EVIDENCE BASED PRACTICE: PROGESTERONE IN THREATENED AND RECURRENT MISCARRIAGE

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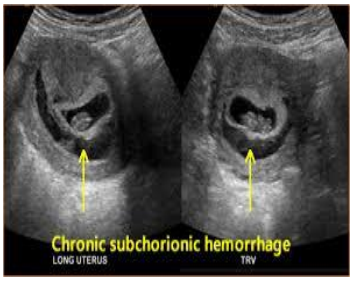
Recurrent Miscarriage

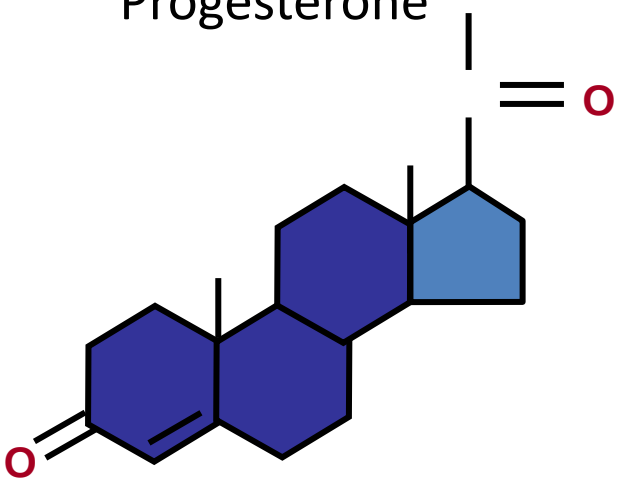
- Defined as 3 or more pregnancy losses up to 24 weeks /viability
- Affects 1% couples
- Multiple risk factors- age, genetic factors, anatomical factors, medical disorders/thrombophilia
- Only unexplained will be addressed here

