Reducing preterm birth with progesterone
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Declarations

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• I am on a Data and Safety Monitoring Committee for Glaxo Smith Kline. I do not receive any personal remuneration for this

• I was Chair of the NICE (National Institute of Clinical Excellence) guideline development committee on Preterm Labour and Birth (published Nov 2015)

• Besins kindly donated the active and placebo drug for this study but were not involved in study design or analysis

Progesterone v. placebo in women with previous preterm birth

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone group n/N</th>
<th>Placebo group n/N</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 34 weeks</td>
<td>30/302</td>
<td>78/300</td>
<td>0.31</td>
<td>0.14 – 0.69*</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>35/801</td>
<td>59/852</td>
<td>0.50</td>
<td>0.33 - 0.75*</td>
</tr>
<tr>
<td>Birthweight &lt; 2500g</td>
<td>94/418</td>
<td>97/274</td>
<td>0.58</td>
<td>0.42 - 0.79*</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>21/801</td>
<td>39/852</td>
<td>0.45</td>
<td>0.27 - 0.76*</td>
</tr>
</tbody>
</table>

Dodd JM et al 2013 Cochrane Review

Progesterone v. placebo in women with cervical shortening

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone group n/N</th>
<th>Placebo group n/N</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 34 weeks</td>
<td>41/219</td>
<td>64 /219</td>
<td>0.64</td>
<td>0.45 – 0.90*</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>21/698</td>
<td>28/691</td>
<td>0.74</td>
<td>0.42 - 1.29</td>
</tr>
<tr>
<td>Birthweight &lt; 2500g</td>
<td>188/693</td>
<td>202/686</td>
<td>0.92</td>
<td>0.78 - 1.09</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>11/791</td>
<td>20/780</td>
<td>0.55</td>
<td>0.26 - 1.13</td>
</tr>
</tbody>
</table>

Dodd JM et al 2013 Cochrane Review

Meta-analysis of vaginal progesterone in women with short cervix

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative risk</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth before 33 weeks</td>
<td>0.58</td>
<td>0.42–0.80</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>0.48</td>
<td>0.30–0.76</td>
</tr>
<tr>
<td>Composite neonatal morbidity and mortality</td>
<td>0.57</td>
<td>0.40–0.81</td>
</tr>
</tbody>
</table>

“Safe” interventions in pregnancy can have long term harm for the baby


"Safe" interventions in pregnancy can have long term harm for the baby

OPPTIMUM - hypotheses being tested:

In women at high risk of preterm labour, does prophylactic vaginal natural progesterone, 200mg daily from 22 – 34 weeks gestation, compared to placebo:

i. Improve obstetric outcome by lengthening pregnancy and thus reducing the incidence of preterm delivery (before 34 weeks gestation)?
ii. Improve neonatal outcome by reducing a composite of death and major morbidity?
iii. Lead to improved childhood cognitive and neurosensory outcomes at two years?

Study design

- Double masked placebo controlled randomised trial
- Study registered (August 2008): ISRCTN14568373
- Abbreviated protocol published
- Women recruited from 65 UK NHS hospitals and one Swedish hospital
- Recruitment period: 2 February 2009 - 12 April 2013.
- Final patient outcome data were collected on 28 August 2015
- Unblinding October 2015
- Oversight with independent trials steering committee and data monitoring committee (Chairs Prof. John Morrison, Galway; and Prof. Henry Halliday, Belfast)

Eligibility (both phases)

Inclusion criteria
- Singleton pregnancy
- Gestation established by scan at 16+0 weeks or earlier
- Aged 16 years or older

Exclusion criteria
- Congenital structural or chromosomal fetal anomaly
- Known sensitivity, contraindications, or intolerance to progesterone or any excipient
- Rupture of the fetal membranes at the time of recruitment
- Prescription or ingestion of medications known to interact with progesterone
- Women currently prescribed progesterone

Informed written consent for both phases

Eligibility (treatment phase)

(i) History in a previous pregnancy of any of:
- Preterm birth
- 2nd trimester loss
- Premature fetal membrane rupture
- Cervical procedure to treat abnormal smears
AND a positive fFN test

(ii) History in a previous pregnancy of sPTB < 34+0 weeks
- regardless of fFN test

(iii) CL ≤ 25mm in the index pregnancy
- regardless of fFN test


Primary outcomes

Obstetric: fetal death or delivery before 34+0 weeks of gestation

Neonatal: a composite of death, bronchopulmonary dysplasia or brain injury on cerebral ultrasound

brain injury defined as any intraventricular haemorrhage (excluding subependymal), parenchymal cystic or hemorrhagic lesion or persistent ventriculomegaly (VI >97th percentile)

Childhood: the Bayley-III cognitive composite score at 22-26 months of chronological age.

