Recurrent pregnancy loss – the role of Progestogens

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Progesterone in early pregnancy

- Follicular phase
  - Adrenal cortex

- Luteal phase
  - Corpus Luteum

- Pregnancy after 8 weeks
  - Trophoblast
Progesterone in early pregnancy

• **Genomic** mediated by nuclear PR Receptors PR-A and PR-B

• **Non-genomic** - membrane bound PR receptors cell signalling pathways
  - Mobilisation of intracellular Ca
  - Activation of MAPK
  - Inhibition of cAMP
Apposition

Adhesion

Invasion

Embryo

Endometrial stroma

Uterine epithelium

Invading trophoblast

Blocks proliferative effect of Estrogen
Induces genes allowing endometrium to respond to
& permits attachment of embryo
Immunomodulation – NK cells / cytokines
Progesterone & miscarriage

Murine Knock out models

- PR-A knockouts: impaired decidualisation and implantation failure
- PR-B knockouts: normal implantation but defective mammary gland development
Progesterone in early pregnancy

Progesterone secretion by Corpus luteum absolute requirement for successful pregnancy

Luteectomy before 8 weeks –

PR and miscarriage

Pregnancy rescued by administration of PR

Administration of anti-progesterone (Mifipristone) → pregnancy loss
Clinical expectation that Progesterone supplementation can prevent recurrent miscarriage

Progesterone & miscarriage

In vitro & In vivo data

Progesterone cardinal role in early pregnancy

low progesterone levels implicated in pathogenesis of pregnancy loss

Clinical expectation that Progesterone supplementation can prevent recurrent miscarriage
The validity of meta-analyses depends on the methodological quality of the included studies, the eligibility criteria used for the meta-analysis and the various reporting biases.

**Jadad score – Alex Jadad 1996**

3 questions

- Was the study described as randomised
- Was the study described as double blind
- Was there a description of withdrawals and dropouts

Randomisation described and appropriate
Method of blinding described and was appropriate
Meta-analysis of trials of progesterone in recurrent miscarriage

<table>
<thead>
<tr>
<th>Study</th>
<th>No of miscarriages</th>
<th>Rate ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swyer 1953²</td>
<td>7/27</td>
<td>0.58 (0.26 to 1.28)</td>
<td>26.14</td>
<td></td>
</tr>
<tr>
<td>Goldzieher 1964³</td>
<td>1/8</td>
<td>0.31 (0.04 to 2.27)</td>
<td>8.99</td>
<td></td>
</tr>
<tr>
<td>Le Vine 1964⁴</td>
<td>4/15</td>
<td>0.50 (0.19 to 1.31)</td>
<td>20.22</td>
<td></td>
</tr>
<tr>
<td>El-Zibdeh 2005⁵</td>
<td>11/82</td>
<td>0.46 (0.23 to 0.93)</td>
<td>44.65</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>132</td>
<td>0.49 (0.31 to 0.76)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=0.39$, df=3, $P=0.94$, $I^2=0\%$

Test for overall effect: $z=3.13$, $P=0.002$

Coomarasamy A et al. BMJ 2011;342:bmj.d1914

Modified Jadad Quality Scores between 0/5 to 2/5)
• Small numbers of patients
• No standardisation of treatment protocols
• Included women with 2 or more miscarriages
• No stratification by age / no of previous losses
• Different types of progesterone supplementation

Progesterone & recurrent miscarriages
- Limitations of existing data
Progesterone and early pregnancy loss – The PROMISE TRIAL

Funding – UK Department of Health
PROMISE: What is it?

Principal objective:

To test the hypothesis that amongst women with unexplained RM that progesterone supplementation (Utrogestan 400 mg bd) started between a +ve PT and no later than 6 weeks and continued until 12 weeks increases the live birth rate by at least 10% compared with placebo.
Inclusion Criteria

- 3 or more unexplained recurrent miscarriages
- Age 18 - 39 yrs at randomisation
- Spontaneous conception