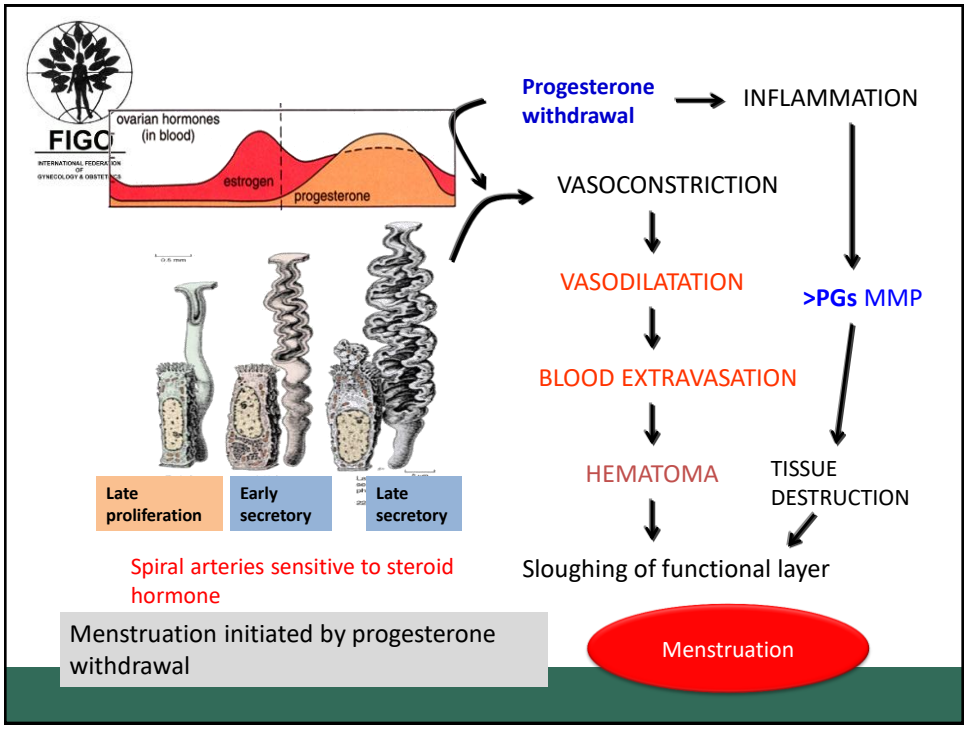
Threatened Miscarriage

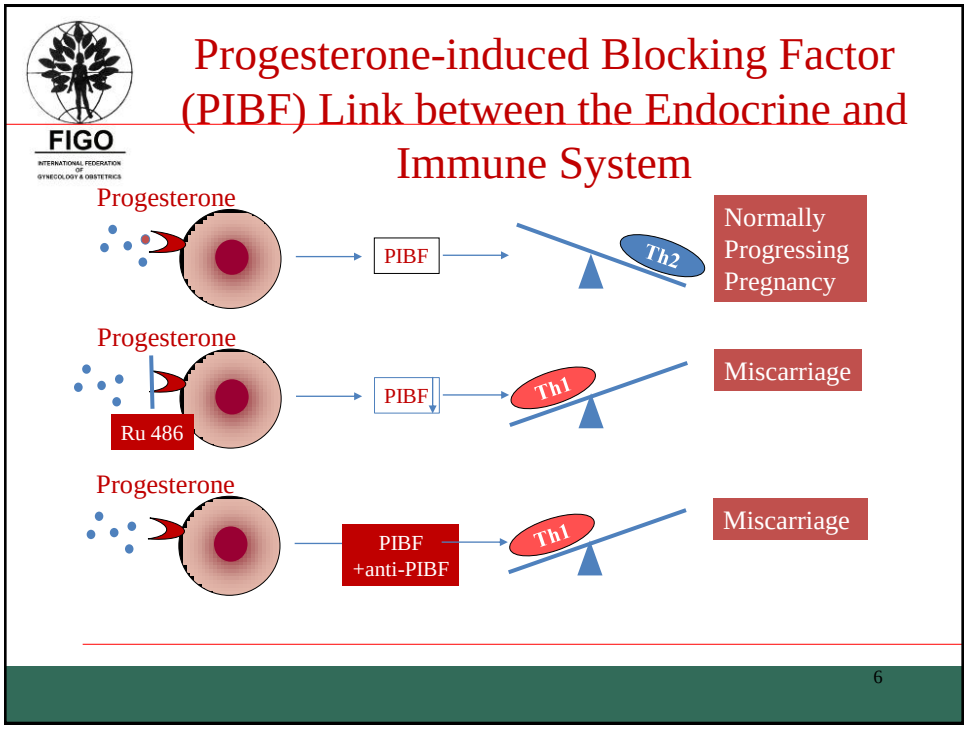
- Defined in bleeding in a viable pregnancy with a closed cervix
- Happens in 15-20% of pregnancies
- Half result in pregnancy loss
- Those that don't have a higher risk of preterm delivery, low birthweight and perinatal death



Progesterone



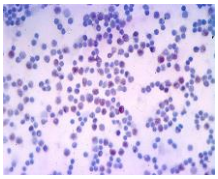

FIGO
ovarian hormones (in blood)
estrogen
progesterone
Late proliferation
Early secretory
Late secretory
Spiral arteries sensitive to steroid hormone
Progesterone withdrawal
INFLAMMATION
VASOCONSTRICTION
VASODILATATION
>PGs MMP
BLOOD EXTRAVASATION
HEMATOMA
TISSUE DESTRUCTION
Sloughing of functional layer
Menstruation initiated by progesterone withdrawal
Menstruation


FIGO
Progesterone-induced Blocking Factor (PIBF) Link between the Endocrine and Immune System
Progesterone
PIBF
Th2
Normally Progressing Pregnancy
Progesterone
Ru 486
PIBF
Th1
Miscarriage
Progesterone
PIBF +anti-PIBF
Th1
Miscarriage
6

Endocrino-immune Interaction

Progesterone modulates the mother-to-be's immune response from

Rejection → Protection



Women with a history of ≥ 3 consecutive miscarriages

'Women with idiopathic recurrent miscarriage may benefit from the immunomodulatory properties of progesterone in early pregnancy.'

