# Recurrent pregnancy loss – the role of Progestogens

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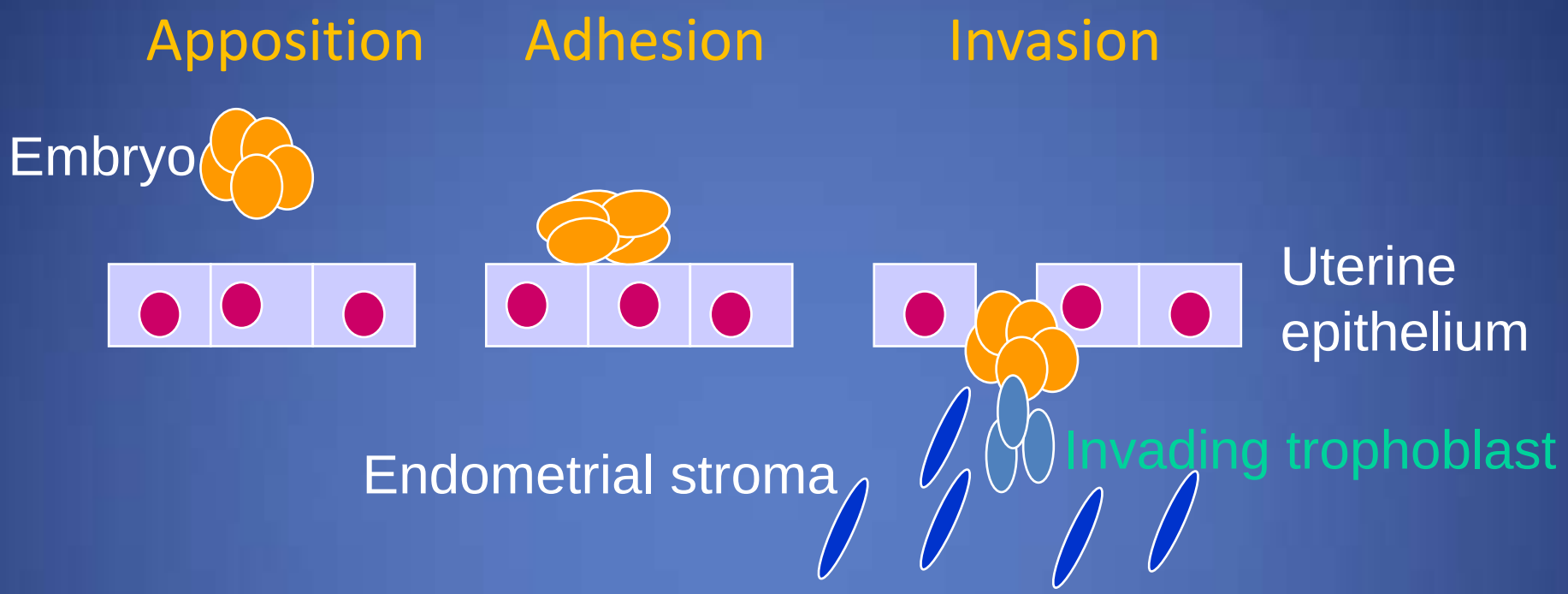
# Progesterone in early pregnancy

| | |
|---|---|
| • 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




Blocks proliferative effect of Estrogen

Induces genes allowing endometrium to respond to & permits attachment of embryo

Immunomdulation – NK cells / cytokines

## 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

Lutectomy before 8 weeks –

⬇ PR and miscarriage

Pregnancy rescued by administration of PR

Administration of anti-progesterone (Mifipristone )

➡ pregnancy loss

# 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

# Progesterone in early pregnancy – Meta-analyses

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.

