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Vaginal micronized progesterone in pregnancy miscarriage, why to start as early as possible?

Paul PIETTE, PharmD
Senior Research fellow
Scientific & Medical Affairs
Besins Healthcare Global

ppiette@besins-healthcare.com

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Financial disclosure

Paul Piette, PharmD
Scientific & Medical Affair
Consultant for Besins Healthcare Global
Lecturer at PREIS School

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Why vaginal micronized progesterone * (Mic P4) in pregnancy miscarriage?

** Instead of oral or synthetic progestagens including dydrogesterone*

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Safety first, but also efficacy ?

- The **precautionary principle** or precautionary approach to risk management states :

> " if an action or policy comes with a suspected risk of causing harm to the public or to the environment, and in the **ABSENCE OF SCIENTIFIC CONSENSUS** that the action or policy is indeed harmful, the **BURDEN OF PROOF** that it is **NOT HARMFUL** fails on **THOSE TAKING THE ACTION** "

https://sisu.ut.ee/env-intro/book/12-major-environmental-principles

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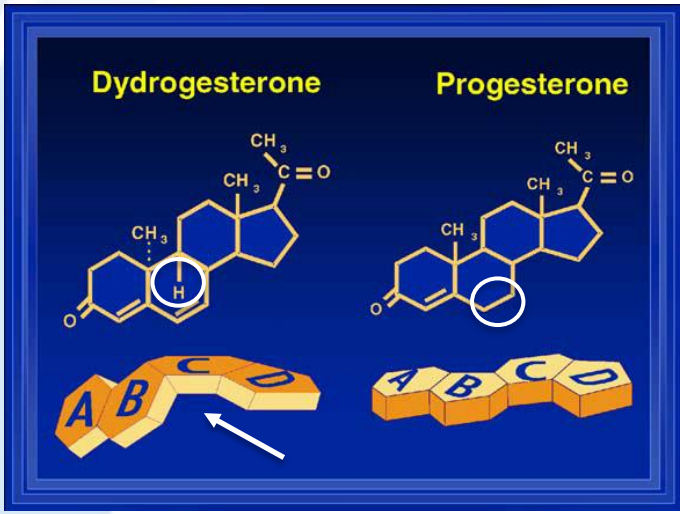
Different progestogens may differ in their hormonal activity depending on their structure



Micronized progesterone (Mic P4) has the same chemical formula and configuration as endogenous hormone produced by ovaries

Dydrogesterone is chemically modified retroprogesterone*
«its hormonal pattern and metabolism differ largely from that of the natural P»

Structure → Metabolism → Pharmacologic activity/effects

Retroprogesterone is characterized by a conspicuous change in the configuration of the steroid molecule.

1. **Kuhl H**. *Endokrinol* 2011; **8** (Sonderheft 1), 157-177.

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Impact of oral Dydrogesterone during early pregnancy

Abstracts

THE LANCET

Association between oral intake of dydrogesterone during early pregnancy and congenital heart disease: a case-control study

Mahmoud Zaqout, Emad Aslem, Mazen Abuqamar, Osama Abughazza, Joseph Panzer, Daniel De Wolf

Findings **Exposure to dydrogesterone during the first trimester of pregnancy was more frequent among mothers of children born with congenital heart disease (75 of 202) than in mothers of children in the control group (36 of 200; adjusted odds ratio 2,71, 95% CI 1,54–4,24, p<0.001].**

Zaqout M, et al. *The Lancet* 2017, August 1st on-line

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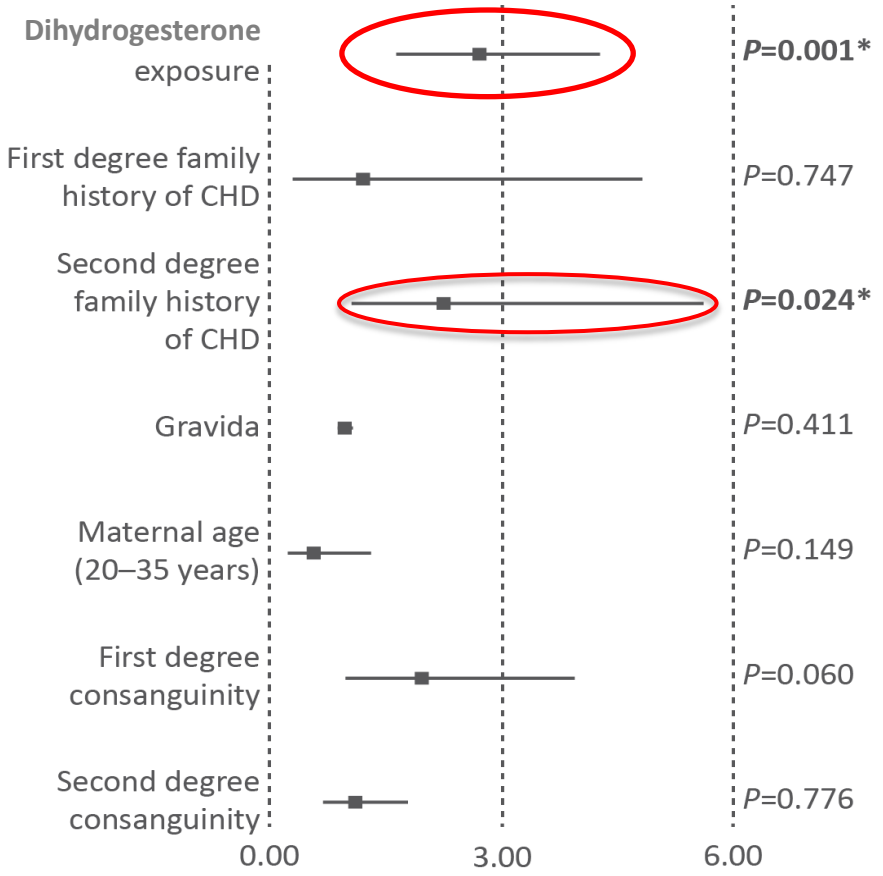
Impact of oral Dydrogesterone during early pregnancy

After controlling for other risk factors (family history of CHD, consanguinity, numbers of gravida and maternal age) in the second logistic model, dydrogesterone exposure was significantly linked to the occurrence of CHD (OR* 2.71, CI 1.64–4.24)

Second-degree family history of CHD also remained significant (OR 2.42, CI 1.04–5.59). According to the odds ratio, dydrogesterone had the strongest correlation to the occurrence CHD followed by second-degree family history of CHD

Multivariate analysis, of risk factors associated with CHD (adjusted OR*)



CHD, congenital heart disease ; CI, confidence interval; OR, odds ratio
Adjusted OR: Separately, each variable was adjusted for family history, consanguinity, maternal age and dydrogesterone treatment. Adjusted OR*: All variables were entered in one model with adjustment for family history, consanguinity, mother's age and dydrogesterone treatment

Adapted from Zaqout M, *et al. Pediatr Cardiol* 2015; **36(7)**: 1483-8

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Mic P4 has major differences in *Pharmacodynamics* versus synthetic progestogens…

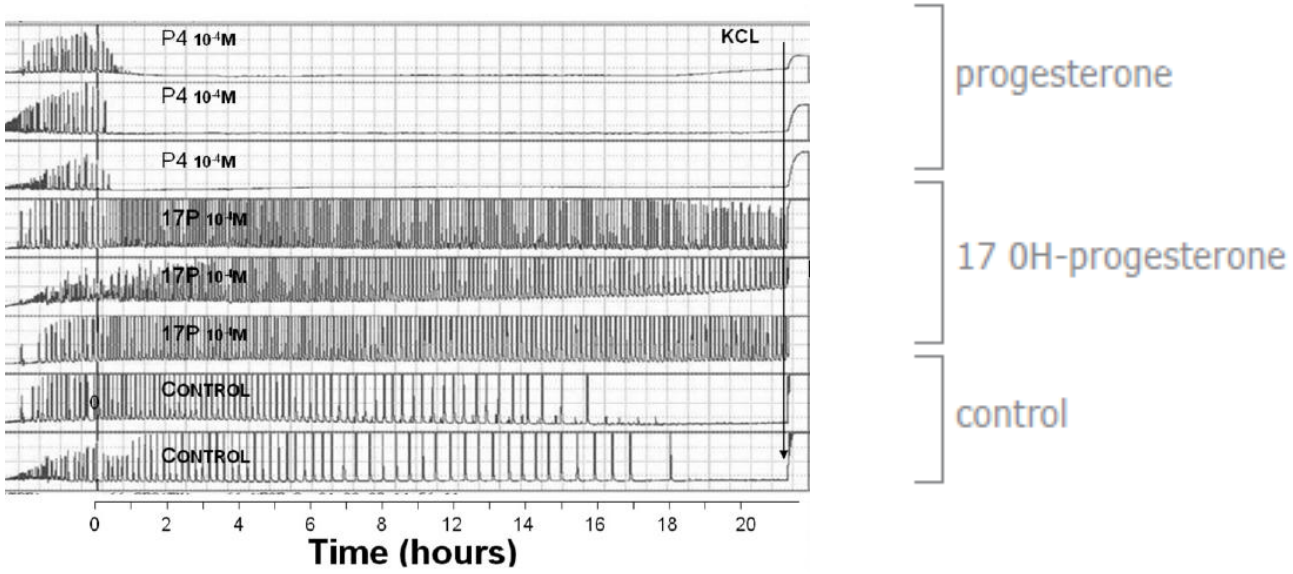
- **Tranquilizing effect** * [1,2,3]
- Anti-androgenic effect [4]
- Diuretic effect [5,6,7]
- **Tocolytic effect** * [8-12]
- **Neuroprotective effect** * [13]

* May be crucial in pregancy misacrriage indication

1. Dennerstein L *et al. Br Med J* 1985; **290**: 1617-1621. 2. **Bitran** *et al. J Neuroendocrinol* 1995; **7(3)**: 171-7. 3. **Rapkin** *et al. Obstet Gynecol* 1997; **90(5)**: 709-14. 4. **Barentsen R**. *Eur Menopause J* 1996; **3(4)** : 266-271. 5. **Wambach G** *et al. Acta Endocrinol 1979*; **92**: 560-7. 6. **Corvol** *et al. In « Progesteron and Progestins » Bardin C (ed)*.Raven Press, N Y, 1983, 179–186. 7. **Rylance PB** et al. *Br Med J 1985*; **290**: 13–4. 8. **Chanrachakul B** et al. Am J Obstet Gynecol 2005; 192: 458-63. 9. **Ruddock NK** et al. Am J Obstet Gynecol 2008; 199: 391-7 . 10. **O'Brien JM** et al. Am J Perinatol 2010; 27: 157-62. 11. **Briery C** et al. J Mat Fet Neonat Med 2014. doi: 10.3109/14767058.2014.892922 . 12. **Rozenberg P** et al. Am J Obstet Gynecol 2012; 206. e1-9. 13.