Statistical analysis (i)

- Primary outcomes were analysed by intention to treat using mixed effects logistic regression / linear regression models
- p-values for the primary outcomes were initially calculated without adjustment for multiple comparisons, then adjusted using a Bonferroni-Holm procedure
- Sensitivity analyses:
  - primary analysis repeated in a per-protocol dataset
  - multiple imputation of missing primary outcome data.

Statistical analysis (ii)

Preplanned subgroup analyses for primary outcomes to include interaction terms for the following subgroups:
- fFN positive/negative
- cervical length ≤ 25mm / > 25mm,
- cervical length ≤ 15mm / >15mm,
- chorio-amnionitis yes / no,
- history of spontaneous preterm birth yes /no
- history of preterm birth yes / no

Sample size calculation

Estimated that sample size of around order of 1125 (375 fFN positive and 750 fFN negative women), would provide:
- 90% power at the 5% level of significance for the primary obstetric outcome, assuming RR of 0.66 and baseline rate of 40% for the primary outcome in the fFN positive and 13% in the fFN negative group
- 80% power for the neonatal outcome assuming RR of 0.4
- 93% power for the childhood outcome assuming a mean difference of 4 points in the Bayley score

Primary outcomes

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Placebo</th>
<th>Progesterone</th>
<th>OR (95%CI) (adj)</th>
<th>P value (adj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal death or delivery &lt; 34 weeks</td>
<td>108/597 (18.1)</td>
<td>96/600 (16.0)</td>
<td>0.86 (0.61, 1.22)</td>
<td>0.67</td>
</tr>
<tr>
<td>Neonatal morbidity or death</td>
<td>60/587 (10.2)</td>
<td>39/589 (6.6)</td>
<td>0.62 (0.38, 1.03)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Difference in means (95%CI)

Cognitive Composite score at 2 years

97.7 ± 17.5 97.3 ± 17.9  -0.48 (-2.77, 1.81) 0.68
### Components of the primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Progesterone</th>
<th>OR (95% CI)</th>
<th>P value (unadj)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstetric outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal death</td>
<td>7/597 (1.2)</td>
<td>8/600 (1.3)</td>
<td>1.14 (0.41, 3.17)</td>
<td>0.80</td>
</tr>
<tr>
<td>Liveborn delivery before 34 weeks</td>
<td>10/590 (1.7)</td>
<td>88/592 (14.8)</td>
<td>0.85 (0.62, 1.15)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Neonatal outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neomortal death</td>
<td>6/597 (1.0)</td>
<td>16/600 (2.1)</td>
<td>0.17 (0.08, 0.49)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>18/574 (3.1)</td>
<td>17/580 (2.9)</td>
<td>0.94 (0.49, 1.78)</td>
<td>0.64</td>
</tr>
<tr>
<td>Brain injury on USS</td>
<td>34/574 (9.9)</td>
<td>18/584 (3.1)</td>
<td>0.50 (0.31, 0.84)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Post hoc survival curve of time to delivery

![Post hoc survival curve of time to delivery](image)

### Subgroup analysis – short cervix

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Progesterone</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstetric outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>0.88</td>
<td>(0.50, 1.53)</td>
<td>0.672</td>
<td>0.69</td>
<td>(0.39, 1.29)</td>
<td>0.191</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Neomortal death</td>
<td>0.74</td>
<td>(0.35, 1.66)</td>
<td>0.432</td>
<td>0.54</td>
<td>(0.25, 1.16)</td>
<td>0.173</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Childhood</td>
<td>2.27</td>
<td>(-0.10, 5.6)</td>
<td>0.247</td>
<td>-2.15</td>
<td>(-7.23, 2.93)</td>
<td>0.408</td>
<td>0.97</td>
<td></td>
</tr>
</tbody>
</table>
Subgroup analysis – short cervix

