontaneous PTB at $\leq 32$, $<35$, and $<37$ weeks

Chorionicity

Gestational ages at delivery for dichorionic (n=801) and monochorionic (n=200) twin pregnancies

Chorionicity

<table>
<thead>
<tr>
<th>Gestational age at delivery</th>
<th>DC/DA (n=1107)</th>
<th>MC/DA (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28 weeks</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>18%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Hack KEA et al. BJOG 2008;115:58-97

Cervical Length

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Singletons</th>
<th>Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>10th</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>25th</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>50th</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

The MFMU Preterm Prediction Study

Obstetrics

Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis

Conde-Agudelo et al. AJOG 2010;128:e1-12

15 studies (n=3001 women)

ROC curves of cervical length at 20-24 weeks to predict spontaneous PTB in asymptomatic women with twins

Conde-Agudelo et al. AJOG 2010;128:e1-12

The value of screening for a short cervical length in twins

- No studies in twins (or other high order multiples) showing that identification of women at risk for PTB by cervical length has any maternal or fetal advantage
- Potential advantage of timely corticosteroids administration
- But...also potential harm by unnecessary hospitalization and...untimely administration of corticosteroids
Cervicovaginal fetal fibronectin has limited accuracy in predicting spontaneous preterm birth in both asymptomatic and symptomatic women with multiple pregnancies because the likelihood ratios for positive and negative test results generated only minimal to moderate changes in the pretest probabilities of preterm birth.

- **Preterm delivery in multiples**
  - Epidemiology & Etiology
  - Prediction
  - Prophylactic Prevention
  - Acute Prevention
  - Fetal/Neonatal Protection

The best method to prevent preterm birth in multiple pregnancies is... to prevent multiple pregnancies.

**Prevention of Preterm Birth in Multiple Pregnancy**

The best preventive measure... single embryo transfer.
Perinatal outcome after fetal reduction from twin to singleton: to reduce or not to reduce?

Table: Fetal reduction of twins to singleton lowers the risk of prematurity and results in improved perinatal outcome compared with non-reduced twins.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Singletons</th>
<th>Nonreduced Reduced twins (n=62)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery (y) median range</td>
<td>39(37–40)</td>
<td>37(32–39) &lt;0.03</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2,670(1,848–4,424)</td>
<td>2,084(1,622–3,710)</td>
<td>0.05</td>
</tr>
<tr>
<td>Early neonatal death (4.4%+)</td>
<td>1.0</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory distress of (7%+)</td>
<td>2.2</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Chorioamnionitis (4%+)</td>
<td>3.3</td>
<td>4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Failed abortion of one twin</td>
<td>2.0</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Mid-trimester abortion</td>
<td>0.0</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>2.0</td>
<td>3.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Peri Stend. 2015;103:428-32

Prevention of Preterm Birth in Multiple Pregnancy

- Bed rest / Hospitalisation
- Progestogens
- Cerclage
- Cervical Pessary

Bed rest / Hospitalisation

Hospitalisation and bed rest for multiple pregnancy (Review)

- Seven trials
- 713 women and 1452 babies

Crowther CA and Han S. Cochrane review 2010

Bed rest in multiple pregnancies and preterm delivery (<37 wks)

Crownther CA and Han S. Cochrane review 2010

Bed rest in multiple pregnancies and preterm delivery (<34 wks)

Crownther CA and Han S. Cochrane review 2010

Bed rest in women a twin pregnancy and cervical dilatation – PTD <37 wks

Crownther CA and Han S. Cochrane review 2010
Bed rest in multiple pregnancies and adverse perinatal outcomes

Summary – Bed Rest

- Lack of any evidence demonstrating that bed rest in multifetal gestation prolongs pregnancy
- Yet, it is the most common intervention

Progestogens

Evidence-based medicine (USA...)

- Short cervix ≤ 20 mm
- History of spontaneous preterm birth

Singletons

Vaginal progesterone

17a - OHPC

What is the “Evidence-based” in multiple pregnancies?

1980

Inefficacy of 17α-Hydroxyprogesterone Caproate in the Prevention of Prematurity in Twin Pregnancy

Anna-Liisa Hari-Kuukainen-Orerl, MD, Antti Kalugga, MD, and Risto Tuimala, MD

Citation: Gynecol 1980;56:692-695

More Twins studies with 17-OHPC...

17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial

C. Andrea Coombs, MD, PhD, Thomas Garo, MD, Kimberly Harrel, MD, and Mary Panos, RN

Manuel Fernandez, MD for the Obstetric Collaborative Research Team

Citation: Obstet Gynecol 2013;122:1006-11
If not 17-OHPC than maybe vaginal progesterone...?