Tocolytic effect of progesterone versus synthetic progestogens

Changes in contractility in progesterone and 17 OH-progesterone treated myometrial strips [2]



- Progesterone reduces myometrial oxytocin-induced contraction [1]
- Progesterone, but not 17 OH-progesterone, directly inhibits uterine contractility [2,3]
- 17P did not delay the interval to delivery after successful preterm labor [4,5]

1. Chanrachakul B et al. *Am J Obstet Gynecol 2005;* **192***: 458-63.* **2. Ruddock NK et al.** *Am J Obstet Gynecol 2008;* **199***: 391-7* . **3. O'Brien JM et al.** *Am J Perinatol 2010*; **27***: 157-62.* **4. Briery C et al***. J Mat Fet Neonat Med 2014.* doi: 10.3109/14767058.2014.892922 . **5. Rozenberg P et al**. *Am J Obstet Gynecol 2012;* **206***. e1-9.*

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Effect of Mic P4 and its metabolites on spontaneous uterine contractility of pregnant women at term

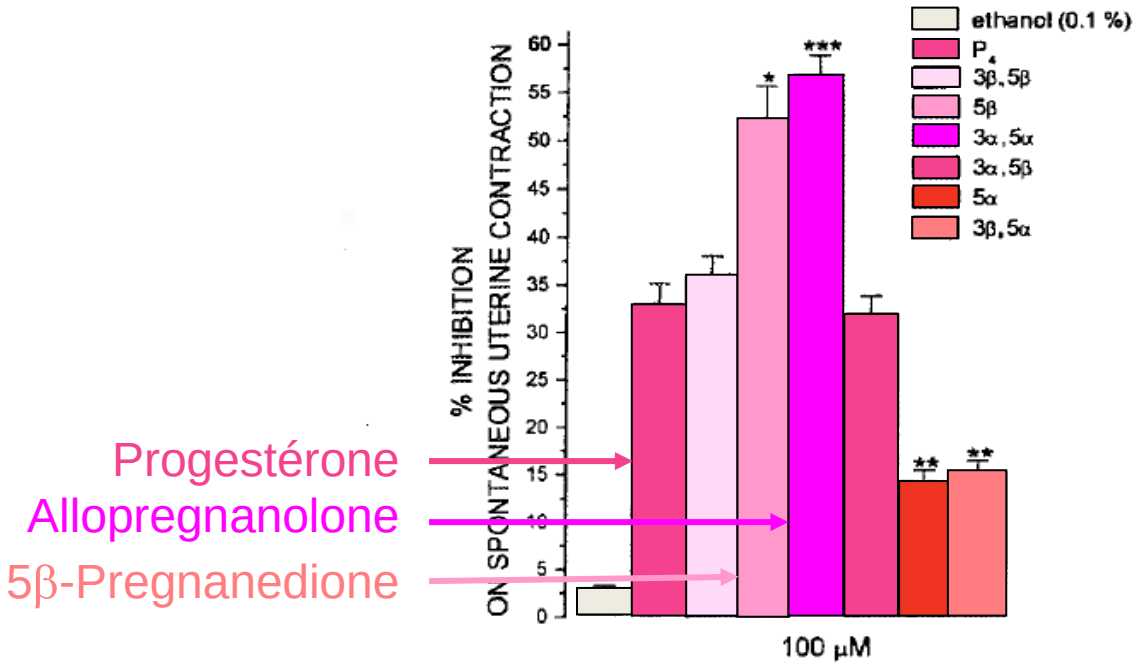

Fig. 3. Comparison of the relaxing effect induced by progestins at equimolar concentration (100 µM) on spontaneous uterine contractility of pregnant women at term. Each bar represents the mean ± SEM ($n \geq 6$). * $p<0.003$, ** $p<0.0005$, *** $p<0.0001$ vs. progesterone (P_4). Note the effect of all progestins was significantly different ($p<0.0001$) vs. ethanol at 17.14 mM (0.1 %), a concentration identical to those use as solvent for progestins.

Perusquia et al. *Life Sciences 2001;* ***68****: 2933 - 2944*

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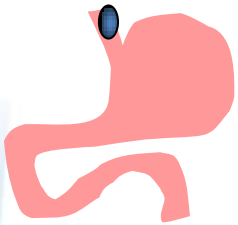
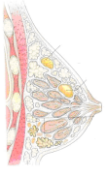
Mic P4 has major differences in *Pharmacodynamics* depending *the routes of administration*

ORAL



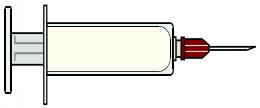
→ 90% metabolized after 1st hepatic passage
→ High inter-individual variability
→ rapid increase in plasma concentration followed by gradual decrease
→ **metabolites 5-α & 5-ß** (allopregnanolone) possess hypnotic and anxiolytic effects (via GABA rec)

TDL



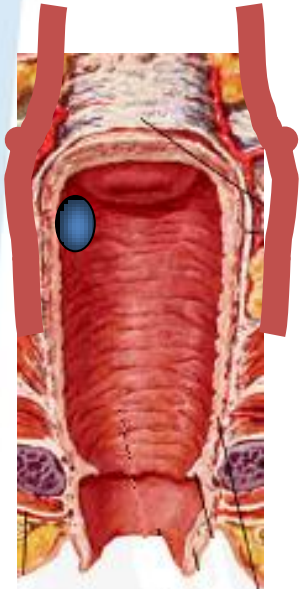
→ **No systemic effect**
→ Optimal concentration in breast tissue

I.M.



Discomfort and painful injection
→ Supraphysiological blood levels
→ At least twice weekly requiring nurse assistance
→ Granulomas (>oil), allergy and dry abscesses
→ Risk for acute eosinophylic pneumonia
→ Choice between daily and "depot"

VAG



Minimal or no *discomfort*
→ Constant systemic levels
→ Avoid first hepatic passage, safest
→ 1st uterine passage

Plagiarized and adapted from ***GC Di Renzo***, personal communication

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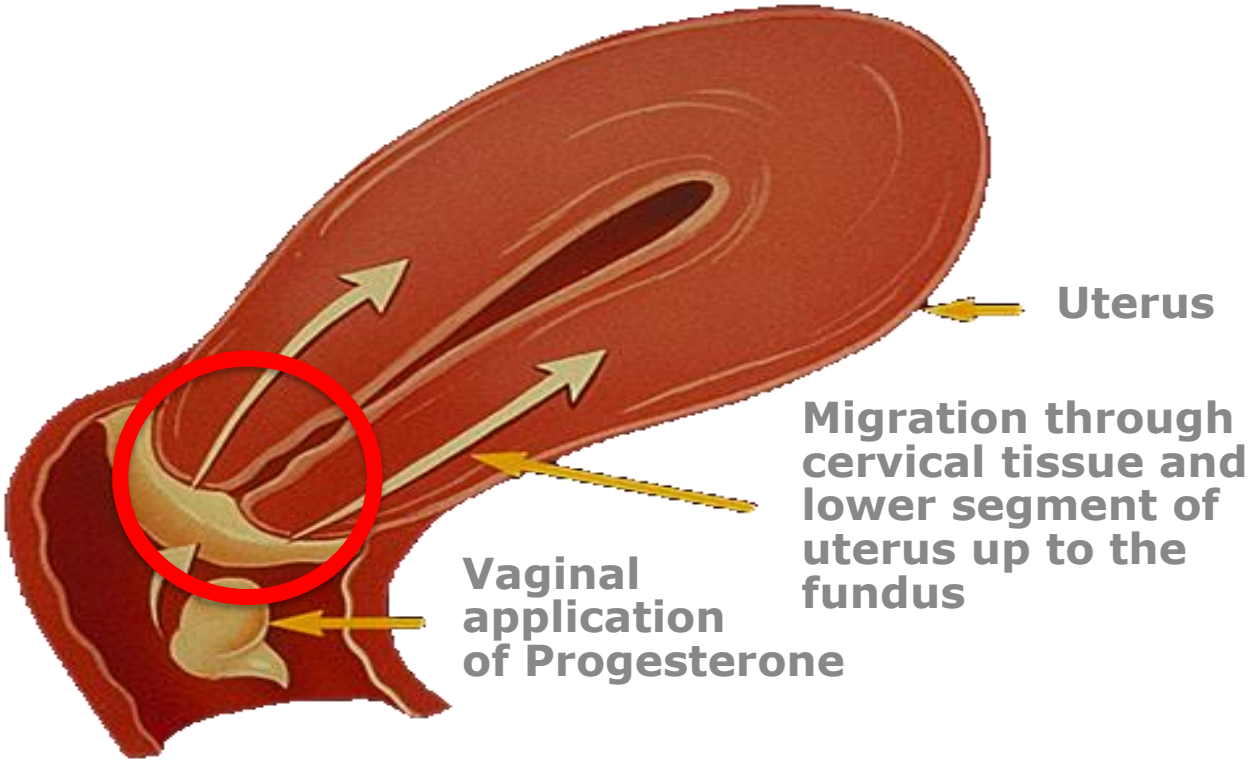
The first choice…exogenous Mic P4

By vaginal route of administration



First uterine pass effect / targeted delivery

Cicinelli E et al, *Obstet Gynecol 2000;* **95***: 403-6*

Why progesterone is so important during the all pregnancy…

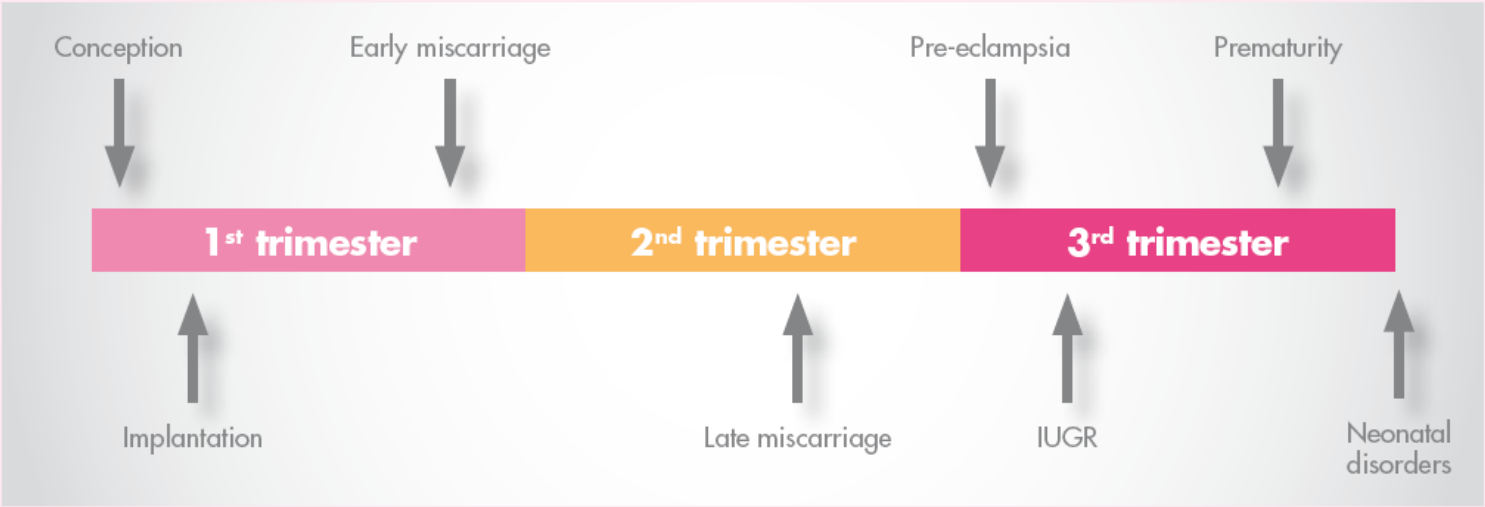
Threatened Miscarriage[1]**:**

vaginal bleeding in a woman with a confirmed pregnancy

Recurrent Miscarriage[2]**:**

three or more consecutive pregnancy losses prior to the 20th week of gestation

Adverse pregnancy outcomes



IUGR = Intra Uterine Growth Restriction

Adapted from Rai[3]

