Cervical length and PTB prevention

Asnat Walfisch MD
What's the story??

- 40 YO G3P2 healthy
- 14 weeks gestation
- s/p PTD twice at weeks 33 (twins) and 31
- No TX in previous pregnancies
- Now coming in for first anatomical scan
- Scan normal, cervix 12 mm
- Oh… and what if she has twins now??
Born too soon...

Incidence

5% - 18%

1 in 8 in the United States
(11.4%)

In Israel - 7%

What’s normal? That depends.... Depends on the week:

Before 22 weeks: 40 mm and after 32 weeks: 30 mm

NORMAL CERVICAL LENGTH — between 14 and 28 weeks

- 15 mm – 2nd centile
- 20 mm – 5th centile
- 25 mm – 10th centile
- 35 mm – 50th centile
- 45 mm – 90th centile
SO.....WHAT IS SHORT??

≤ 20 mm in women with no prior preterm delivery

< 25 mm in women with a prior preterm delivery
Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D., Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group∗
CONCLUSIONS

In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.
Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial

S. S. HASSAN¹,², R. ROMERO¹,³,⁴, D. VIDYADHARI⁵, S. FUSEY⁶, J. K. BAXTER⁷, M. KHANDELWAL⁸, J. VIJAYARAGHAVAN⁹, Y. TRIVEDI¹⁰, P. SOMA-PILLAY¹¹, P. SAMBAREY¹², A. DAYAL¹³, V. POTAPOV¹⁴, J. O’BRIEN¹⁵,¹⁶, V. ASTAKHOV¹⁷, O. YUZKO¹⁸, W. KINZLER¹⁹, B. DATTEL²⁰, H. SEHDEV²¹, L. MAZHEIKA²², D. MANCHULENKO²³, M. T. GERVASI²⁴, L. SULLIVAN²⁵, A. CONDE-AGUDELO¹, J. A. PHILLIPS²⁶ and G. W. CREASY²⁷,
Progesterone reduced the rate of Respiratory Distress Syndrome by 61%
OPPTIMUM strongly suggests that the efficacy of progesterone in improving outcomes is either non-existent or weak. Given the heterogeneity of the preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial.

**Interpretation** Vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long-term benefit or harm on outcomes in children at 2 years of age.

With the concluding words of her plenary talk at the 2016 Society for Maternal–Fetal Medicine Annual Meeting – ‘I wouldn’t advise my daughter take vaginal progesterone’ – had Jane Norman
Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data

Roberto Romero, MD; Kypros Nicolaides, MD; Agustin Conde-Agudelo, MD, MPH; Ann Tabor, MD; John M. O’Brien, MD; Elcin Cetingoz, MD; Eduardo Da Fonseca, MD; George W. Creasy, MD; Katharina Klein, MD; Line Rode, MD; Priya Soma-Pillay, MD; Shalini Fusey, MD; Cetin Cam, MD; Zarko Alfrevic, MD; Sonia S. Hassan, MD

PTB BEFORE 33 WEEKS OF GESTATION

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (fixed) (95% CI)</th>
<th>Vaginal progesterone n/N</th>
<th>Placebo n/N</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonseca 2007</td>
<td></td>
<td>22/125</td>
<td>38/125</td>
<td>45.4</td>
<td>0.58 (0.36-0.92)</td>
</tr>
<tr>
<td>O’Brien 2007</td>
<td></td>
<td>1/12</td>
<td>4/19</td>
<td>3.7</td>
<td>0.40 (0.05-3.13)</td>
</tr>
<tr>
<td>Rode 2011</td>
<td></td>
<td>3/7</td>
<td>5/14</td>
<td>4.0</td>
<td>1.20 (0.40-3.63)</td>
</tr>
<tr>
<td>Hassan 2011</td>
<td></td>
<td>21/235</td>
<td>36/223</td>
<td>44.1</td>
<td>0.55 (0.33-0.92)</td>
</tr>
<tr>
<td>Cetingoz 2011</td>
<td></td>
<td>1/9</td>
<td>2/6</td>
<td>2.9</td>
<td>0.33 (0.04-2.91)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>48/388</td>
<td>85/387</td>
<td>100.0</td>
<td>0.58 (0.42-0.80)</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0\%$
Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study


<table>
<thead>
<tr>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors vaginal progesterone</td>
<td>Favors placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 0\%$
Test for overall effect: $Z = 3.48, P = 0.0005$

Figure 3 Forest plot of the effect of vaginal progesterone on the risk of preterm birth ≤ 34 weeks of gestation or fetal death.
The "stitch"
POTENTIAL CANDIDATES??