Di Renzo GC, et al. Gynecol Endocrinol 2012; 28(11): 825-32.

Publication of Indian Society of Assisted Reproduction
Journal of Human Reproductive Sciences
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J Hum Reprod Sci. 2012 Sep-Dec; 5(3): 248–251.
doi: 10.4103/0974-1208.106335
PMCID: PMC3604830

Progesterone supplementation in women with otherwise unexplained recurrent miscarriages

Munawar Hussain,[1,2] Samawal El-Hakim,[3] and David J Cahill[1,4]

- Women with recurrent miscarriages recruited
- 3 groups depending on serum progesterone levels at start and 48 hours later
- Those with inadequate P, progesterone vaginal pessaries 400 mg BD until 12 weeks
- 213 pregnancy cycles
- Reduction in miscarriage rate 35% vs 45%
- Compared with general rate – no placebo arm

Cochrane Database of Systematic Reviews

Progestogen for preventing miscarriage

New search | Review | Intervention

David M Haas ✉, Patrick S Ramsey

First published: 31 October 2013

- 14 trials(2158 women)
- No statistically significant reduction of miscarriages between progesterone or placebo
- Subgroup analysis of those with recurrent miscarriages
  - 4 trials(225 women)
  - Significant reduction of miscarriage rate (OR 0.39; 95% CI 0.21 -0.72)
- No difference in route of administration
- No difference in rate of PTB, neonatal death, fetal genital anomalies

What is the evidence of the uncertainty?

Limitations of existing data

- The quality of the four trials was poor (modified Jadad quality scores ranged from 0/5 to 2/5
- Participant numbers of patients was very small (N=132)
- Confidence intervals were wide
- 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 and route of administration

Coomarasamy A et al. BMJ 2011; 342: d1914. doi: 10.1136/bmj.d1914

PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation

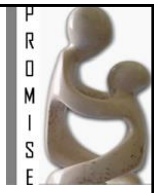
The study found no evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained recurrent miscarriages.

Coomarasamy A, Williams H, Truchanowicz E, Seed P T, Small R, Quenby S, Gupta P, Dawood F, Koot Y E, Atik R B, Bloemenkamp K W, Brady R, Briley A, Cavallaro R, Cheong Y C, Chu J, Eapen A, Essex H, Ewies A, Hoek A, Kaaijk E M, Koks C A, Li T, MacLean M, Mol B W, Moore J, Parrott S, Ross J A, Sharpe L, Stewart J, Trépel D, Vaithilingam N, Farquharson R G, Kilby M D, Khalaf Y, Goddijn M, Regan L & Rai R.

▶ Detailed Author information

Health Technology Assessment Volume: 20, Issue:41, Published in May 2016

The PROMISE trial (UK)



Principal objective:

Progesterone supplementation (Utrogestan® 400 mg bid) started between **a positive pregnancy** test and no later than 6 weeks and continued until 12 weeks in women with **unexplained recurrent miscarriage** increases the live birth rate by at least 10% compared with placebo

Trial design

Randomised, double-blind, placebo controlled

Setting

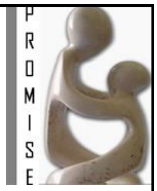
8 centres (36 in UK and 9 in The Nederland)

Number of participants

836

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

The PROMISE trial (UK)



Inclusion Criteria

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

Exclusion criteria

- Involuntary delay in conception of > 12 months
- APS or other thrombophilic disorder
- Uterine cavity abnormality
- Abnormal parental karyotype