From Raj Rai, 2015, March, World Congress of Human Reproduction

1. **Griebel et al.** *Am Fam Physican 2005; 72:1243-1250*
2. **Pandey et al.** *Arch Gynecol Obstet 2005;* ***272****: 95-108*

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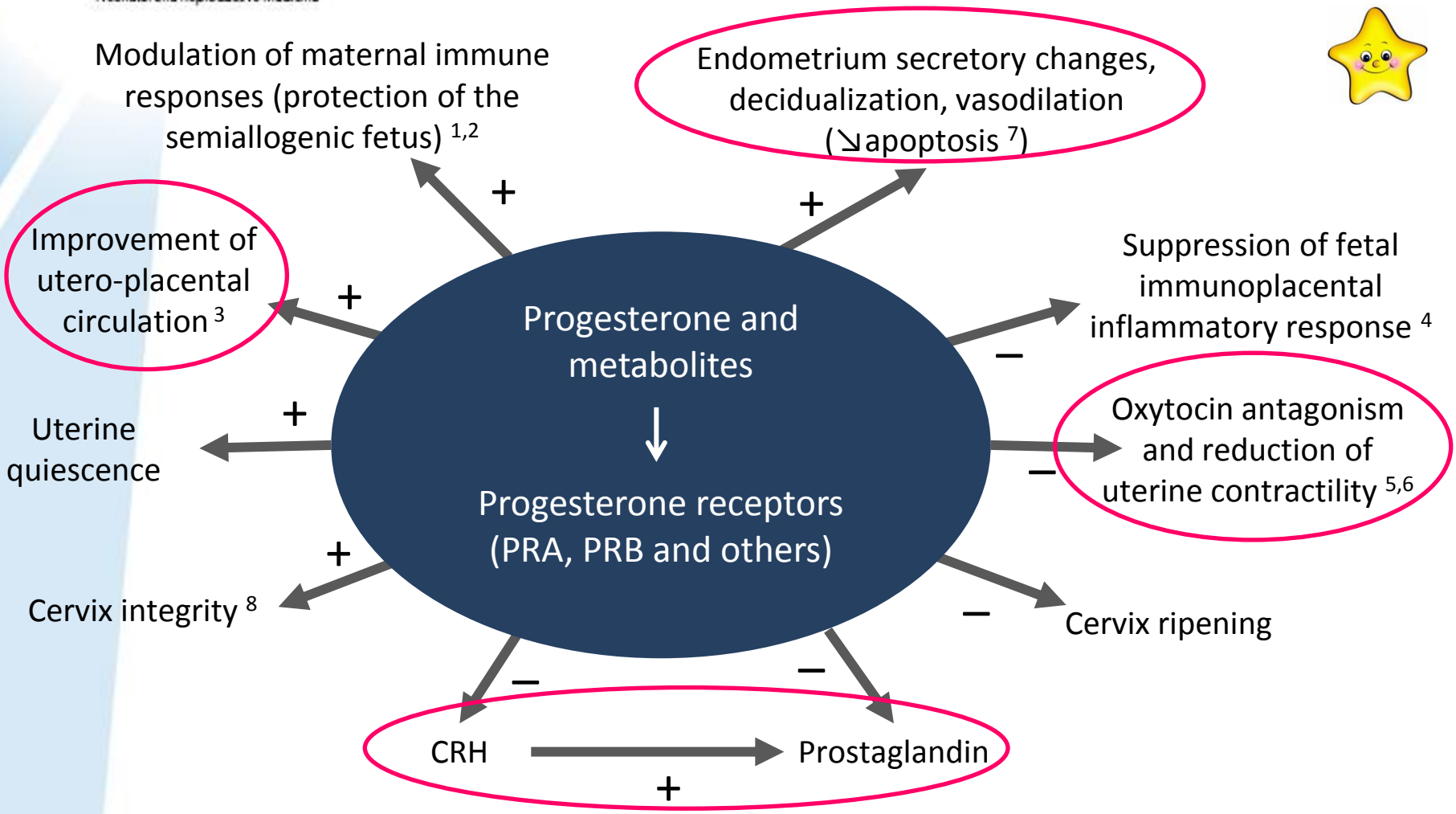
Progesterone for threatened miscarriage has a unique pharmacodynamics profile



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2. Druckmann R, Druckmann MA. *J Steroid Biochem Mol Biol*. 2005;97:389-396.
3. Czajkowski K, et al. *Fertil Steril*. 2007;87:613-618.
4. Schwartz N, et al. *Am J Obstet Gynecol*. 2009;201:211.e1-9.
5. Fanchin R, et al. *Hum Reprod*. 2000;15 Suppl 1:90-100.
6. Perusquía M, Jasso-Kamel J. *Life Sci*. 2001;68:2933-2944.
7. Lovely LP, et al. *J Clin Endocrinol Metab*. 2005;90:2351-2356.
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Vaginal progesterone in the treatment of recurrent miscarriage (RM)
Why to start as early as possible?

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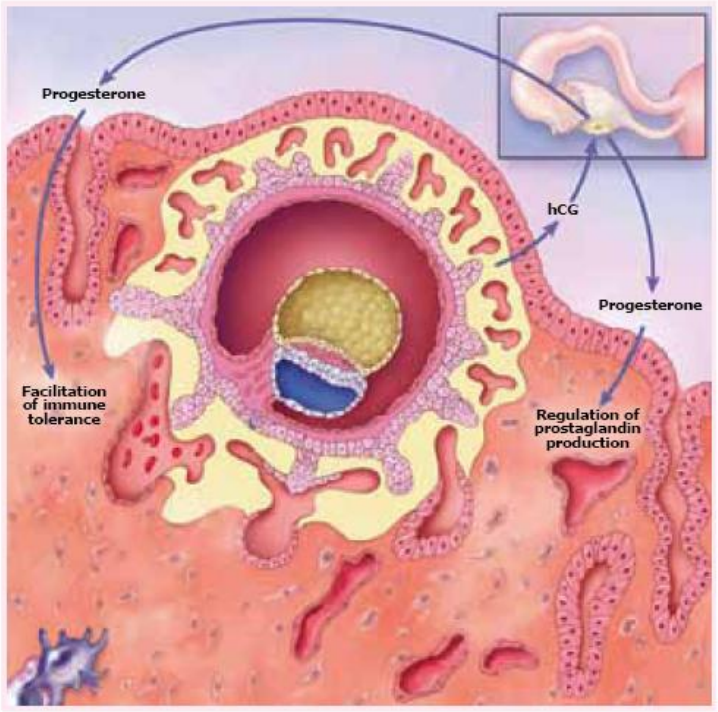
Role of Physiological progesterone

Maintains pregnancy:

- modulates maternal immune responses[3,4]
- reduces uterine contractility[5,6,7]
- improves the utero-placental circulation[8,9]
- suppresses fetal inflammatory response[10]

Maintenance of early pregnancy



Adapted from Norwitz[1]

1. **Norwitz ER et al.** *N Engl J Med 2001;* ***345****: 1400-8*
3. **Druckmann R et al.** *J Steroid Biochem Mol Biol 2005;* ***97****: 389-96*
4. **Szekeres-Bartho J et al.** *Int Immunopharmacol 2001;* ***1****: 1037-48*
5. **Fanchin R et al.** *Hum Reprod 2000;* ***15****: 90-100*
6. **Perusquía M et al.** *Life Sci 2001;* ***68****: 2933-44*
7. **Chanrachakul B et al.** *Am J Obstet Gynecol 2005;* ***192****: 458-63*
8. **Liu J et al.** *Mol Hum Reprod 2007;* ***13****: 869-74*
9. **Czajkowski K et al.** *Fertil Steril 2007;* ***87****: 613-8*
10. **Schwartz N et al.** *Am J Obstet Gynecol 2009;* ***201****: 211-9*

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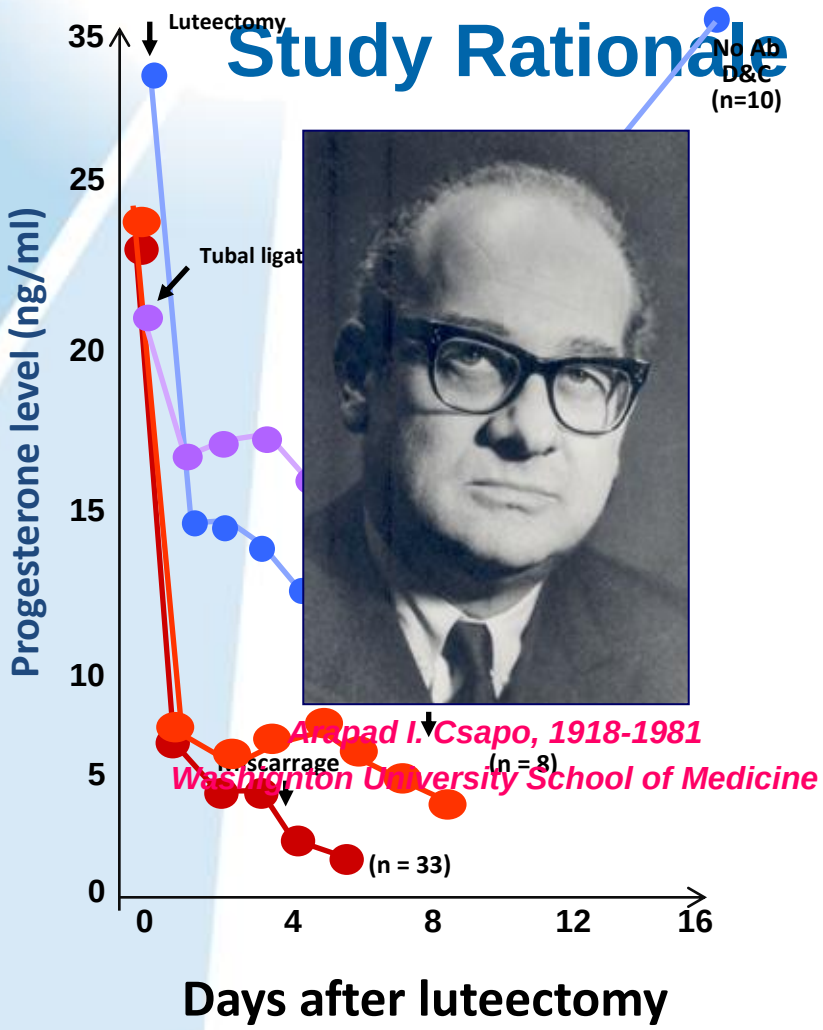
Mic Progesterone and pregnancy maintenance

Study Rationale



Arapad I. Csapo, 1918-1981
Washington University School of Medicine

- 57 pregnant desired tubal ligation (GA – $6^4/7$ to $8^6/7$ wks)

- <7 wks – tubal ligation (control)
- <7 wks – tubal ligation + luteectomy
- ≥8 wks – tubal ligation + luteectomy

7 pregnant women <7 wks

Tubal ligation + luteectomy + progesterone

No miscarriage

Csapo, A et al. The effect s of luteectomy and progesterone replacement therapy in early pregnant patients, **Am. J. Obstet. Gynecol. 1973**,115: 759-65. **Csapo** A. The Fetus and Birth. Ciba Foundation Symposium 47; 1977.

