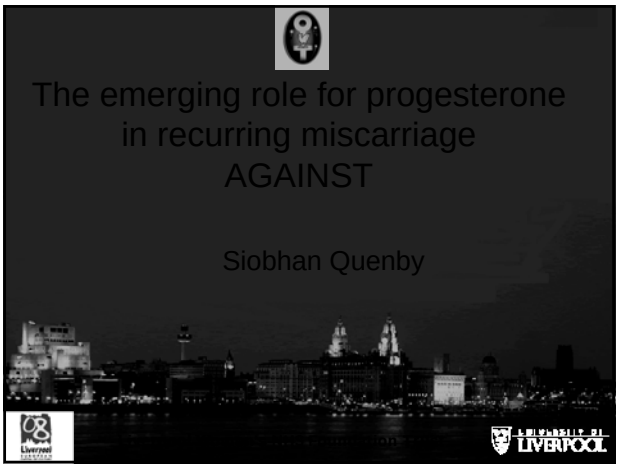


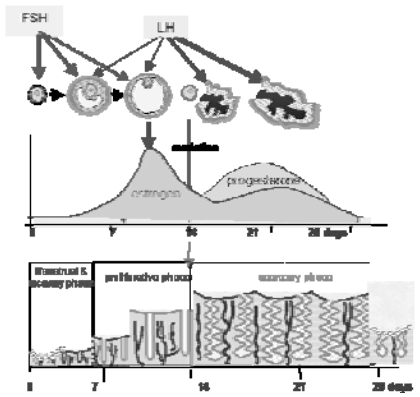
Background

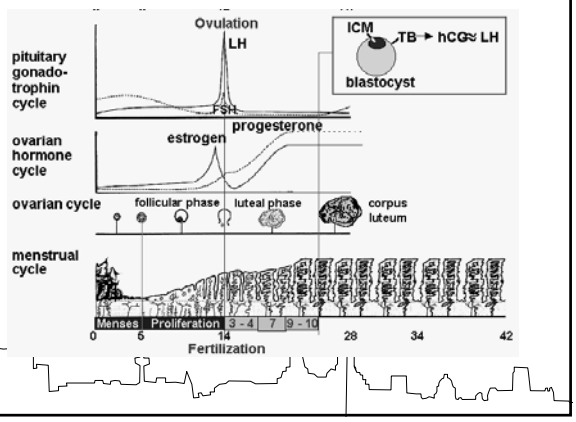
- Member of MRHA EAG
- Recently changed recommendations for use progesterone in
  - threatened and
  - ? In recurrent miscarriage
- Debate

- **2005 health professional query:**
- Committee's previous advice
  - indications for Gestone and Duphaston in threatened abortion and recurrent miscarriage should be removed from the licence?
- To reconsider this

Progesterone

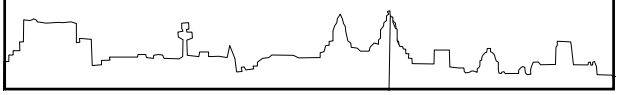
- an endogenous hormone
- derived from cholesterol steroids
- produced by the corpus luteum & placenta, adrenals.
- half-life of about 5 minutes,
- 66% metabolised in the liver accounting
- metabolite is pregnanediol.
- progesterone bound to albumin and corticosteroid binding globulin.
- rapidly absorbed
- nearly all of a low oral dose is metabolised in the liver.





Rationale

- Originally progesterone was thought to swap from corpus luteum production to placenta at 10-12 weeks gestation