Hypothesis: doses in multiple pregnancies should be higher...

More than 15 RCTs in multiple pregnancies...ALL NEGATIVE

Why lack of efficacy in multiple pregnancies?

Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multi-centre trial

- Randomized to receive:
  - 200 mg vaginal progesterone / day
  - 400 mg vaginal progesterone / day
  - or placebo

Maybe will work in Triplets?

Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial

- 24 to 31 6/7 wks
- Asymptomatic
- Cervical length ≤ 25 mm
- Randomized to receive (or not) IM 500mg 17-OHPC twice weekly
- until 36 wks or PTD


Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or preterm birth in pregnancies: a double-blind randomized clinical trial

- Andrew Logan, FRCOG, 50 Kenton Lane, NW9, London, UK
- Mortal Perinatal Collaborative Research Network


BJOG 2013;120:194.e1-8

BJOG 2013;120:50-57

BJOG 2009;113:385-92
Adverse impact on gestational age at delivery in multiples?

Relationship between 17α-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation

Most RCTs that investigated the effectiveness of vaginal progesterone or IM 17P vs placebo/non-intervention in women with twins

The PIs were contacted and requested to provide individual participant data

13 Studies included - individual data of 3768 women:
- 1089 - IM 17Pc (6 studies)
- 917 - vaginal progesterone (7 studies)
- 1762 - control

Prevention of preterm delivery by 17α-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial

Is there any hope for progesterone in multiples?

Effectiveness of progesterone to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

• RCTs that investigated the effectiveness of vaginal progesterone or IM 17Pc vs placebo/non-intervention in women with twins

• The PIs were contacted and requested to provide individual participant data

• 13 Studies included - individual data of 3768 women:
  - 1089 - IM 17Pc (6 studies)
  - 917 - vaginal progesterone (7 studies)
  - 1762 - control

Failure of 17α-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial

...until more data become available regarding rates of pregnancy loss, GDM, and other possible complications, we believe that the use of progesterone in attempt to prevent preterm birth in situations where its benefits have not yet been established should be limited to controlled clinical trials.
Is 17α-hydroxyprogesterone caproate contraindicated in twin gestations?
R. Romero, A. Conde-Agudelo

- Administration of 17-OHPC in women with a cervical length ≥25mm at randomization and <24 wks’ gestation was associated with a significantly increased risk of the composite perinatal outcome.
- Given that 86-93% of women with a twin gestation have a cervical length ≥25 mm at mid-gestation and that 17-OHPC had no beneficial effects in those with a cervical length ≤25 mm, we strongly agree with the authors of this IPD meta-analysis that 17-OHPC is contraindicated in twin gestations.
- The administration of vaginal progesterone to women with twin gestations and a short cervix (≤25 mm) may reduce the rate of PTB and lower the rate of a composite neonatal morbidity and mortality…but it should be considered ‘hypothesis-generating’.

Summary - Progesterone

- No benefit in multiple pregnancy
- IM 17-HPC may be even harmful
- Vaginal progesterone may be an option in twins with an asymptomatic short cervix in the second trimester but RCT’s are needed
Ultrasound-indicated cerclage in asymptomatic twins

Cerclage for Short Cervix on Ultrasoundography

Meta-Analysis of Trials Using Individual Patient-Level Data

Patient-level meta-analysis of cerclage in twins with a cervical length < 25 mm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cerclage (n=24)</th>
<th>No cerclage (n=25)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth (&lt;35 wks)</td>
<td>18/24 (75%)</td>
<td>9/25 (36%)</td>
<td>2.15 (1.15-4.01)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>11/48 (23%)</td>
<td>3/50 (6%)</td>
<td>2.66 (0.83-8.54)</td>
</tr>
</tbody>
</table>

Berghella et al. Obstet Gynecol 2005

Cervical cerclage for preterm birth prevention in twin gestation with short cervix: a retrospective cohort study

A retrospective cohort study (2006-2014)

• 40 consecutive DCDA twins (CL <25 mm at 16-24 weeks and cerclage) and 40 matched controls

Ultrasound Obstet Gynecol 2016

Physical examination-induced cerclage in asymptomatic twins

Only one randomized clinical trial (7 twins)

<table>
<thead>
<tr>
<th>RCT (n=23) - Prolapsed membranes &lt; 27 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerclage</strong></td>
</tr>
<tr>
<td>n = 13 (3 twins) bed rest + abx + indomethacin</td>
</tr>
<tr>
<td><strong>No cerclage</strong></td>
</tr>
<tr>
<td>n = 10 (4 twins) bed rest + abx</td>
</tr>
</tbody>
</table>