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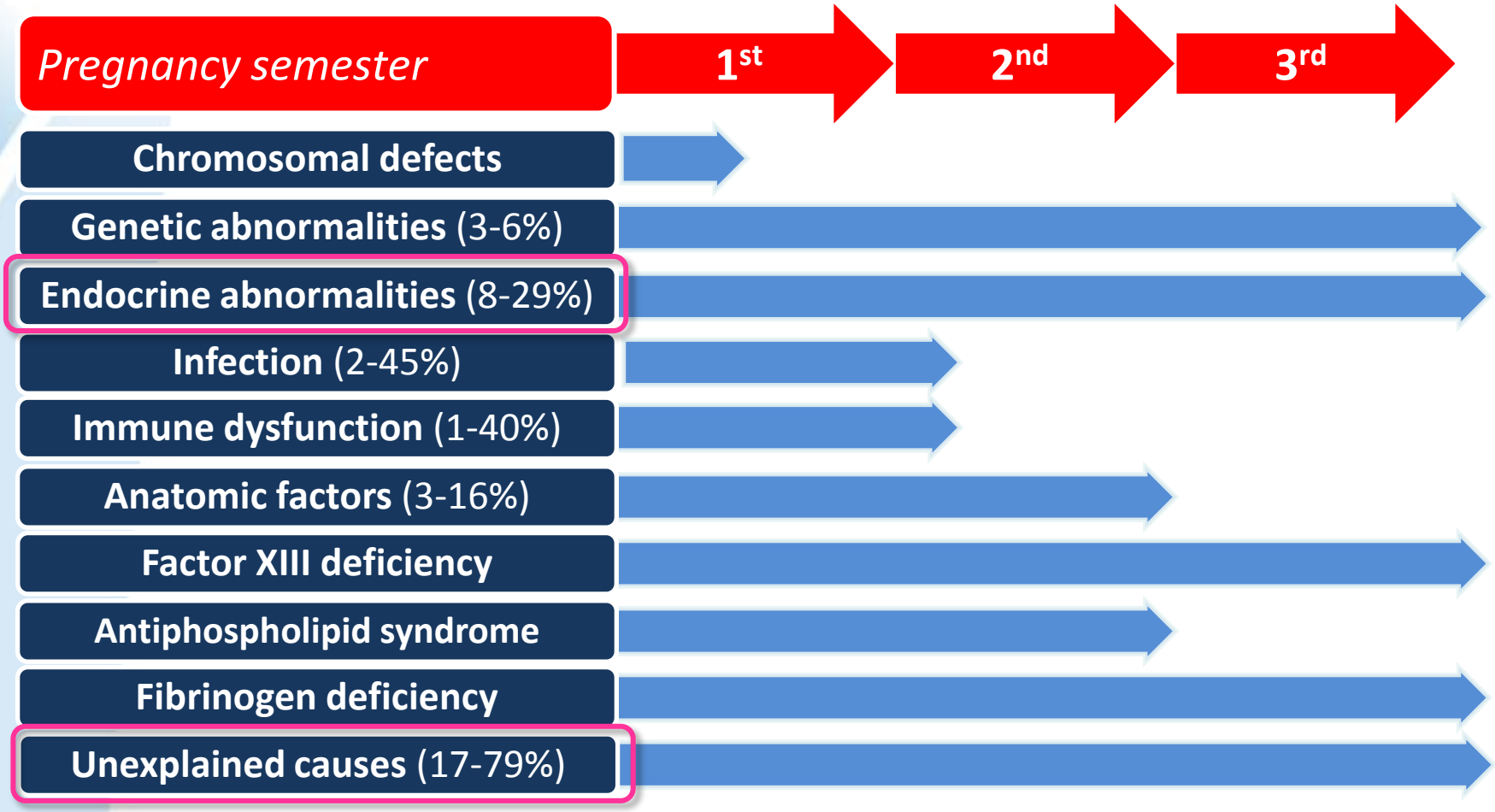
Recurrent miscarriage – combination of different factors



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Bukulmez O, Arici A. Obstet Gynecol Clin North Am 2004; 31: 727-744
Peng HQ, et al. Pediatr Dev Pathol 2006; 9: 14-19.
Inbal A, Muszbek L. Semin Thromb Hemost 2003; 29: 171-174.
Arredondo F, Noble LS. Semin Reprod Med 2006; 24: 33-39.

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Progesterone in Recurrent miscarriage: when to start ?

The hypothesis that, progesterone supplementation in women with recurrent pregnancy losses should be started **from the luteal phase,** when we have the opportunity to influence on implantation stage, was brilliantly confirmed in two large international RCTs published in December 2016 and April 2017

Stephenson MD, et al. *Fertil Steril, Dec* 2016. doi.org/10.1016/j.fertnstert.2016.11.029
Ismail A. M. et al, *Journal of Maternal - Fetal & Neonatal Medicine, April, 2017*. doi: 10.1080/14767058.2017.1286315

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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

New research from the Yale School of Medicine in New Haven, CT, in collaboration with the University of Illinois at Chicago,

The use of **luteal start** vaginal micronized progesterone (Utrogestan® vaginal capsules 100mg - 200mg X 2 times a day) was associated with improved pregnancy success in a strictly defined cohort of women with Recurrent Pregnancy Losses

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

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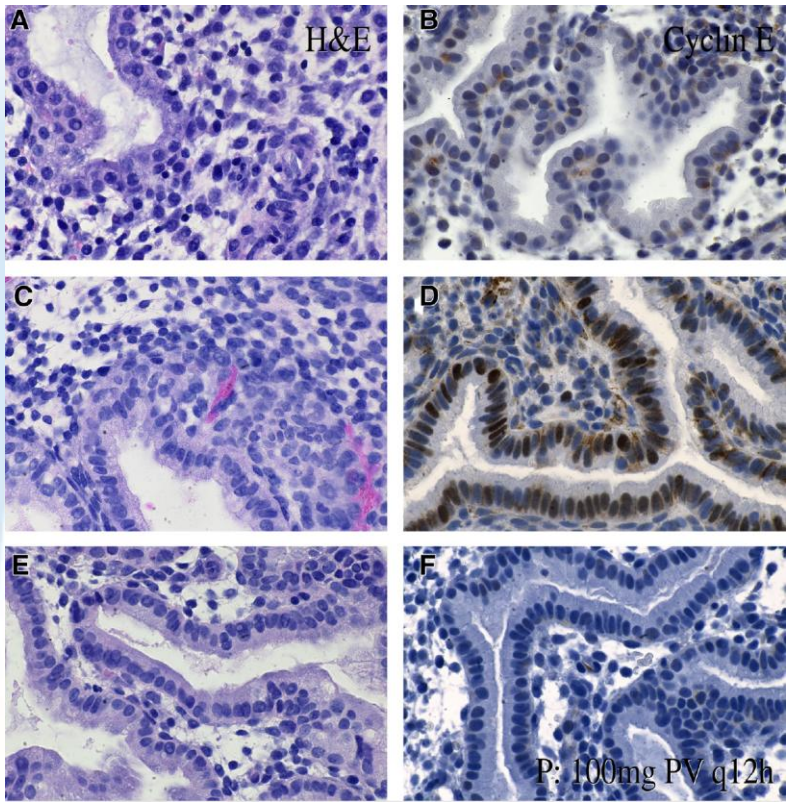
H & E- and nCyclinE-stained endometrial biopsies obtained 9–11 days after the LH surge



(A) Biopsy revealing normal histologic dating
(B) Normal nCyclinE expression (C) Biopsy revealing normal histologic dating
(D) abnormally increased glandular epithelial nCyclinE expression.
Repeat biopsy of same patient shown in panels C and D treated with 100 mg of vaginal micronized P every 12 hours beginning 3 days after the LH surge, now with
(E) normal histology
(F) normal absent glandular epithelial nCyclinE expression.

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

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

Prior and subsequent pregnancy outcomes of cohort with elevated and normal nCyclinE expression in endometrial glands and no other endometrial findings (n=116 women)

	Initial EB at 9–11 d after LH surge		
Variable	**Abnormal nCyclinE (> 20%) (n = 59 women)**		**Normal nCyclinE (≤20%) (n = 57 women)**
Prior pregnancies	255		244
Success: term and preterm, n (%)	16 (6)		27 (11)
Fetal demise, n (%)	8 (3)		3 (1)
PL (<10 wk) n (%)[a]	219 (86)		206 (84)
PL, mean (SD, range)	3.7 (1.7, 2–11)		3.6 (1.2, 2–6)
Maternal age (y) at PL, mean (SD, range)	32.6 (3.7, 24–42)		32.9 (3.5, 19–41)
Other, n (%)[b]	12 (5)		8 (3)
	Vaginal micronized P	**Empiric vaginal micronized P**	**No vaginal micronized P**
Subsequent pregnancies	83	43	37
Success: term, preterm, and ongoing, n (%)	57 (69)	29 (67) **86/126**	19 (51) **19/37 ***
Fetal demise, n (%)	1 (1)	0	1 (3)
PL (<10 wk) n (%)[a]	24 (29)	14 (32)	14 (38)
PL, mean (SD, range)	1.1 (0.5, 1–3)	1.4 (1.0, 1–3)	1.3 (0.6, 1–3)
Maternal age (y) at PL, mean (SD, range)	35.8 (2.9, 30–43)	34.5 (3.3, 31–40)	36.4 (3.7, 31–42)
Other, n (%)[b]	1 (1)	0	3 (8)

EB = endometrial biopsy; LH = luteinizing hormone; PL = pregnancy loss.

[a] Miscarriage, resolved pregnancy of unknown location, and biochemical pregnancy loss.

[b] Ectopic pregnancy, termination or pregnancy, and/or lost to follow-up before 10 wk of gestation.

