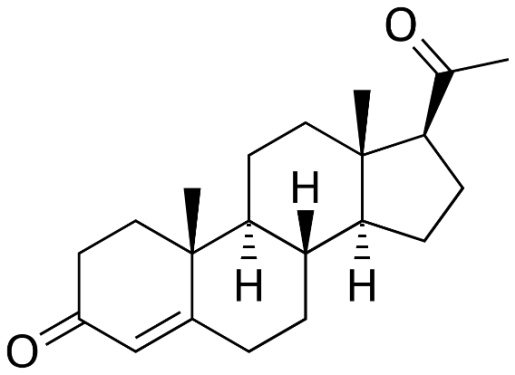
Vaginal Micronized Progesterone for Pregnancy Maintenance

dr. Hervi Wiranti, SpOG

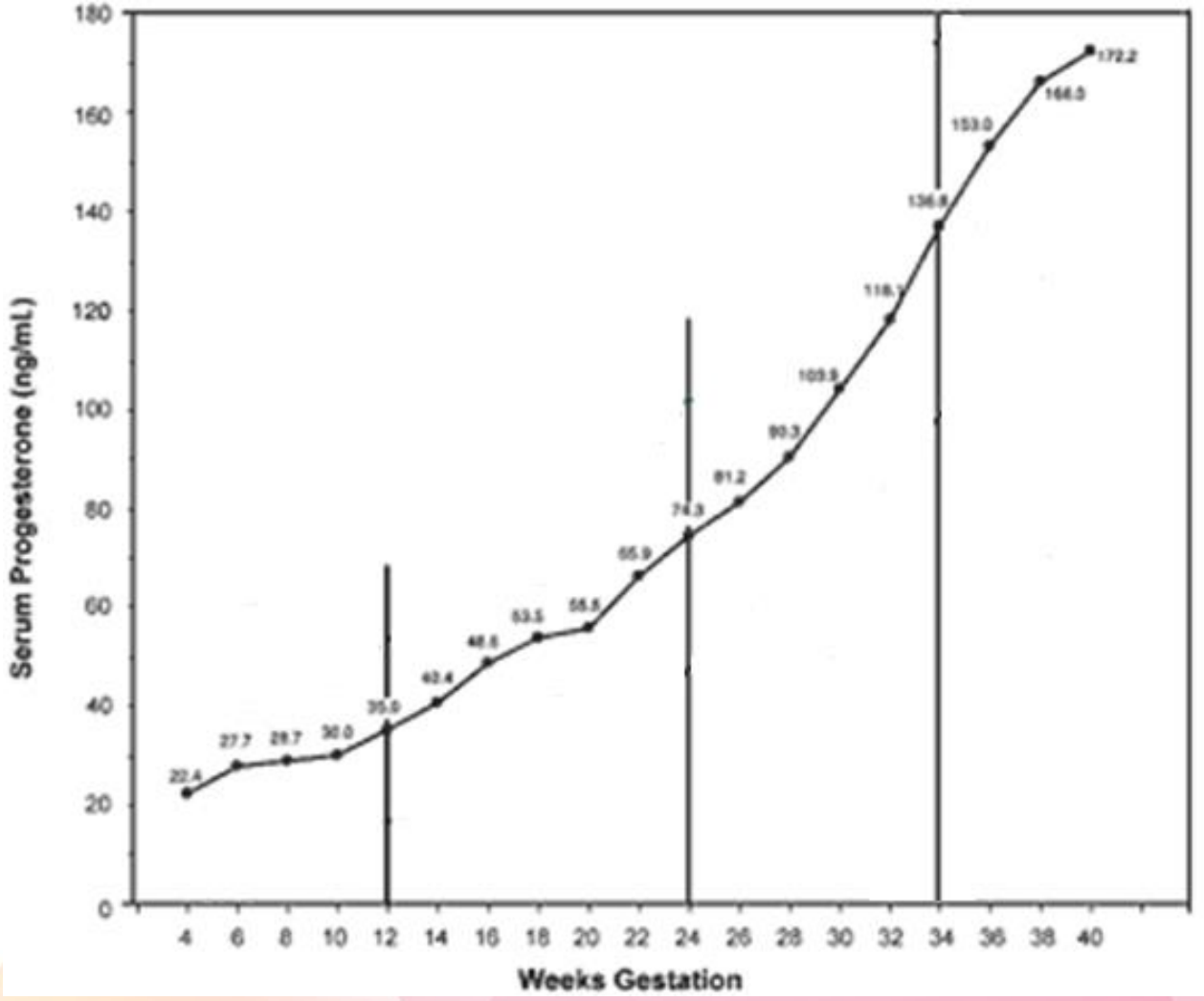
Overview Progesterone in Pregnancy

What is progesterone?

- Progesterone is an endogenous steroid hormone, produced by the adrenal cortex and the gonads (ovaries and testes)
- Secreted by the ovarian corpus luteum during the first ten weeks of pregnancy