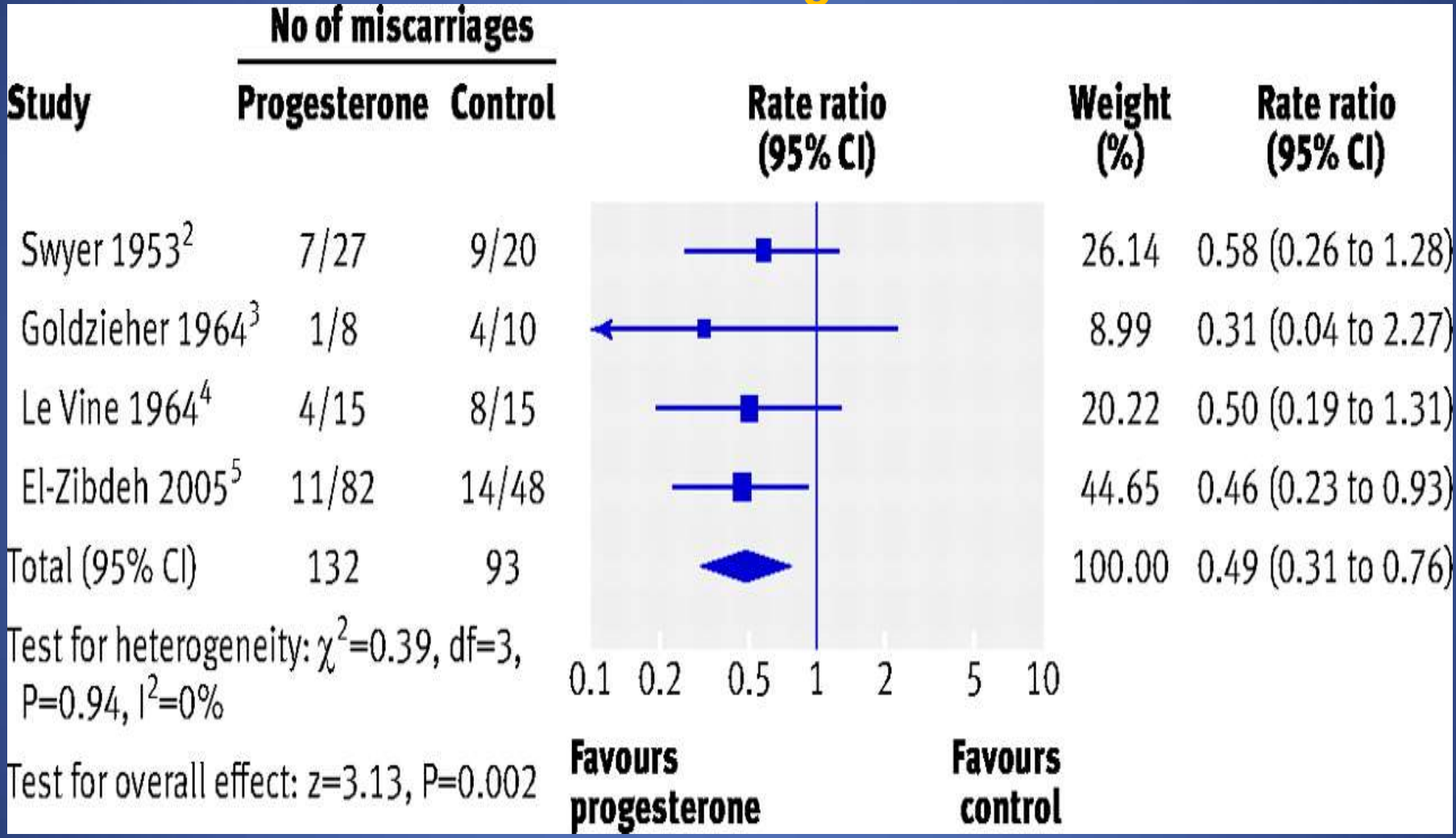
## Jadad score – Alex Jadad 1996

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




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

Modified Jadad Quality Scores between 0/5 to 2/5)

thebmj

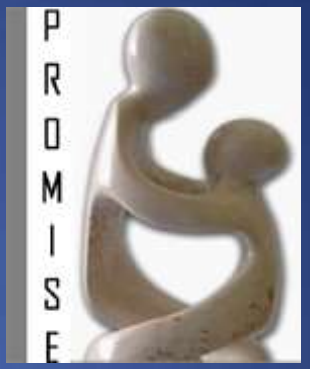
## Progesterone & recurrent miscarriages
## - Limitations of existing data