*** odds ratio = 2.1 (95% confidence interval, 1.0 - 4.4).**

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

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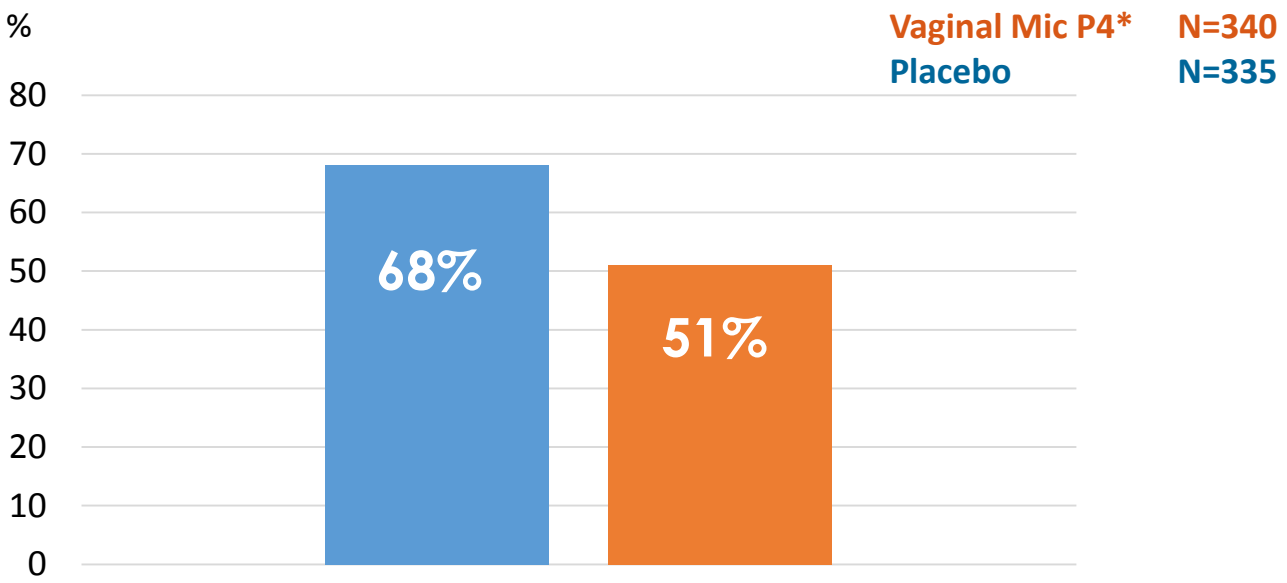
Luteal start vaginal micronized progesterone improves pregnancy success in women with recurrent pregnancy loss



Odds ratio = 2.1 (95% confidence interval, 1.0 - 4.4).

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 Recurrent Pregnancy Loss

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

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

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2017
http://dx.doi.org/10.1080/14767058.2017.1286315

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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 and Ahmed F. Amin

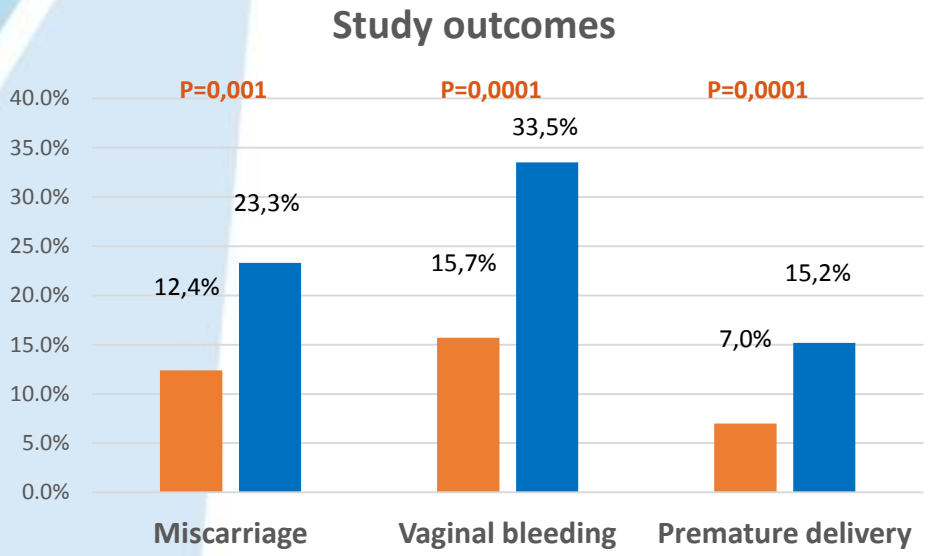
Department of Obstetrics and Gynecology, Women's Health Hospital, Assiut University, Assiut, Egypt

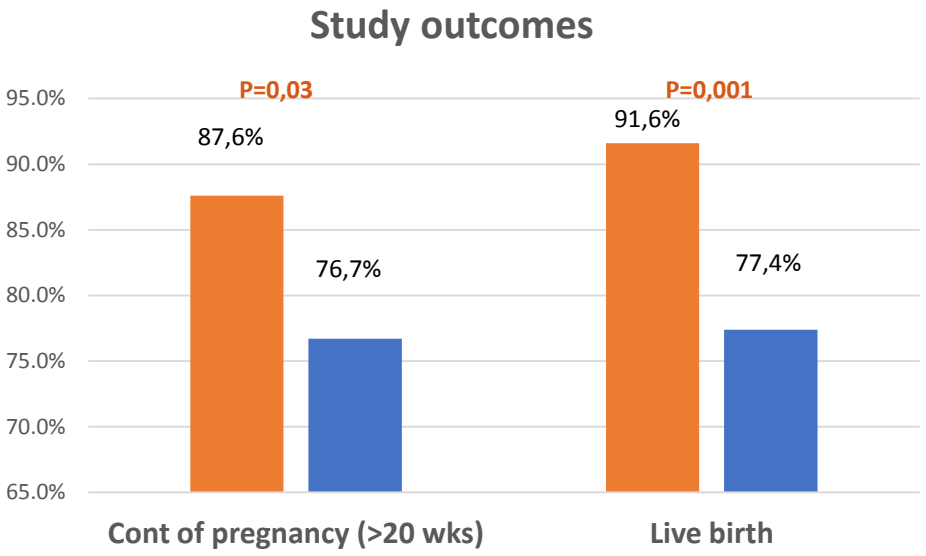
POPULATION	Women with unexplained recurrent miscarriages
INTERVENTION	400 mg progesterone taken vaginally twice daily, started in the luteal phase and continued to 28 weeks
COMPARISON	Placebo
OUTCOMES	Miscarriage

Ismail AM et al. *J Matern Fetal Neonatal Med* 2017; **15**: 1-7.

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

Vaginal Mic P4* **N=340**
Placebo **N=335**





* MicP4 = vaginal micronised progesterone 400 mg BID

Ismail AM et al. *J Matern Fetal Neonatal Med* 2017; **15**: 1-7.

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

Table 2. The study outcomes.

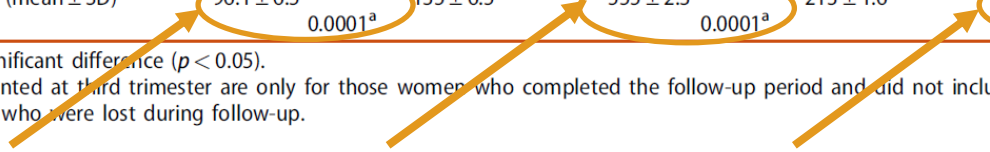
Characteristics	Progesterone group ($n = 340$)	Placebo group ($n = 335$)	p value
Rate of miscarriage	42/340 (12.4%)	78/335 (23.3%)	0.001[a]
Continuation rate of pregnancy beyond 20 weeks	298/340 (87.6%)	257/335 (76.7%)	0.03[a]
Rate of first trimester vaginal bleeding	54/340 (15.7%)	100/335 (33.5%)	0.0001[a]
Live birth rate	273/298 (91.6%)	199/257 (77.4%)	0.001[a]
Gestational age at delivery (weeks) (mean ± SD)	37.4 ± 0.4	34.1 ± 1.2	0.001[a]
Rate of premature delivery	21/298 (7.0%)	39/257 (15.2%)	0.0001[a]
Spontaneous	8 (38.1%)	14 (35.9%)	
Iatrogenic	13 (61.9%)	25 (64.1%)	

SD: standard deviation.
[a]Statistically significant difference.

Table 3. Changes in the serum inflammatory cytokines in the study participants all over the pregnancy.

Group	IL-2		IL-10		INF-γ	
	Progesterone group	Placebo group	Progesterone group	Placebo group	Progesterone group	Placebo group
Preconception (mean ± SD)	197.38 ± 7.9	196.58 ± 7.14	100.15 ± 8.8	101.16 ± 9.2	13.58 ± 3.43	13.03 ± 0.87
p value	0.170		0.150		0.132	
First trimester (mean ± SD)	135.3 ± 6.3	160 ± 6.2	312 ± 2.46	129 ± 6.2	5.6 ± 4.1	10.8 ± 3.1
p value	0.0001[a]		0.0001[a]		0.0001[a]	
Second trimester (mean ± SD)	106.5 ± 6.6	145 ± 6.2	511.5 ± 2.3	223.1 ± 1.6	5.5 ± 2.3	9.1 ± 1.6
p value	0.0001[a]		0.0001[a]		0.0001[a]	
Third trimester[b] (mean ± SD)	96.1 ± 6.5	135 ± 6.5	555 ± 2.3	213 ± 1.6	5.0 ± 1.1	11.3 ± 2.3
p value	0.0001[a]		0.0001[a]		0.0001[a]	

[a]Statistically significant difference ($p < 0.05$).
[b]The data presented at third trimester are only for those women who completed the follow-up period and did not include those who stopped the treatment or those who were lost during follow-up.



Ismail AM et al. *J Matern Fetal Neonatal Med* 2017; **15**: 1-7.

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What about PROMISE trial
Vaginal progesterone in women with recurrent miscarriage

Randomized, double-blind, placebo controlled multicentre study

Objective
To access whether treatment with vaginal progesterone would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage.

Study population
836 women with recurrent miscarriage, i.e. at least 3 miscarriages, aged 18-39 years, conceiving spontaneously

Intervention
One group (N= 404) receives vaginal progesterone pessaries 400 mg twice daily (Utrogestan®) and the other group (N=432) receives placebo pessaries of identical appearance twice daily from a time soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) through 12 weeks of gestation.

Outcome measures
Primary: **Live birth rate after 24 weeks of gestation.**
Secondary: Miscarriage rate, gestational age at delivery, adverse events, serum progesterone luteal phase

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

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PROMISE trial
Vaginal progesterone in women with recurrent miscarriage

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

The NEW ENGLAND JOURNAL of MEDICINE

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PROMISE trial
Results by geographical location and number of previous losses

In a *post hoc analysis*, **by geographical location**:
Absolute rate difference of 4.4 % (NS) favouring P4.

Geographical location				p-value
United kingdom	212/312 (**67.9%**)	207/326 (**63,5%**)	1,07(0,96-1,20)	0.24
Netherlands	50/86 (58,1%)	64/102 (62.7%)	0,93(0,73-1,17)	0.52
				0.27

Number of previous losses	Progesterone Live birth / total (%)	Placebo Live birth / total (%)	%age difference	p-value
3	148/218 (67.9%)	159/236 (67.4%)	+0.5%	0.91
4	61/82 (74.4%)	70/103 (68.0%)	+6.4%	0.33
5	28/55 (50.9%)	21/48 (43.8%)	+7.1%	0.47
6 or more	27/47 (57.4%)	20/40 (50.0%)	**+7.4%**	0.49

Coomarasami A, et al. *Health Technol Assess* 2016; **20(41)**: 1-92.