The PROMISE trial (UK)
STUDY DESIGN

1568 WOMEN RANDOMISED

836 CONCEIVED NATURALLY

404 PROGESTERONE 432 PLACEBO

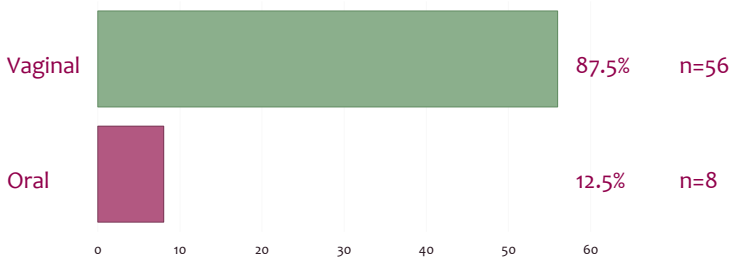
LIVE BIRTH RATE 65.8% VS 63.3%
NO SIGNIFICANT DIFFERENCE

PROGESTERONE STARTED AFTER POSITIVE PREGNANCY TEST

Why vaginal progesterone?

International clinician survey

If you use progesterone, do you use vaginal progesterone or oral dydrogesterone?



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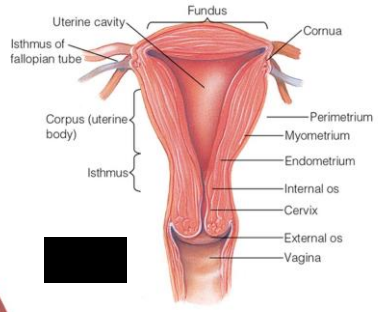
Why vaginal progesterone?

Local effect



[redacted]

[redacted]

The role of progesterone in recurrent miscarriage
PROMISE criticisms: ROUTE

Why vaginal progesterone?

IVF experience

Preterm birth studies

Conclusions

- **First well designed RCT** with **live birth rate** as primary outcome (different from RR of miscarriage outcome in previous studies with progesterone[1] or dydrogesterone[2])
- **Vaginal progesterone was started from positive urinary pregnancy test** (≤ 6 weeks of gestation) until week 12 of pregnancy.
- **Main limitation of the study:**
  Progesterone treatment was initiated only after urinary pregnancy test was confirmed, and thus this study result cannot address, as the authors mention, whether progesterone supplementation should be more effective in reducing the risk of miscarriage if administered during the luteal phase of the cycle,
  BEFORE confirmation of pregnancy

NEJM March 2016: Letter to the Editor

1 Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev 2013; 10: CD003511.
2 Kumar A, Begum N, Prasad S, Aggarwal S, Sharma S. 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. Fertil Steril 2014;102(5): 1357.e3 1363.e3.

Original Article

Peri-conceptional progesterone treatment in women with unexplained recurrent miscarriage: a randomized double-blind placebo-controlled trial

Alaa M. Ismail, **Ahmed M. Abbas**, Mohammed K. Ali & Ahmed F. Amin

Pages 1-7 | Received 14 Oct 2016, Accepted 20 Jan 2017, Accepted author version posted online: 23 Jan 2017, Published online: 15 Feb 2017

700 women – 350 in each arm (progesterone pessary 400 mg BD vs placebo)

Starting from luteal phase to 28 weeks

Miscarriage rate	12.4% vs 23.3%	(p= 0.001)
Pregnancy > 20 weeks	87.6 versus 76.7%	(<0.05)
Live birth rate	91.6 versus 77.4%	($p < 0.05$).

Conclusions: Progesterone is more effective than placebo in reducing the risk of miscarriage if administered in the luteal phase of the cycle, before confirmation of pregnancy in women with history of unexplained RM.