- 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 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

# PROMISE

## 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

# Promise - Primary and Secondary Outcomes

**Table 2. Primary Outcome and Secondary Outcomes.**

| Outcome | Progesterone | Placebo | Relative Risk (95% CI) | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Pregnancy outcomes | | | | |
| Clinical pregnancy at 6 to 8 weeks | 326/398 (81.9) | 334/428 (78.0) | 1.05 (0.98–1.12) | 0.16 |
| Ongoing pregnancy at 12 weeks | 267/398 (67.1) | 277/428 (64.7) | 1.04 (0.94–1.14) | 0.47 |
| Ectopic pregnancy | 6/398 (1.5) | 7/428 (1.6) | 0.92 (0.31–2.72) | 0.88 |
| Miscarriage* | 128/398 (32.2) | 143/428 (33.4) | 0.96 (0.79–1.17) | 0.70 |
| Stillbirth | 1/398 (0.3) | 2/428 (0.5) | 0.54 (0.05–5.92) | 0.61 |
| Live birth after 24 weeks 0 days of gestation† | 262/398 (65.8) | 271/428 (63.3) | 1.04 (0.94–1.15) | 0.45 |
| Twin live births after 24 weeks 0 days of gestation† | 4/398 (1.0) | 5/428 (1.2) | 0.86 (0.23–3.18) | 0.82 |
| Gestation outcomes among women with live births | | | | |
| Live birth before 28 weeks 0 days of gestation | 1/262 (0.4) | 1/271 (0.4) | 1.03 (0.06–16.49) | 0.98 |
| Live birth before 34 weeks 0 days of gestation | 10/262 (3.8) | 10/271 (3.7) | 1.03 (0.44–2.45) | 0.94 |
| Live birth before 37 weeks 0 days of gestation | 27/262 (10.3) | 25/271 (9.2) | 1.12 (0.67–1.87) | 0.68 |
| Neonatal outcomes‡ | | | | |
| Any congenital anomaly | 8/266 (3.0) | 11/276 (4.0) | 0.75 (0.31–1.85) | 0.54 |
| Genital congenital anomaly | 1/266 (0.4) | 1/276 (0.4) | 1.04 (0.07–16.50) | 0.98 |
| Newborn survival to 28 days† | 260/261 (99.6) | 269/269 (100) | 1.00 (0.99–1.00) | 0.32 |

* 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, 0.0; 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.

Coomarasamy A et al. N Engl J Med 2015;373:2141-2148

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# Promise trial - Conclusion