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Obtained results are controversal

- Progesterone supplementation was started too late after positive pregnancy test (but no later than 6 weeks) and continued by 12 weeks (and not 20 weeks).
- HLA typing and evaluation of the abortus material for genetic abnormalities were not performed in all patients
- Reliable analysis of progesterone efficacy in preventable pregnancy losses was virtually impossible
- Pregravid preparation for women with 3 and more unexplained pregnancy losses were not performed.

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

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PROMISE: practical importance

- The use of micronized progesterone (Utrogestan ®) in the first trimester of pregnancy at a dose of 800 mg / day **confirmed it's safety for mother and fetus**
- The incidence of congenital anomalies was not different in the vaginal progesterone group and placebo

The NEW ENGLAND JOURNAL of MEDICINE

Level 1 of evidence

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

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What did we learn from PROMISE trial ?

PROMISE is the first well designed Randomized Controlled Trial with **live birth rate** as primary outcome in this indication (different from RR of miscarriage outcome in previous studies with progesterone[1] or dydrogesterone[2])

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**

New Engl J Med March 2016: Letter to the Editor

[1] **Haas DM**, et al. *Cochrane Database Syst Rev* 2013; **10**: CD003511.
[2] Kumar A, et al. *Fertil Ster*il 2014; **102(5)**: 1357-63.

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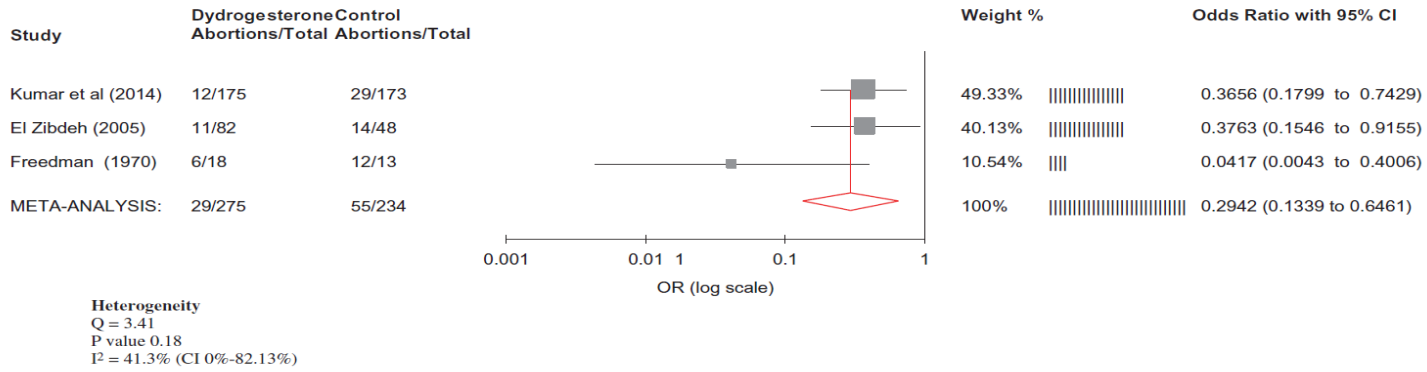
What about other Progestogens in RM *(eg DHG)*

A systematic review of dydrogesterone
Based on **only 3 trials:**
1 randomised (RCT)
1 open label quasi randomised
1 non-randomised



Only ONE randomised trial by *Kumar et al* 2014

348 women - majority randomised **after** 6.5 weeks gestation
Significant benefit of dydrogesterone

Carp H. *Gynecol Endocrinol* 2015; **31(6)**: 422-30.

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Randomisation process ???

a double-blind, randomized, parallel, placebo-controlled trial

Ashok Kumar, M.D., Ph.D.,[a] Nargis Begum, M.Sc., Ph.D.,[a] Sudha Prasad, M.D.,[a] Sarita Aggarwal, M.D.,[b] and Shashi Sharma, Ph.D.[c]

[a] Department of Obstetrics & Gynecology, Maulana Azad Medical College & Lok Nayak Hospital, New Delhi; [b] Department of Biochemistry, Maulana Azad Medical College, New Delhi; and [c] Institute of Cytology and Preventive Oncology, Noida, India

"The blinding of study participants and investigators (A.K. and S.P.) was done … according to a simple randomization sequence developed with the use of computers by S.S. The packets were then distributed to the participants by N.B., using the random numbers in sequence."

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Comparative characteristics of PROMISE versus Kumar studies

Study	PROMISE, 2015	Kumar, 2014
The investigators	Dr. Arri Coomarasamy, Birmingham, UK	Dr. Ashok Kumar, Delhi, India
The Sponsors	Imperial College, London, **UK**	Maulana Azad Medical College & Lok Nayak Hospital, **INDIA**
Study design	**Multicenter**, randomized, placebo-controlled	Double blind, randomized, placebo-controlled, in parallel groups
Investigational centers	**United kingdom** (36 centers), the **Netherlands** (9 centers)	Medical College Maulana Azad clinic, New Delhi, **India**
Inclusion criteria*	Unexplainable miscarriages ≥ 3 Age 18–39 years (avg: **32,9**) Spontaneous pregnancy	Unexplainable miscarriage ≥ 3 Age 18–35 years (avg: **25,3**) Spontaneous pregnancy
Number of subjects in the study/in act.treated group	836 / **404**	348 / **175**
Primary endpoint	Live birth after 24 weeks of gestation.	Occurrence of another pregnancy loss
Start of the therapy	After the positive urine pregnancy test, **≤ 6 weeks of gestation**	After the confirmation of fetal heart beating, weeks 4-8 of gestation (**mainly > 6,5 weeks**)
Medication and way of administration	Vaginal micronized progesterone	Oral dydrogesterone
Daily dose	800 mg (400 mg BID)	20 mg (10 mg BID)
Duration of the therapy	**Until 12 weeks of the pregnancy**	**Until 20 weeks of the pregnancy**

** In both studies, no confirmed diagnosis of progesterone insufficiency*

Kumar A, et al et al. *Fertil Steril* 2014; **102**:1357–63.

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Oral Dydrogesterone in prevention of recurrent pregnancy lost

Baseline characteristics and pregnancy outcome of participants who completed the follow-up.

	Healthy pregnant control	Recurrent pregnancy loss (N = 348)		*P* value for groups compared		
Characteristic (mean ± SD)	Controls (group 1), N = 174	Placebo (group 2), N = 173	Dydrogesterone (group 3), N = 175	1 vs. 2	1 vs. 3	2 vs. 3
Age (y)	25.4 ± 3.2	25.0 ± 3.6	25.3 ± 3.8	.22	.68	.45
BMI (kg/m^2)	21.7 ± 4.2	22.1 ± 4.2	22.2 ± 4.3	.33	.31	.96
Years of education, N (%)						
Illiterate	33 (18.9)	28 (16.2)	32 (18.3)			
<10	45 (25.9)	49 (28.3)	48 (27.4)	1.00	.92	.89
10–12	79 (45.4)	82 (47.4)	76 (43.4)			
>12	17 (9.8)	14 (8.1)	19 (10.9)			
Hb (g%)	11.2 ± 1.0	11.2 ± 1.1	11.2 ± 1.3	.79	.70	.90
Gestational age at recruitment (wks)	6.6 ± 2.1	6.5 ± 1.2	6.5 ± 1.1	.48	.31	.56
Pregnancy outcome						
Abortion, N (%)	6/174 (3.5)	29/173 (16.8)	12/175 (6.9)	.0001[a]	.22	.004[b]
Gestational age at delivery (wks)	38.2 ± 3.2	37.2 ± 2.4	38.0 ± 2.0	.005[a]	.63	.002[b]
Baby weight (g)	2,545.3 ± 554.3	2,421.4 ± 321.6	2,489.5 ± 541.0	.02[a]	.35	.19
Baby weight (kg), N (%)						
<2.5	21 (12.5)	22 (15.3)	15 (9.2)	.51	.38	.12
2.5–4.0	147 (87.5)	122 (84.7)	148 (91.8)			

Note: For pregnancy outcome: controls (group 1) N = 168; placebo (group 2) N = 144; dydrogesterone (group 3) N = 163. SD = standard deviation.
[a] *P* value significant (< .05), controls vs. placebo group.
[b] *P* value significant (< .05), placebo group vs. dydrogesterone group.

Kumar. Dydrogesterone and cytokine modulation. Fertil Steril 2014.

157/428 (**36,7%**) in PROMISE trial

↓

Normal rate in RM !!!

Kumar A, et al et al. *Fertil Steril* 2014; **102**:1357–63.

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PROMISE trial vs Kumar: Why the results are different?

Maternity ages at inclusion are different!

- Percentage of chromosomal abnormalities in miscarriages in the age range of 18 to 35 is in average 25%, reaching 74% in the age range of 35-39 years
- The PROMISE study the percentage of women aged 35 to 39 years might reach 25%
- Maternity age at inclusion was **32.9 years** in PROMISE (progesterone group) vs. **25.3 years** in the study by Kumar(dydrogesterone group).
- At least for 65 to 70 pregnancies in the PROMISE study, adverse outcomes could not be prevented irrespectively of the prescription of any supporting therapy, including progestagens.

Therefore it is by far inappropriate to compare efficacy of dydrogesterone and micronized progesterone based on the results of those two studies

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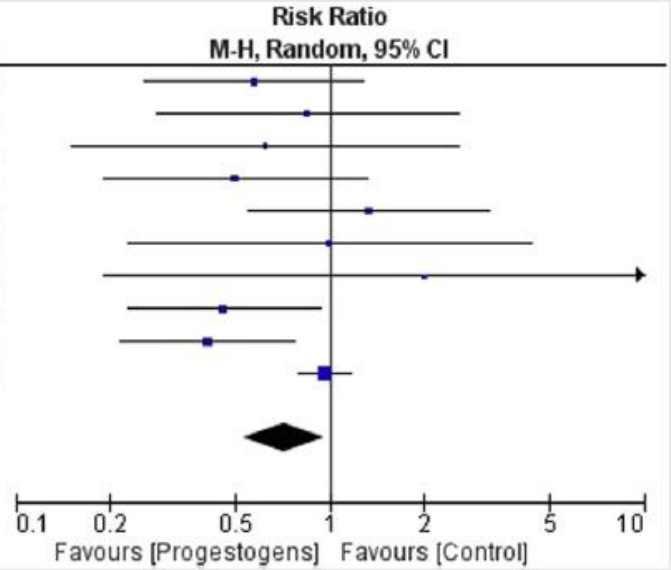
Systematic Review

Fertility and Sterility

FIGURE 1

Study or Subgroup	Progestogens Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Swyer 1953	7	27	9	20	10.3%	0.58 [0.26, 1.28]	1953
Shearman 1963	5	27	5	23	6.2%	0.85 [0.28, 2.58]	1963
Goldzieher 1964	2	8	4	10	4.0%	0.63 [0.15, 2.59]	1964
Le Vine 1964	4	15	8	15	7.8%	0.50 [0.19, 1.31]	1964
Klopper 1965	8	18	5	15	8.9%	1.33 [0.55, 3.22]	1965
MacDonald 1972	3	20	3	20	3.8%	1.00 [0.23, 4.37]	1972
Reijnders 1988	2	32	1	32	1.6%	2.00 [0.19, 20.97]	1988
El-Zibdeh 2005	11	82	14	48	12.2%	0.46 [0.23, 0.93]	2005
Kumar 2014	12	175	29	173	13.9%	0.41 [0.22, 0.78]	2014
Coomarasamy 2015	128	398	143	428	31.4%	0.96 [0.79, 1.17]	2015
Total (95% CI)		**802**		**784**	**100.0%**	**0.72 [0.53, 0.97]**	
Total events	182		221				

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 13.40$, $df = 9$ ($P = 0.15$); $I^2 = 33\%$
Test for overall effect: $Z = 2.16$ ($P = 0.03$)



Forest plot for the risk of recurrent miscarriage in women with unexplained recurrent miscarriage. df = degrees of freedom; M-H = Mantel-Haenszel.