1. ‘History-indicated’ cerclage
2. ‘Ultrasound-indicated’ cerclage
3. ‘Physical exam-indicated’ cerclage
Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial

Meekai S To, Zarko Alfrevic, Victoria C F Heath, Simona Cicero, Ana Maria Cacho, Paula R Williamson, Kypros H Nicolaides, on behalf of the Fetal Medicine Foundation Second Trimester Screening Group*
**Interpretation**  The insertion of a Shirodkar suture in women with a short cervix does not substantially reduce the risk of early preterm delivery.
Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth

A Meta-Analysis

Vincenzo Berghella, MD, Timothy J. Rafael, MD, Jeff M. Szychowski, PhD, Orion A. Rust, MD, and John Owen, MD, MSPH
CONCLUSION: In women with previous spontaneous preterm birth, singleton gestation, and cervical length less than 25 mm, cerclage significantly prevents preterm birth and composite perinatal mortality and morbidity.
Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis

Agustin Conde-Agudelo, MD, MPH; Roberto Romero, MD, DMedSci; Kypros Nicolaides, MD; Tinnakorn Chaiworapongsa, MD; John M. O’Brien, MD; Elcin Cetingoz, MD; Eduardo da Fonseca, MD; George Creasy, MD; Priya Soma-Pillay, MD; Shalini Fusey, MD; Cetin Cam, MD; Zarko Alfirevic, MD; Sonia S. Hassan, MD
CONCLUSION: Based on state-of-the-art methods for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous preterm birth.
Berghella approach to transvaginal ultrasound (TVU) measurement of cervical length for screening singleton gestations

<table>
<thead>
<tr>
<th>Past pregnancy history</th>
<th>TVU cervical length screening</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior preterm birth</td>
<td>Start at 14 weeks and end at 24 weeks</td>
<td>Every two weeks as long as cervix is at least 30 mm*</td>
</tr>
<tr>
<td>14 to 27 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior preterm birth</td>
<td>Start at 16 weeks and end at 24 weeks</td>
<td>Every two weeks as long as cervix is at least 30 mm*</td>
</tr>
<tr>
<td>28 to 36 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior preterm birth</td>
<td>One exam between 18 and 24 weeks</td>
<td>Once*</td>
</tr>
</tbody>
</table>

TVU: transvaginal ultrasound.
* Increase frequency to weekly in women with TVU cervical length of 25 to 29 mm. If <25 mm before 24 weeks, consider cerclage.
• If ≤20 mm before 25 weeks, vaginal progesterone supplementation.
Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial

Maria Goya, Laia Pratcorona, Carme Merced, Carlota Rodó, Leonor Valle, Azahar Romero, Miquel Juan, Alberto Rodríguez, Begoña Muñoz, Belén Santacruz, Juan Carlos Bello-Muñoz, Elisa Llurba, Teresa Higuera, Luis Cabero*, Elena Carreras*, on behalf of the Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group

Lancet 2012; 379: 1800–06
<table>
<thead>
<tr>
<th>Adverse outcomes</th>
<th>Cervical pessary group (n=190)</th>
<th>Expectant management group (n=190)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotising enterocolitis</td>
<td>0</td>
<td>2 (1%)</td>
<td>--</td>
<td>0.4987</td>
</tr>
<tr>
<td>Intraventricular haemorrhage†</td>
<td>0</td>
<td>2 (1%)</td>
<td>--</td>
<td>0.4987</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>5 (3%)</td>
<td>23 (12%)</td>
<td>0.20 (0.06–0.55)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0</td>
<td>2 (1%)</td>
<td>--</td>
<td>0.4987</td>
</tr>
<tr>
<td>Treatment for sepsis</td>
<td>3 (2%)</td>
<td>12 (6%)</td>
<td>0.24 (0.04–0.90)</td>
<td>0.0317</td>
</tr>
<tr>
<td>Composite adverse outcomes</td>
<td>5 (3%)</td>
<td>30 (16%)</td>
<td>0.14 (0.04–0.39)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth