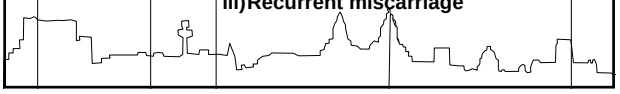


AUTHORISED PROGESTOGENIC PRODUCTS IN THE UK

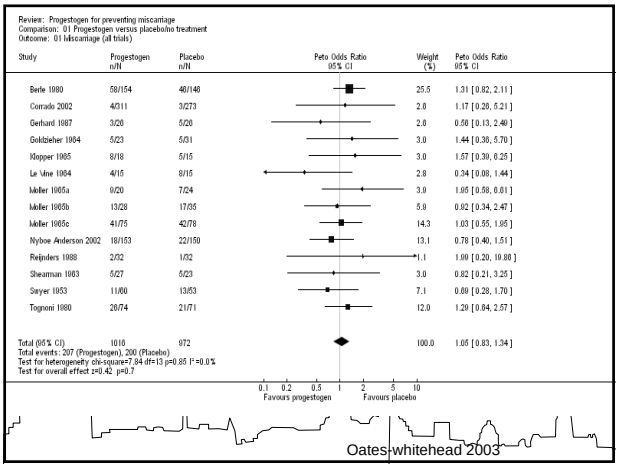
- **Natural progesterone**
  - Gestone and Crinone
  - Cyclogest– not authorised in pregnancy
- **Dydrogesterone**
  - (Duphaston)
  - potent orally active
  - similar to endogenous progesterone
  - rapidly absorbed
  - Its primary metabolite, also a potent progestogen.
- medroxprogesterone acetate and norethisterone
  - **not authorised in pregnancy**.

Progesterone

Gestone	IM	**i) Maintenance of early pregnancy in cases of a history of recurrent miscarriage due to inadequate luteal phase.** **ii)** Embryo transfer –until weeks 8-16 of pregnancy
Crinone	Vaginal gel	**i)** During IVF – ii) Treatment of infertility
Dydrogesterone		
Duphaston	oral	i) Infertility, **ii) Threatened abortion** **iii)Recurrent miscarriage**



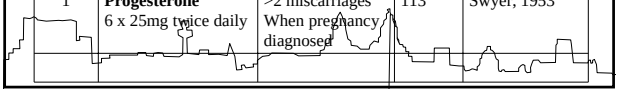
- What does the Cochrane library say?



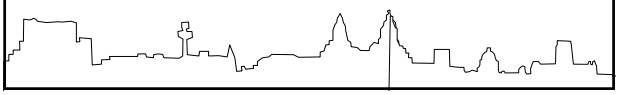
Oates-whitehead 2003

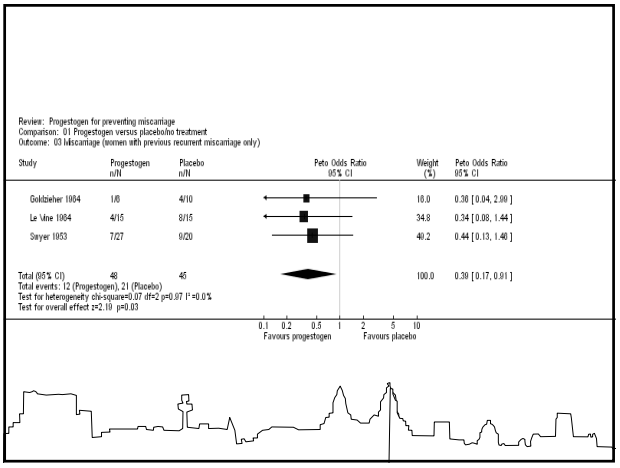
No. studies	Type of progestogen	Treatment regimen	No. of women	Author, date of study
Oral progestogen				
1	medroxyprogesterone acetate	10mg/day	54	Goldzeiher, 1964
3	medroxyprogesterone acetate	20mg/day for 3 days; 10mg/day for 11 days	40;63; 153	Molterabe, 1965a,b,c
1	cyclopentylenol ether of progesterone	Twice daily	33	Klopper, 1965
1	Hydroxyprogesterone caproate	250 – 500mg/week	50	Sheerman, 1963

Oral or IM				
1	Oral allylestrenol (90%) or IM hydroxyprogesterone caproate (10%)	15-20mg/day or 250mg daily	300	Berle, 1980
1	Oral allylestranol or IM hydroxyprogesterone caproate	10mg/day or 25mg every 5 days	139	Tognoni, 1980
Vaginal suppositories				
1	**Progesterone**	6 x 25mg	303	Nyboe Anderson, 2002
1	**Progesterone**	200mg thrice daily	56	Gerhard, 1987
Gluteal pellets				
1	**Progesterone** 6 x 25mg twice daily	>2 miscarriages When pregnancy diagnosed	113	Swyer, 1953



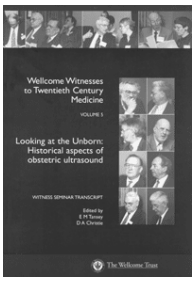
IM progestogen				
2	Hydroxyprogesterone caproate	500mg	30;64	Le Vine, 1964 Reijnders, 1988
1	Natural progesterone followed by hydroxyprogesterone caproate	200mg for 3 days/340mg twice weekly for 11 days	584	Corrado, 2002