Saccone. Progestogens for miscarriage. Fertil Steril 2016.

Summary

Vaginal progesterone vs oral dydrogesterone

- Stephenson M, *et al – vag.P4* benefit
- Ismail AM, *et al - vag.P4* benefit
- Coomarasami A, *et al* - PROMISE favoring vag.P4 (NS)
- Kumar A, *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

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Micronized progesterone in the treatment of threatened miscarriage

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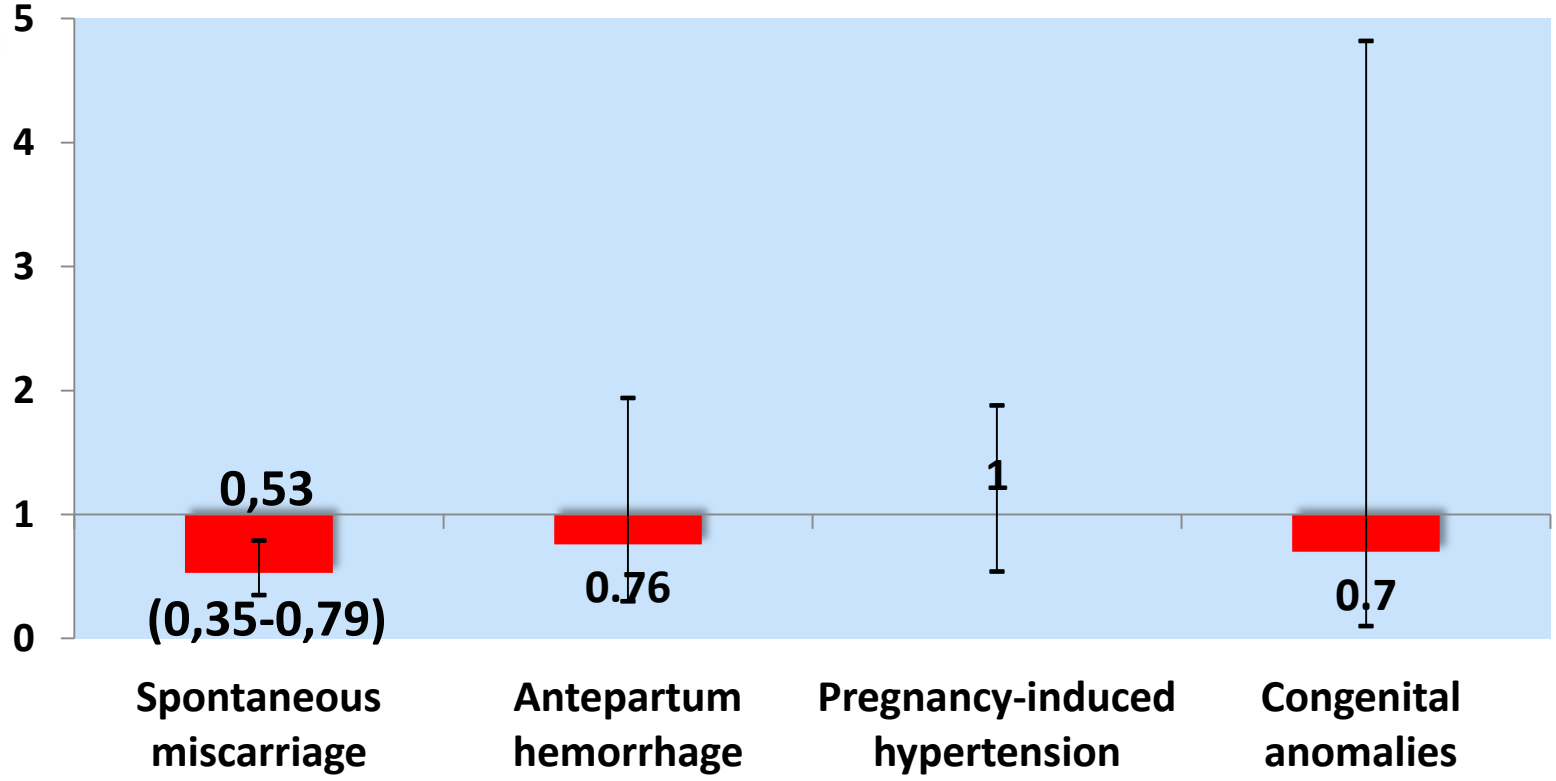
Risks (RR, 95% CI) with progesterone use in women with threatened abortion vs. placebo or no treatment



Wahabi HA, et al. *Cochrane Database of Systematic Reviews* 2011, Issue **12**. Art. No.: CD005943..

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Progesterone for treatment of Threatened Miscarriage: P vs placebo/ no treatment in the most recent *Cochrane Review*.

Progestogens are effective in the treatment of threatened miscarriage with no evidence of increased rates of pregnancy-induced hypertension or antepartum haemorrhage as harmful effects to the mother, nor increased occurrence of congenital abnormalities on the newborn.

However, the analysis was limited by the small number and the poor methodological quality of eligible studies (four studies) and the small number of the participants (421), which limit the power of the meta-analysis and hence of this conclusion.

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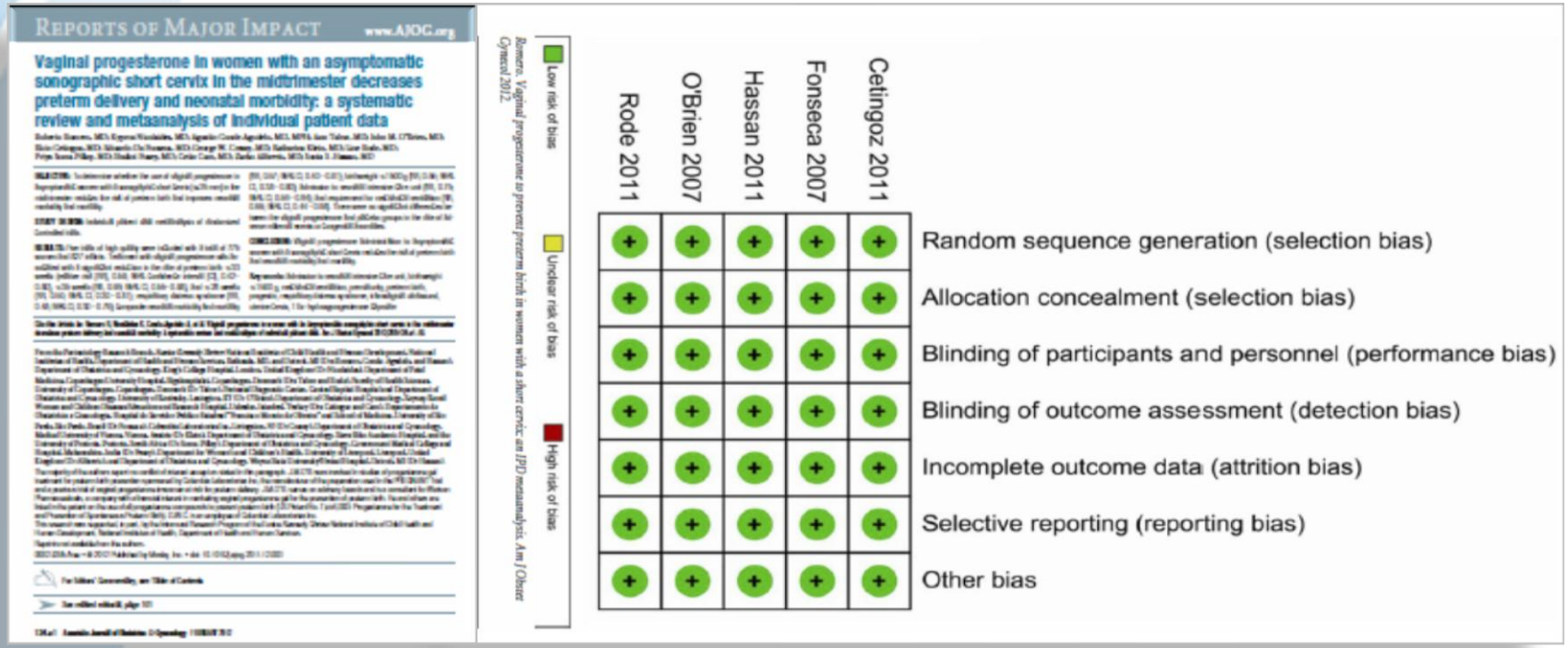
Results and conclusion of meta-analysis depends on quality of included researches



Romero R, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. Am J Obstet Gynecol 2012; 206:124.e1-19.