Kypros H. Nicolaides, M.D., Argyro Syngelaki, Ph.D., Liona C. Poon, M.D., Gemma Picciarelli, M.D., Natasa Tul, M.D., Aikaterini Zamprakou, M.D., Evdoxia Skyfta, M.D., Mauro Parra-Cordero, M.D., Ricardo Palma-Dias, M.D., Ph.D., and Jesus Rodriguez Calvo, M.D.
Algorithm

Universal screening (?)
Cx length prior to 24 weeks

Singleton gestation

Short cervix (<25mm)
Previous PTB

Vag. Progesterone
Cerclage

Short cervix (<20mm)
No previous PTB

Vag. Progesterone

Multiple gestation

??

40 YO G3P2 healthy
14 weeks gestation
s/p PTD twice at weeks 33 (twins) and 31
No TX in previous pregnancies
Now coming in for first anatomical scan
Scan normal, cervix 12 mm
Oh… and what if she has twins now??


BOTH NEGATIVE TRIALS, BOTH NON SELECTED TWIN PREGNANCIES

BOTH POSITIVE TRIALS, ONLY SHORT CERVIX IN TWIN PREGNANCIES
OBSTETRICS

Cerclage in twin pregnancy with dilated cervix between 16 to 24 weeks of gestation: retrospective cohort study

Amanda Roman, MD; Burton Rochelson, MD; Pasquale Martinelli, MD; Gabriele Saccone, MD; Kemoy Harris, MD; Noelia Zork, MD; Melissa Spiel, MD; Karen O’Brien, MD; Ilia Calluzzo, MD; Kristy Palomares, MD, PhD; Todd Rosen, MD; Vincenzo Berghella, MD; Adiel Fleischer, MD
CONCLUSION: Cerclage, indomethacin, and antibiotics in twin pregnancies with dilated cervix $\geq 1$ cm before 24 weeks were associated with significant longer latency period from diagnosis to delivery (6.7 weeks), decreased incidence of spontaneous preterm birth at any given gestational age, and improved perinatal outcome when compared with expectant management.
Approach to sonographic screening of cervical length in pregnancy and management of pregnant women with a short cervix

When and how often should cervical length be measured?

Singleton pregnancy, no prior preterm birth

- Single TVUS measurement of cervical length between 18 and 24 weeks of gestation
  - Cervical length ≥ 20 mm?
    - Yes: Routine prenatal care
    - No: Prescribe vaginal progesterone suppository daily through 36 weeks of gestation. No additional cervical length measurements.

Singleton pregnancy, previous preterm birth at 14 to 27 weeks of gestation*

- TVUS measurement of cervical length at 14 weeks of gestation
  - Cervical length ≥ 30 mm?
    - Yes: Repeat measurement every two weeks through 24 weeks as long as cervical length remains ≥ 30 mm
    - No: Cervical length 26 to 29 mm?
      - Yes: Repeat measurement weekly through 24 weeks as long as measurement remains 26 to 29 mm
      - No: Cervical length ≤ 25 mm. Options include:
        - Place cerclage and continue hydroxyprogesterone caproate.
        - Place cerclage and substitute vaginal progesterone for hydroxyprogesterone caproate.
        - Substitute vaginal progesterone for hydroxyprogesterone caproate. No cerclage.

Singleton pregnancy, previous preterm birth at 28 to 36 weeks of gestation*

- TVUS measurement of cervical length at 16 weeks of gestation
  - Cervical length ≥ 30 mm?
    - Yes: Repeat measurement every two weeks through 24 weeks as long as cervical length remains ≥ 30 mm
    - No: Cervical length ≤ 25 mm. Options include:
      - Place cerclage and continue hydroxyprogesterone caproate.
      - Place cerclage and substitute vaginal progesterone for hydroxyprogesterone caproate.
      - Substitute vaginal progesterone for hydroxyprogesterone caproate. No cerclage.

Multiple gestation

- No TVUS cervical length screening

This is the author's approach to monitoring cervical length and management of women with a short cervix. This remains a controversial area and variations of this approach exist worldwide.

TVUS: transvaginal ultrasound.

* In addition to cervical length screening, offer hydroxyprogesterone caproate beginning at 16 weeks of gestation and continuing through the 36th week of gestation to reduce the risk of recurrent spontaneous preterm birth.