Summary

Vaginal progesterone vs oral dydrogesterone

- Coomarasami et al (PROMISE) favoring vag.P4 (NS)
- Ismail et al – vag.P4 benefit
- Kumar et al – oral DHG benefit
- Meta-analysis (incl. PROMISE) benefit
  - However, 7 of the 10 trials before 1990, and poor quality
  - Largest trial (PROMISE) more patients that all other 9 put together – results not statistically significant

ORIGINAL ARTICLE: EARLY PREGNANCY

Luteal start vaginal micronized progesterone improves pregnancy success in women with recurrent pregnancy loss

Mary D. Stephenson, M.D., M.Sc.,[a,b] Dana McQueen, M.D., M.A.S.,[a] Michelle Winter, M.D.,[b] and Harvey J. Kliman, M.D., Ph.D.[c]

[a] University of Illinois Recurrent Pregnancy Loss Program, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, Illinois; [b] University of Chicago, Chicago, Illinois; and [c] Department of Obstetrics, Gynecology and Reproductive Sciences, Reproductive and Placental Research Unit, Yale University School of Medicine, New Haven, Connecticut

The use of luteal start vaginal micronized P (*Utrogestan*® vaginal capsules 100mg - 200mg BID) was associated with improved pregnancy success in a strictly defined cohort of women with RPL

Stephenson MD, et al. *Fertil Steril* 2016; doi.org/10.1016/j.fertnstert.2016.11.029

Cochrane Database of Systematic Reviews

Progestogen for treating threatened miscarriage

New search | Conclusions changed | Review | Intervention

Hayfaa A Wahabi, Amel A Fayed, Samia A Esmaeil, Rasmieh A Al Zeidan

First published: 7 December 2011

Editorial Group: Cochrane Pregnancy and Childbirth Group

- 4 studies (421 participants)
- Reduction in the rate of spontaneous miscarriage with progestogens compared with placebo (RR 0.53; 95%CI 0.35 to 0.79)
- No increase in antepartum haemorrhage (RR 0.76; 95% CI 0.30-1.94)
- No increase in pregnancy induced hypertension (RR 1.00 95% CI 0.54 to 1.88)
- No difference in rate of congenital abnormalities (RR 0.70 ;95% CI 0.10 to 4.82

Threatened miscarriage & Clinical Data: where is the evidence?

Most published studies with either micronized progesterone or dydrogesterone on management of threatened miscarriage

1. are underpowered in achieving clinical endpoints with any statistical significance[1].
2. Contains important confounding variables which either weaken or totally invalidate their conclusions[1].
3. Based on scarce data from two methodologically poor trials, there is no evidence to support the routine use of progestogens for the treatment of threatened miscarriage[2].

1.Coomarasamy A et al. BMJ 2011; 342: d1914. doi: 10.1136/bmj.d1914

2.Wahabi HA, Abed Althagafi NF, Elawad M. Progestogen for treating threatened miscarriage. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD005943. DOI: 10.1002/14651858.CD005943.pub2.

Progestogens in threatened miscarriage: conclusions

- Cochrane Reviews was limited by the small number and the poor methodological quality of eligible studies (four studies; N=421)
- Only one of the four studies met the predefined criteria on some level (Pandian, 2009)
- A large randomized, double-blind, placebo-controlled multicenter trial (N>4000) was mandatory and is now underway to evaluate the effectiveness of progesterone to prevent miscarriage in women with early pregnancy bleeding - The PRISM trial (Coomarasamy 2014)

Wahabi HA, et al. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005943. DOI: 10.1002/14651858.CD005943.pub4

PRISM

Progesterone In Spontaneous Miscarriage

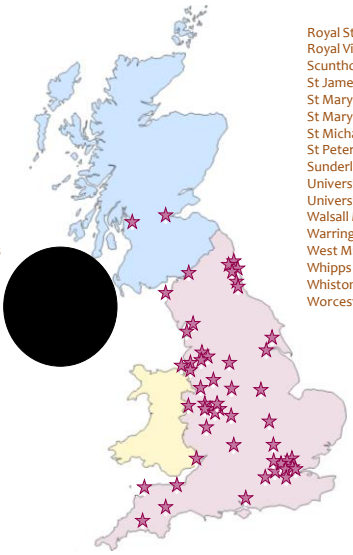
The effectiveness of progesterone to prevent miscarriage in women with early pregnancy bleeding