Exclusion criteria

- Involuntary delay in conception of > 12 months
- APS or other thrombophilic disorder
- Uterine cavity abnormality
- Abnormal parental karyotype
# Table 2. Primary Outcome and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy at 6 to 8 weeks</td>
<td>326/398 (81.9)</td>
<td>334/428 (78.0)</td>
<td>1.05 (0.98–1.12)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ongoing pregnancy at 12 weeks</td>
<td>267/398 (67.1)</td>
<td>277/428 (64.7)</td>
<td>1.04 (0.94–1.14)</td>
<td>0.47</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>6/398 (1.5)</td>
<td>7/428 (1.6)</td>
<td>0.92 (0.31–2.72)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Miscarriage</strong></td>
<td>128/398 (32.2)</td>
<td>143/428 (33.4)</td>
<td>0.96 (0.79–1.17)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1/398 (0.3)</td>
<td>2/428 (0.5)</td>
<td>0.54 (0.05–5.92)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Live birth after 24 weeks 0 days of gestation</strong></td>
<td>262/398 (65.8)</td>
<td>271/428 (63.3)</td>
<td>1.04 (0.94–1.15)</td>
<td>0.45</td>
</tr>
<tr>
<td>Twin live births after 24 weeks 0 days of gestation</td>
<td>4/398 (1.0)</td>
<td>5/428 (1.2)</td>
<td>0.86 (0.23–3.18)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Gestation outcomes among women with live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth before 28 weeks 0 days of gestation</td>
<td>1/262 (0.4)</td>
<td>1/271 (0.4)</td>
<td>1.03 (0.06–16.49)</td>
<td>0.98</td>
</tr>
<tr>
<td>Live birth before 34 weeks 0 days of gestation</td>
<td>10/262 (3.8)</td>
<td>10/271 (3.7)</td>
<td>1.03 (0.44–2.45)</td>
<td>0.94</td>
</tr>
<tr>
<td>Live birth before 37 weeks 0 days of gestation</td>
<td>27/262 (10.3)</td>
<td>25/271 (9.2)</td>
<td>1.12 (0.67–1.87)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Neonatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any congenital anomaly</td>
<td>8/266 (3.0)</td>
<td>11/276 (4.0)</td>
<td>0.75 (0.31–1.85)</td>
<td>0.54</td>
</tr>
<tr>
<td>Genital congenital anomaly</td>
<td>1/266 (0.4)</td>
<td>1/276 (0.4)</td>
<td>1.04 (0.07–16.50)</td>
<td>0.98</td>
</tr>
<tr>
<td>Newborn survival to 28 days†</td>
<td>260/261 (99.6)</td>
<td>269/269 (100)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* The median gestational age at miscarriage was 7.3 weeks (interquartile range, 6.0 to 8.7) in the progesterone group and 7.1 weeks (interquartile range, 6.0 to 8.5) in the placebo group (relative risk, 0.9; 95% CI, 0.6 to 0.4; P=0.87).

† The end point is listed per trial participant.

‡ The end point is listed per neonate.
• Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages.
Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials

Gabriele Saccone, Corina Schoen, Jason M. Franasiak, Richard T. Scott Jr., Vincenzo Berghella 2017
Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial

Kumar et al 2014

Dydrogesterone (brand name = Duphaston)-

Orally active
Binds almost exclusively to PR (B > A)
Lacks oestrogenic / androgenic / anabolic properties
<table>
<thead>
<tr>
<th>First Author</th>
<th>Miscarriage</th>
<th></th>
<th>Livebirth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progestogen</td>
<td>Control</td>
<td>Progestogen</td>
<td>Control</td>
</tr>
<tr>
<td>El-Zibdeh et al 2005</td>
<td>11/82</td>
<td>14/48</td>
<td>71/82</td>
<td>34/48</td>
</tr>
<tr>
<td></td>
<td>13.4%</td>
<td>29%</td>
<td>86.6%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No data on gestation at randomisation</td>
<td></td>
</tr>
<tr>
<td>Kumar et al 2014</td>
<td>12/175</td>
<td>19/173</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.9%</td>
<td>16.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Randomised after confirmation of live pregnancy NO difference in miscarriage within 4 weeks of randomisation</td>
<td></td>
</tr>
<tr>
<td>Coomarasamy et al 2015 (PROMISE)</td>
<td>128/398</td>
<td>143/428</td>
<td>262/398</td>
<td>271/428</td>
</tr>
<tr>
<td></td>
<td>32.2%</td>
<td>33.4%</td>
<td>68.8%</td>
<td>63.3%</td>
</tr>
</tbody>
</table>
Progesterone in Early Pregnancy - Conclusions

Recent RCTs – of varying quality – discordant results

Highlight the differences between different preparations, route of administration, dosing and timing of intervention

Head to head studies needed

Recruitment criteria 3 or more miscarriages not 2 or more

Routine use of progesterone / progestagens NOT indicated
Inhibits NK cell activity
Th2 dominant cytokine response
Controls MMP activity
Upregulates TF and PAI-1 activity