- 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

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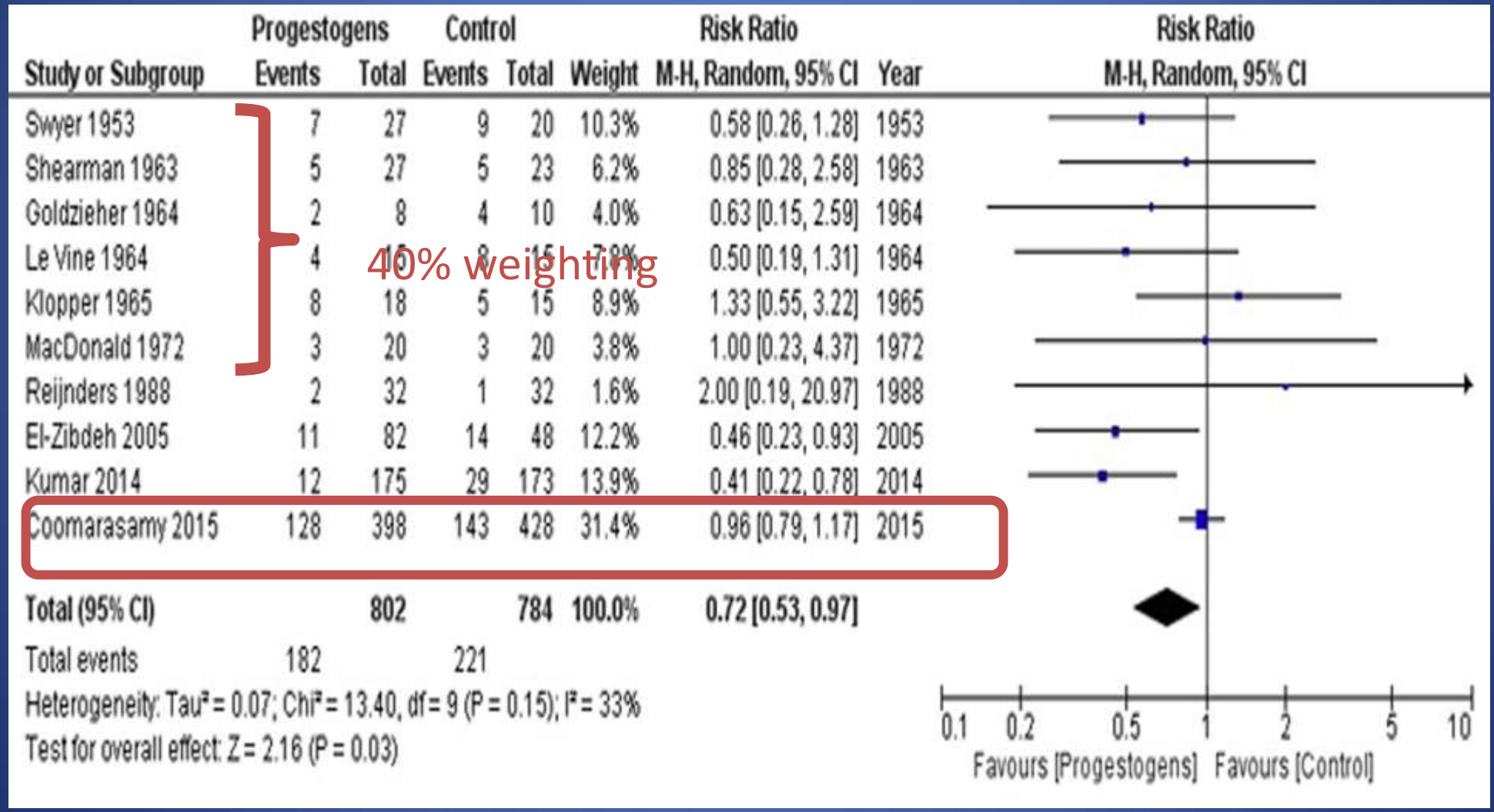
# Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials

Gabriele Saccone, Corina Schoen, Jason M. Franasiak, Richard T. Scott Jr., Vincenzo Berghella 2017

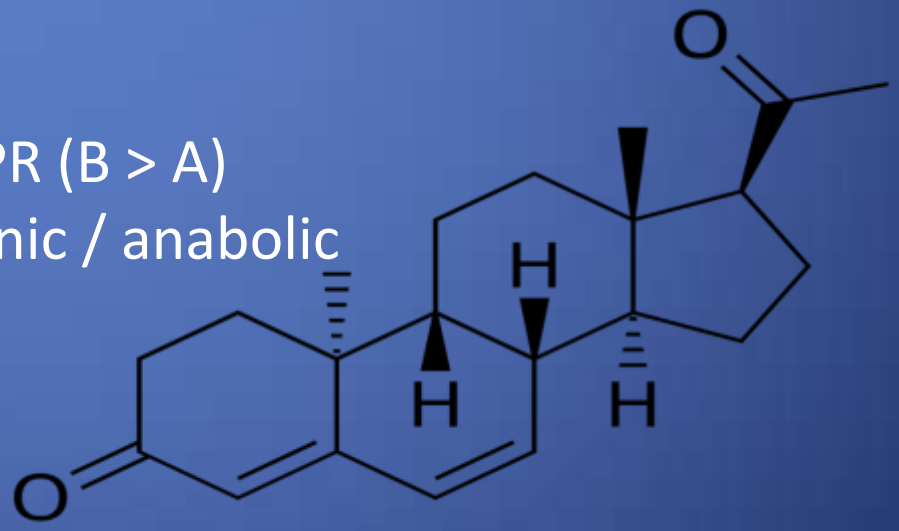


# Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial

Kumar et al 2014

Dydrogesterone (brand name = Duphaston)-

Orally active
Binds almost exclusively to PR (B > A)
Lacks oestrogenic / androgenic / anabolic properties