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>× ≥ 25mm</td>
<td></td>
<td></td>
<td></td>
<td>× ≤ 25mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetric</td>
<td>0.68</td>
<td>(0.50, 1.57)</td>
<td>0.672</td>
<td>445</td>
<td>0.69</td>
<td>(0.39, 1.20)</td>
<td>0.191</td>
<td>251</td>
</tr>
<tr>
<td>Neonatal</td>
<td>0.74</td>
<td>(0.35, 1.56)</td>
<td>0.432</td>
<td>436</td>
<td>0.54</td>
<td>(0.25, 1.15)</td>
<td>0.113</td>
<td>246</td>
</tr>
<tr>
<td>Childhood</td>
<td>0.27</td>
<td>(4.10, 1.56)</td>
<td>0.247</td>
<td>311</td>
<td>-2.15</td>
<td>(-7.23, 3.93)</td>
<td>0.408</td>
<td>179</td>
</tr>
</tbody>
</table>

Some secondary outcomes: childhood

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Progesterone</th>
<th>OR, HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death between trial entry and end of study</td>
<td>16 / 568 (2.7)</td>
<td>20 / 600 (3.3)</td>
<td>1.26 (0.65, 2.42)</td>
<td>0.5</td>
</tr>
<tr>
<td>Moderate/severe neurodev. impairment at 2 years</td>
<td>35 / 403 (8.7)</td>
<td>47 / 379 (12.4)</td>
<td>1.48 (0.98, 2.33)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

OPPTIMUM - Conclusions

- OPPTIMUM is the largest trial of progesterone to prevent preterm birth
- After adjusting for multiple comparisons, we did not disprove the null hypotheses that progesterone does not:
  - Prevent preterm birth
  - Reduce adverse neonatal outcome
  - Have a beneficial effect on childhood outcome
- No evidence of benefit in any identifiable subgroups
- Infrequent (but significantly increased) events of renal /GI /respiratory harm deserve consideration in other studies

Clinical use of progesterone for preterm birth prevention

- Progesterone administration is endorsed in some national guidelines (NICE UK, SMFM USA)
- 17 OHP is licenced for preterm birth prevention in the USA
- The FDA did not approve the use of vaginal progesterone for preterm birth prevention in women with a short cervix.
- There is little information about about longer term effects on the child


Placebo Progesterone OR, HR (95% CI) P value
Death between trial entry and end of study 16 / 568 (2.7) 20 / 600 (3.3) 1.26 (0.65, 2.42) 0.5
Moderate/severe neurodev. impairment at 2 years 35 / 403 (8.7) 47 / 379 (12.4) 1.48 (0.98, 2.33) 0.087

Systematic review of strategies to prevent preterm birth with analysis of effects on a population basis

- Smoking cessation 0.01%
- Single embryo transfer at ART 0.06%
- Avoidance of non medically indicated elective delivery 0.29%
- Cervical cerclage 0.15%
- Progesterone prophylaxis 0.01%

Implementing all of these, rates would fall from 9.59% to 9.07% of livebirths

Chang HH Lancet 2013 381: 223 - 234

Summary

- Some evidence that progesterone prevents preterm birth in women at risk, although OPPTIMUM suggests it may not be as effective as previously thought
- By the time the child is 2 years of age, any “benefit” has disappeared
- Progesterone is not the panacea for the problems of preterm birth – we need to find alternatives.

Acknowledgements

- OPPTIMUM was funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales. The views expressed in this presentation are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.
- OPPTIMUM co authors: Neil Marlow, Claudia-Martina Messow, Andrew Shennan, Philip R Bennett, Steven Thornton, Stephen C Robson, Alex McConnachie, Stavros Petrou, Neil J Sebire, Tina Lavender, S Whyte, J Norrie
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- Collaborators, study midwives, pharmacists
- Trial steering committee, data monitoring committee
- The women who participated