A randomised placebo-controlled trial

Professor Arri Coomarasamy
School of Clinical and Experimental Medicine
University of Birmingham , c/o Academic Unit, Birmingham Women's Hospital
Mindelsohn Way. Birmingham B15 2TG
Telephone: 0121 627 2775
Email: a.coomarasamy@bham.ac.uk

PRISM TRIAL RECRUITMENT CENTRES

Airedale General Hospital, Steeton
Birmingham Heartlands Hospital
Birmingham Women's Hospital
Bradford Royal Infirmary
Burnley General Hospital, East Lancashire
Chelsea and Westminster Hospital, London
Cumberland Infirmary, Carlisle
Derriford Hospital, Plymouth
East Surrey Hospital, Redhill
Glasgow Royal Infirmary
Guys and St Thomas Hospitals, London
Hinchingbrooke Hospital, Huntingdon
Hull Royal Infirmary
James Cook University Hospital, South Tees
John Radcliffe Hospital, Oxford
Kings College Hospital, London
Liverpool Women's Hospital
Musgrove Park Hospital, Taunton
New Cross Hospital, Wolverhampton
North Devon District Hospital, Barnstaple
North Tyneside General Hospital
Princess Royal Hospital, Telford
Queen Alexandra Hospital, Portsmouth
Queen's Hospital, Burton
Queen's Medical Centre, Nottingham
Royal Devon and Exeter Hospital
Royal Hallamshire Hospital, Sheffield
Royal Infirmary of Edinburgh
Royal London Hospital
Royal Preston Hospital



Royal Stoke University Hospital
Royal Victoria Infirmary, Newcastle
Scunthorpe General Hospital
St James University Hospital, Leeds
St Mary's Hospital, Manchester
St Mary's Hospital, London
St Michael's University Hospital, Bristol
St Peter's Hospital, Chertsey
Sunderland Royal Hospital
University College Hospital, London
University Hospital, Coventry
Walsall Manor Hospital
Warrington Hospital
West Middlesex University Hospital, London
Whipps Cross University Hospital, London
Whiston Hospital, Merseyside
Worcestershire Royal Hospital, Worcester

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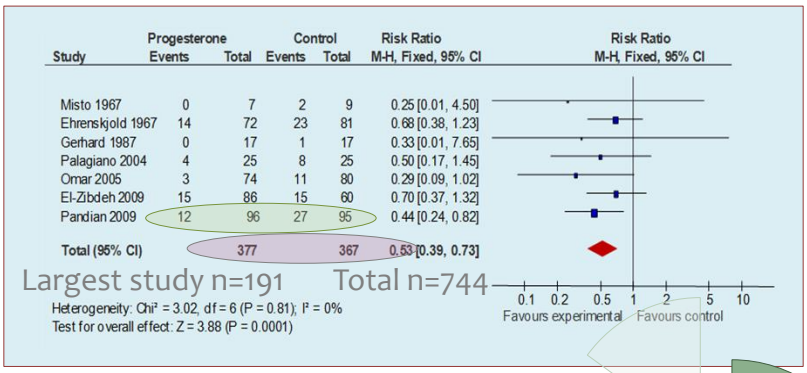
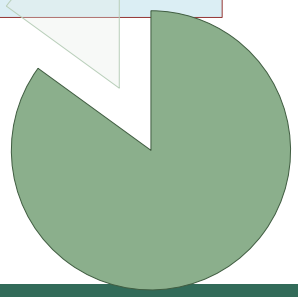


3532 / 4150 = 85%
randomised to date



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PRISM - Aim and Objectives

Primary aim

PRISM will test the hypothesis that in women presenting with vaginal bleeding in the first trimester progesterone (Utrogestan **400 mg vaginal capsules, twice** daily) started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac and continued to 16 completed weeks of gestation, compared with placebo **increases maternities with live births beyond 34 completed weeks by at least 5%.**

CONCLUSION

CONCLUSION

- What do we already do?
- Does it work?
- Is it harmful?
- What's the best route to minimise side effects and maximise any potential effect?