| First Author | Miscarriage | | Livebirth | |
|---|---|---|---|---|
| | Progestogen | Control | Progestogen | Control |
| El-Zibdeh et al 2005 | 11/82<br>13.4% | 14/48<br>29% | 71/82<br>86.6% | 34/48<br>71% |
| Kumar et al 2014 | 12/175<br>6.9% | 19/173<br>16.8% | Not reported | |
| Coomarasamy et al 2015 (PROMISE) | 128/398<br>32.2% | 143/428<br>33.4% | 262/398<br>68.8% | 271/428<br>63.3% |

No data on gestation at randomisation

Randomised after confirmation of live pregnancy

NO difference in miscarriage within 4 weeks of randomisation

# Progesterone in Early Pregnancy - Conclusions

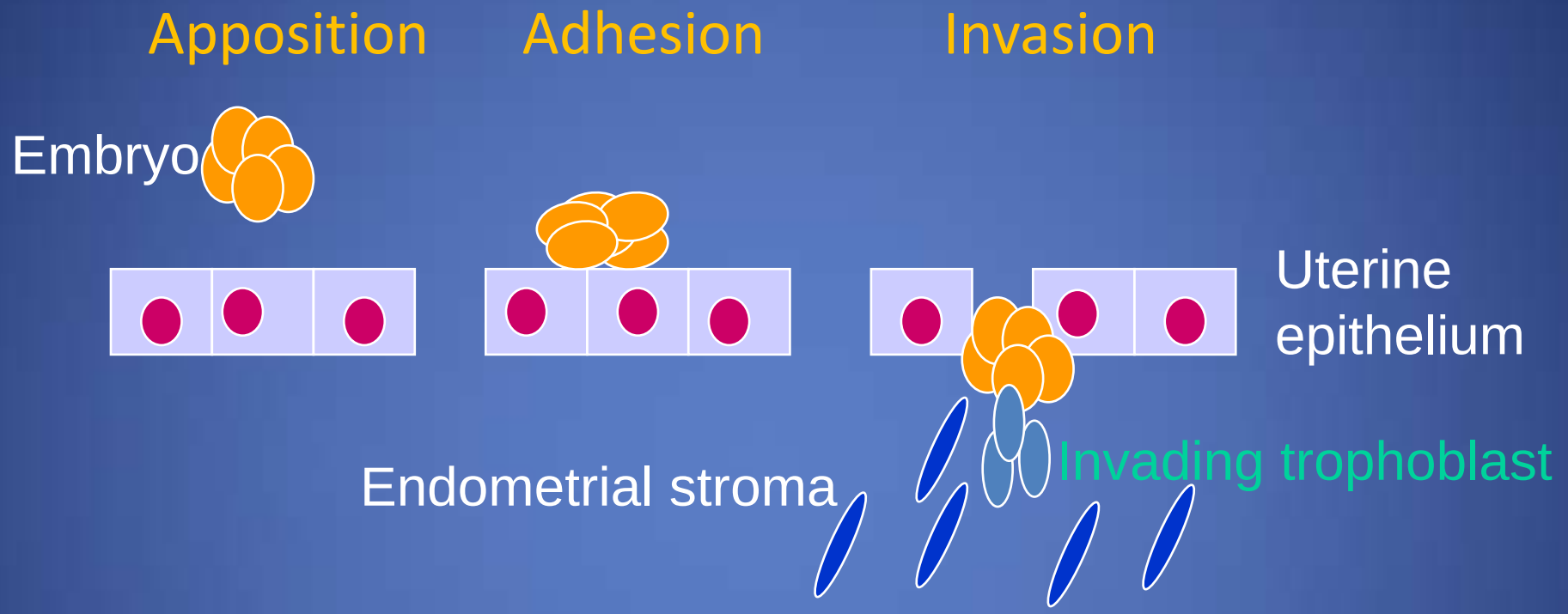
Recent RCTs – of varying quality – discordant results

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