PTD <34 wks

| 54% (7/13) | p = 0.02 | Conclusion: Cerclage prolonged gestation |

Althuisius S et al. AJOG 2003:189:907

Efficacy of ultrasound-indicated cerclage in twin pregnancies

Amanda Romine, SPH, Barton Burchenal, MD, Nathan S. Fox, MD; Matthew Hoffmann, MD, MPH; Vincento Bergelli, MD; Yvande Patel, MD; Ilia Callison, MD; Gabrielle Succone, MD; Adid Fischkeller, MD

A retrospective cohort study of 140 asymptomatic twin pregnancies with CL <25 mm at 16-24 weeks (1995-2012)

Ultrasound indicated cerclage in asymptomatic twins

• May be useful according to recent data from retrospective studies
• But, there is a need for adequate RCT’s

Ultrasound Obstet Gynecol 2015:212:788e1-e6

Outcomes after physical examination-induced cerclage in twin gestations

Ladly S. MBCh, MD, MPH; Phepa Y. Rajan, MD; William A. Goodman, MD, MBA

Outcomes of emergency or physical examination-induced cerclage in twin pregnancies compared to singleton pregnancies

• 2 retrospective studies (104 twins and 12 twins)
• Comparing twins to singletons
• Women with a twin pregnancy who received a physical examination-induced cerclage may experience similar obstetric outcomes as women with singleton gestations
• Cerclage should be considered an option for patients with twin pregnancies and a dilated cervix in the 2nd trimester

Cerclage Pessary
Silicone Arabin Pessary

Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix?

Birgit Arabin1,2, Johan R. Halbesma1,2, Fred Vork1, Michael Hübner2, and Jim van Eyk1,2

<table>
<thead>
<tr>
<th>Pregnancy outcome for 26 twin pregnancies</th>
<th>Pessary (n=23)</th>
<th>No Pessary (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28 Weeks (n, %)</td>
<td>0</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;32 Weeks (n, %)</td>
<td>0</td>
<td>7 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;36 Weeks (n, %)</td>
<td>8 (35)</td>
<td>12 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Interval from TVS to delivery (days, mean, range)</td>
<td>85 (43-129)</td>
<td>67 (21-100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks, mean)</td>
<td>35.8 (34-37.6)</td>
<td>33.3 (24.6-37.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Vaginal pessary may be a cost-effective preventive treatment in patients at risk for spontaneous PTB
- Prospective controlled trials are needed

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

Conclusions

- In unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.
- However, a cervical pessary significantly reduces risk of poor perinatal outcome and preterm birth in women with multiple pregnancies and a cervical length of less than 38 mm (<25th percentile at 16-20 weeks)

Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pessary</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous birth at &lt; 34 wks</td>
<td>13.6% (95/688)</td>
<td>12.9% (76/589)</td>
<td>1.05 (0.79-1.41)</td>
</tr>
<tr>
<td>Gestational age at birth (median, IQR)</td>
<td>35.6 (34.3-37.9)</td>
<td>35.7 (35.2-35.9)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (mean)</td>
<td>2331 (2020-2740)</td>
<td>2353 (2050-2732)</td>
<td></td>
</tr>
<tr>
<td>&lt; 2500 g</td>
<td>66.2% (95/688)</td>
<td>69.1% (407/589)</td>
<td>0.97 (0.9-1.05)</td>
</tr>
<tr>
<td>&lt; 1500 g</td>
<td>10.2% (60/688)</td>
<td>11% (65/589)</td>
<td>0.92 (0.66-1.29)</td>
</tr>
</tbody>
</table>

Summary

- Prediction of preterm birth in multiple pregnancies is hard with a short cervical length in the second trimester being the best predictor for preterm birth
- Prevention of preterm birth:
  - Bed rest – not effective
  - Progesterone – IM: not effective, potential harmful  
    Vaginal: maybe in short cervix
  - Cerclage – more research (RCT’s) is needed, maybe useful in selected case with an asymptomatic short cervix or cervical dilatation
  - Cervical pessary – may be effective in asymptomatic short cervix

האם הם טובים两边吗

?

* טובים两边吗
  - יש להם שכר טוב
  - ב.setScale: ci. או " escalate, המוחוק את המברק; יואל, הכרדה, או "escalate, עם שמי, לצביח, מה א実際に שמיע
  - והך לוח: לאומד, אורי, שמי, מתחמק, האזורת-昕,��, ייעודו
  - קהל הפרק ד