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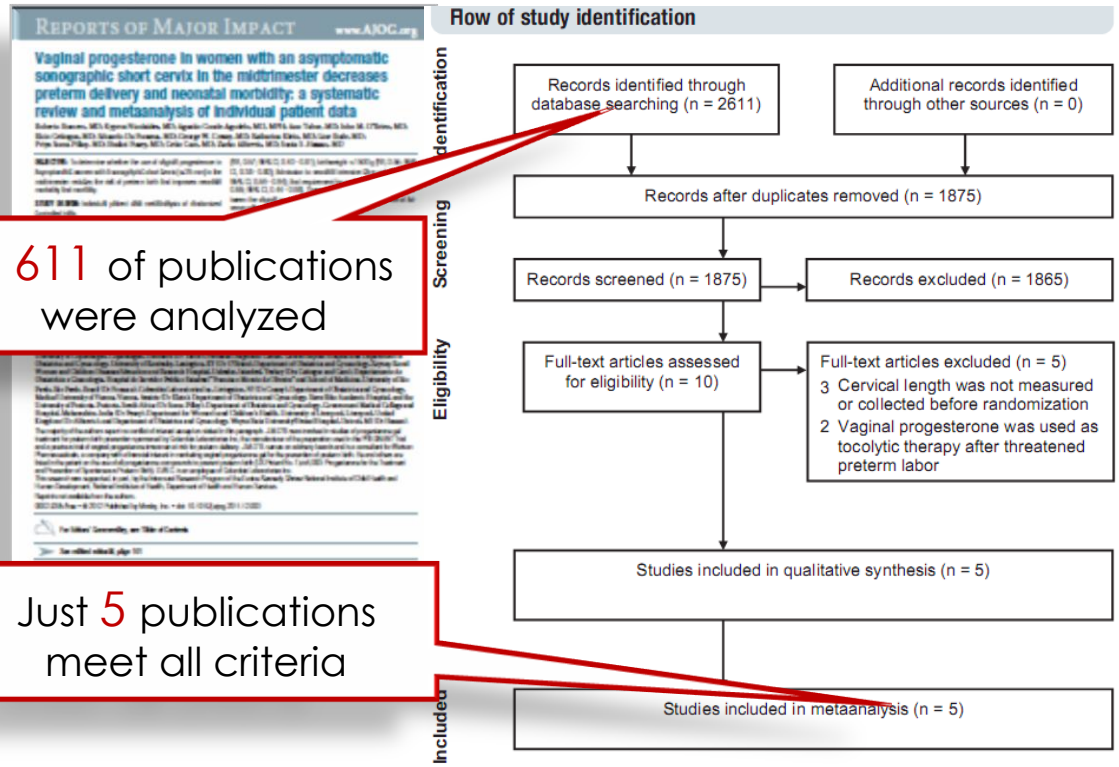
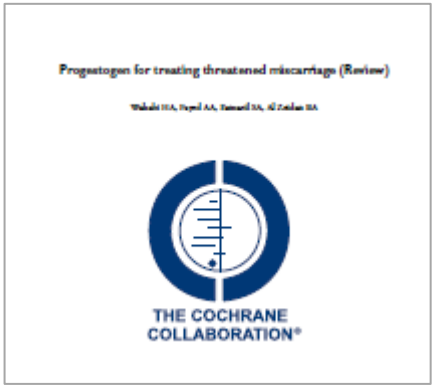
Careful selection = reliability



Romero R, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. Am J Obstet Gynecol 2012; 206:124.e1-19.

The weaker the design, the less reliable conclusions are

Gerhard, 1987	Palagiano 2004	El-Zibdeh 2009	Pandian 2009
X	X	±	+
X	+	X	+
+	+	X	X
+	±	+	+
X	X	X	+
X	X	X	+
X	X	X	+



Authors Opinion (citation):
With the exception of Pandian 2009, all studies were of poor methodological quality

Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12.

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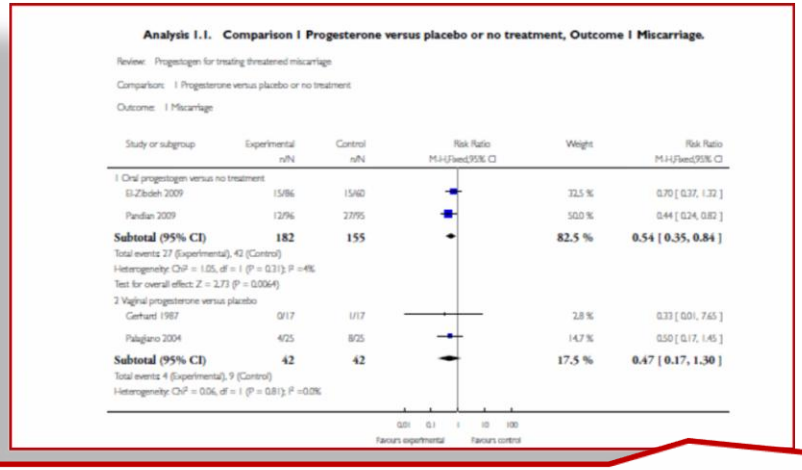
The weaker the design, the less reliable conclusions are



Analysis 1.1. Comparison 1 Progesterone versus placebo or no treatment, Outcome 1 Miscarriage.

Review: Progestogen for treating threatened miscarriage

Comparison: 1 Progesterone versus placebo or no treatment

Outcome: 1 Miscarriage

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral progestogen versus no treatment					
El-Zibdeh 2009	15/86	15/60		32.5 %	0.70 [0.37, 1.32]
Pandian 2009	12/96	27/95		50.0 %	0.44 [0.24, 0.82]
Subtotal (95% CI)	**182**	**155**		**82.5 %**	**0.54 [0.35, 0.84]**
Total events: 27 (Experimental), 42 (Control)					
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² =4%					
Test for overall effect: Z = 2.73 (P = 0.0064)					
2 Vaginal progesterone versus placebo					
Gerhard 1987	0/17	1/17		2.8 %	0.33 [0.01, 7.65]
Palagiano 2004	4/25	8/25		14.7 %	0.50 [0.17, 1.45]
Subtotal (95% CI)	**42**	**42**		**17.5 %**	**0.47 [0.17, 1.30]**
Total events: 4 (Experimental), 9 (Control)					
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%					

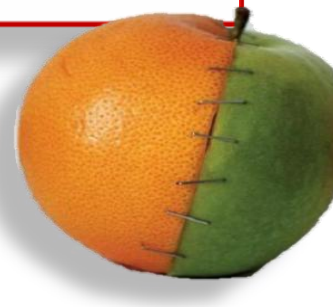
0.01 0.1 1 10 100

Favours experimental | Favours control

Formally: there is no essential difference between a progesterone and lack of treatment

BUT…

Obviously incorrect data were estimated



Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12.

The weaker the design, the less reliable conclusions are

In the study by Gerhard 1987, 64 women were randomized; eight women were excluded and the remaining 56 women were analyzed.
We included only a subgroup of 34 women in this review as they fulfilled the inclusion criteria of confirmation of fetal viability by ultraso… commencement of treat… to the t… pregno… were r… placeb… receive… in the f… vagina… group r…

Gerhard, 1987: Progesterone supplementation in vaginal supp. **25 mg x2** per day

Palagiano 2004 evaluated 50 women with previous diagnosis of inadequate luteal phase, a current diagnosis of threatened miscarriage
and confirmed fetal viability. Gestational age at the time of enrolment to the study was six to 12 weeks. The treatment group received 90… progesterone (Crinone® 8%… g… a… s… l…

Palagiano, 2004: Crinone 90 mg during **5 days**

Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Cochrane Database of Systematic Reviews 2011, Issue 12.

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Randomized trials of progestogens versus placebo or no treatment

Study	Intervention	Duration of treatment	Comparison	Risk of Bias
Misto 1967 n=25	20-40mg oral dydrogesterone	Once daily for 6-15 days, sometimes for longer periods and for several cycles.	Placebo	Method of randomisation unclear; allocation concealment adequate. Blinding of patients and study personnel
Ehrenskjold 1967 n=153	20mg oral dydrogesterone	20mg stat then tapering dose (20mg after 12 hours/20 mg every 8 hours until symptoms ceased/10mg am and pm for 5 days/ 5mg am and pm for at least7 days.	No treatment	Method of randomisation unclear; allocation concealment adequate; Blinding of patients and study personnel
Gerhard 1987 n=34	25mg progesterone vaginal suppositories twice daily	Until the woman either miscarried or for 14 days after bleeding stopped	Placebo	Method of randomisation unclear; allocation concealment unclear. No blinding for participants or study personnel
Palagiano 2004 n=50	90 mg progesterone (Crinone 8%) vaginal suppositories	Once daily for 5 days	Placebo	Method of randomisation unclear; allocation concealment adequate. No blinding for participants or study personnel
Omar 2005 n=154	Dydrogesterone	40 mg dydrogesterone stat, followed by 10 mg twice a day until the bleeding stopped.	No treatment	Method of randomisation unclear; no allocation concealment; no blinding of patients and study personnel
El-Zibdeh 2009 = n	10 mg oral dydrogesterone twice daily.	Treatment started as soon as the woman was enrolled in the trial and continued for 1 week after bleeding had stopped	No treatment	Quasi-randomised- allocated according to day of the week. No allocation concealement, no blinding for participants or study personnel.
Pandian 2009 n=191	Oral dydrogesterone	40 mg oral dydrogesterone stat followed by 10 mg dydrogesterone twice daily; treatment continued until 16 weeks'	No treatment	Method of randomisation and allocation concealement adequate. No blinding of participants or study personnel.

Findings: Seven studies, including a total of 744 women, were identified. These studies were small and of poor quality, with none reporting the method of allocation concealment. The modified Jadad quality score varied from 1/6 to 3/6.

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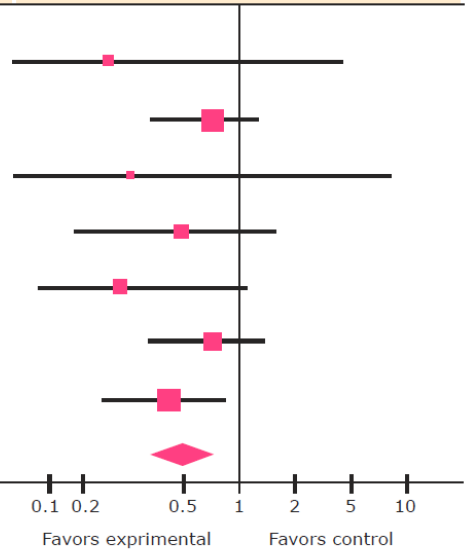
Meta-analysis of the 7 studies

Study	Progesterone Events	Progesterone Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Misto 1967	0	7	2	9	0.25 (0.01, 4.50)
Ehrenskjold 1967	14	72	23	81	0.68 (0.38, 1.23)
Gerhard 1987	0	17	1	17	0.33 (0.01, 7.65)
Palagiano 2004	4	25	8	25	0.50 (0.17, 1.45)
Omar 2005	3	74	11	80	0.29 (0.09, 1.02)
El-Zibdeh 2009	15	86	15	60	0.70 (0.37, 1.32)
Pandian 2009	12	96	27	95	0.44 (0.24, 0.82)
Total (95% CI)		337		367	0.53 (0.39, 0.73)



Heterogeneity: $Chi^2=3.02$, df=6 (P=0.81); $I^2=0\%$
Test for overall effect: Z=3.88 (P=0.0001)

- Individual studies were too small to show an effect, but a meta-analysis of these seven studies showed a statistically significant reduction in miscarriage rate with progestogen use (RR 0.53, 95% CI: 0.39 to 0.73).
- There was no heterogeneity across the studies (I2=0%), suggesting consistency across the studies.

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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

BIRMINGHAM CLINICAL TRIALS UNIT

UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

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CONCLUSION

- The **role of progesterone** in the **physiopathology of pregnant women** is **crucial** from conception until delivery.

- There is **strong biological plausibility** to support exogenous progesterone for the management of recurrent, threatened miscarriage, and for the prevention of preterm birth in women at risk with a short cervix and/or a history of preterm delivery.

- The **optimal** dose, **route of administration** and **duration** remains to be determined in **symptomatic women** and in **pregnancy maintenance after tocolysis.**

- **Neonatal effects, health infant** and cost-effectiveness with vaginal micronized progesterone are now available with a level 1 of evidence (*PROMISE, PREDICT, PREGNANT, OPPTIMUM trials*).