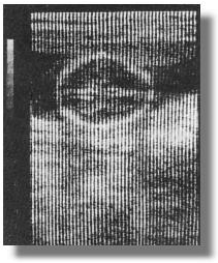




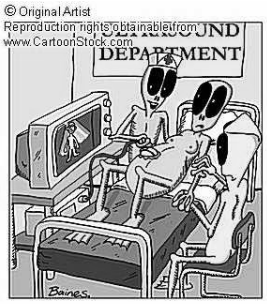
Cochrane

- Poor quality
  - ? Randomisation method
  - Inadequately powered
- No idea
  - Dose? Route? timing
  - Di Renzo 2005

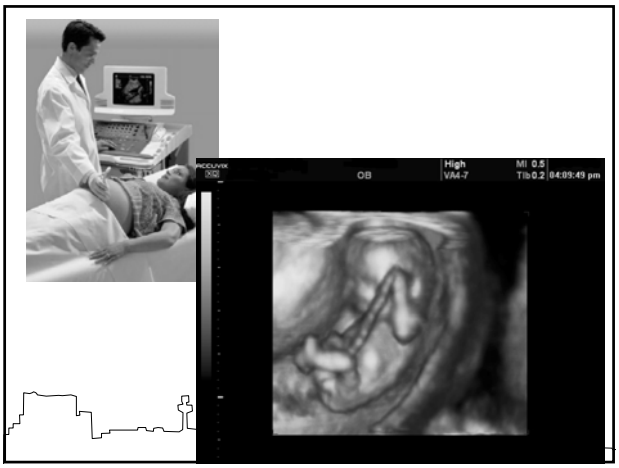




"It's a girl!"



"Don't worry, they normally look like little humans during the early scans."

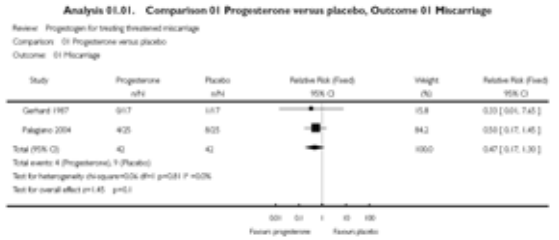


If works with RM should also work with threatened miscarriage

- Cochrane?

Cochrane review threatened miscarriage

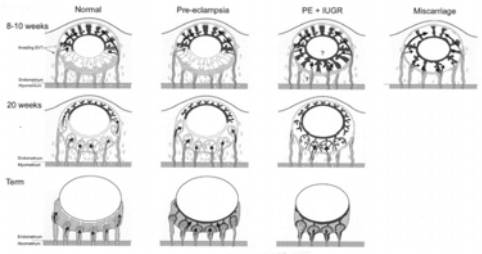
-



Wahabi et al 2007

Too late

- BY time realised pregnant placenta produces enough progesterone itself.



Burton and Jauniaux *J Soc Gynecol Investig 2004;11:342–5*

New studies in RM

Outcome	Dydrogesterone (n=82)	hCG (n=50)	Control (n=48)
Abortion (n;%)	11 (13)*	9 (18)	14 (29)
Viable pregnancy (n;%)	71 (87)	41 (82)	34 (71)

*p=0.028 vs control
El-Zibah et al.,2005

- Not blind,
- small numbers no power calculation

Safety

- Androgenic?
  - Hypospadias
    - Common 5-30/100000 male births
    - Possibly increased if progesterone in pregnancy
    - Carmichael et al., 2005
- Thrombosis?
  - As has OC/pill and HRT same progesterone

Side effects

- Liverpool
  - Constipation
  - Depression
  - General lethargy
  - Vaginal soreness
  - Messy discharge
- nausea, breast changes, oedema, weight gain, cholestatic jaundice, depression, headache, insomnia, alopecia, hirsutism, transient dizziness, acne
- allergic reactions and rashes,

RECOMMENDATIONS

- removing the indication of ‘threatened miscarriage’ from the product licence for Duphason on the basis of a lack of efficacy
- ‘recurrent miscarriage’ ?
- the option to re-consider if further RCT.

Acknowledgements

Jane Woolley MHRA

RECOMMENDATIONS

- removing the indication of ‘threatened miscarriage’ from the product licence for Duphaston on the basis of a lack of efficacy;
- retaining the indication of ‘recurrent miscarriage’ in the product licences for Duphaston and Gestone, but with amendments to the SPC to clarify the definition of recurrent miscarriage as 3 or more prior consecutive miscarriages and to remove reference to luteal phase defect,
- the option to re-consider if further RCT.