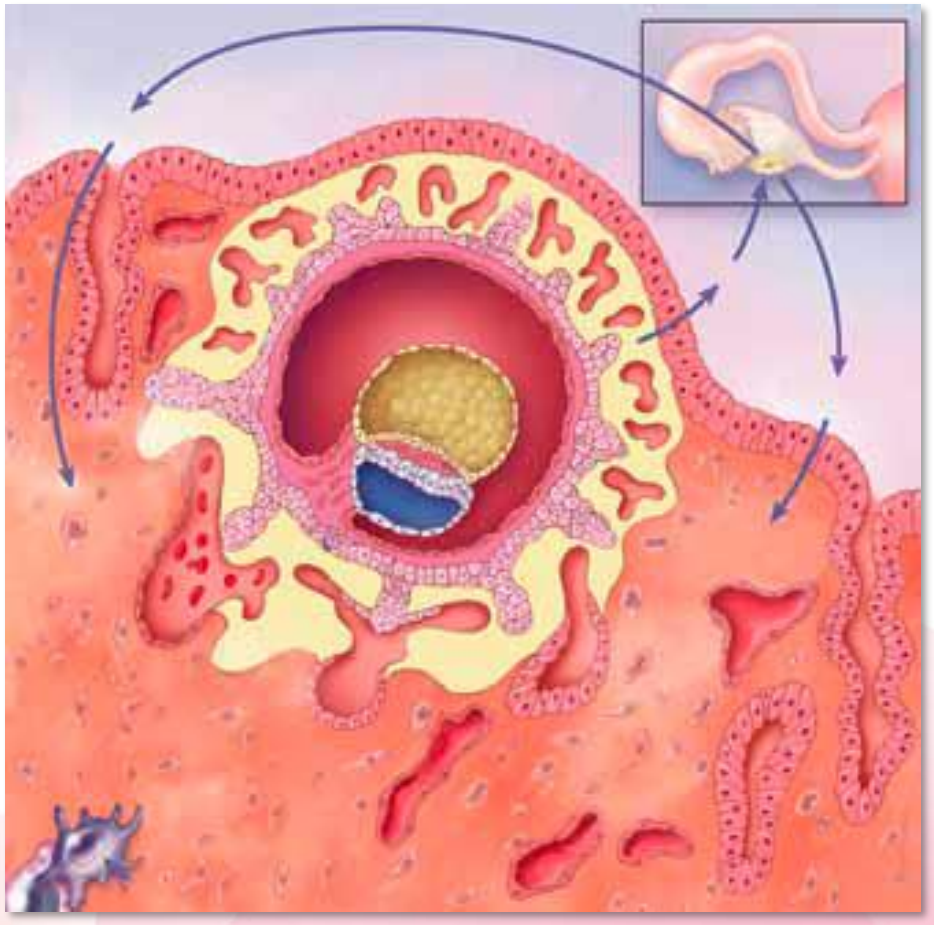
Low progesterone in early pregnancy is associated with threatened miscarriage



Ku et al. BMC Pregnancy and Childbirth 2018; **18(1)**: 360-366

Role of Physiological Progesterone

- Prepares endometrium for implantation
  - Promotes differentiation of endometrial stromal and epithelial cells → Endometrial differentiation & Uterus growth
  - Reduces physiological cell death occurring just before menstruation
- Maintains pregnancy
  - Modulates maternal immune responses
  - Reduces uterine contractility
  - Improves utero-placental circulation
  - Suppresses fetal inflammatory response



Characteristics of Micronized Progesterone vs Synthetic Progestins

Natural Micronized Progesterone (MP)

=

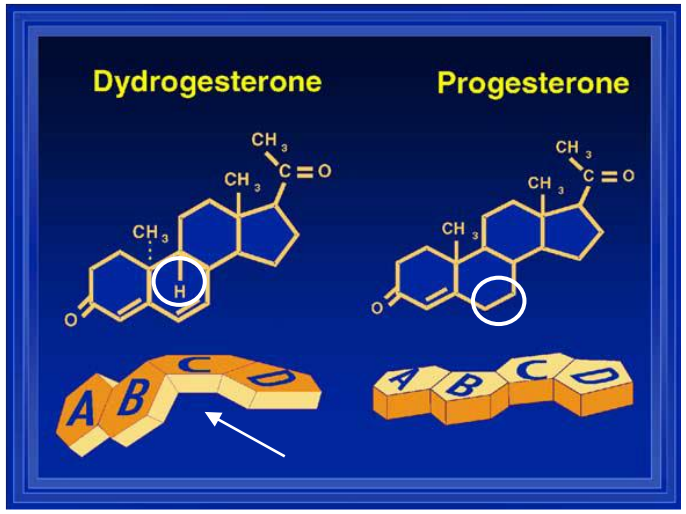
Exact chemical duplicate of the Progesterone produced by the human body

(*"bio- or body-identical"*)

≠

Synthetic analogues of Progesterone labeled *Progestogens* or *Progestins*

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

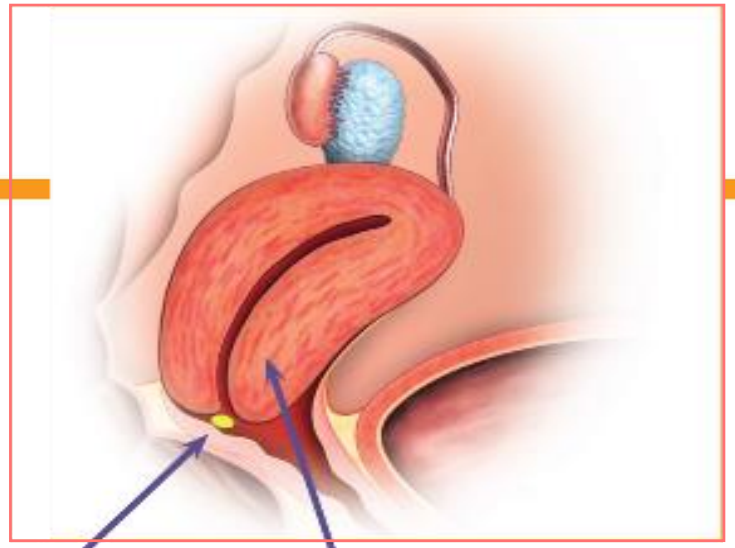
Dydrogesterone is chemically modified retroprogesterone*
«its hormonal pattern and metabolism differ largely from that of the natural P»

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.

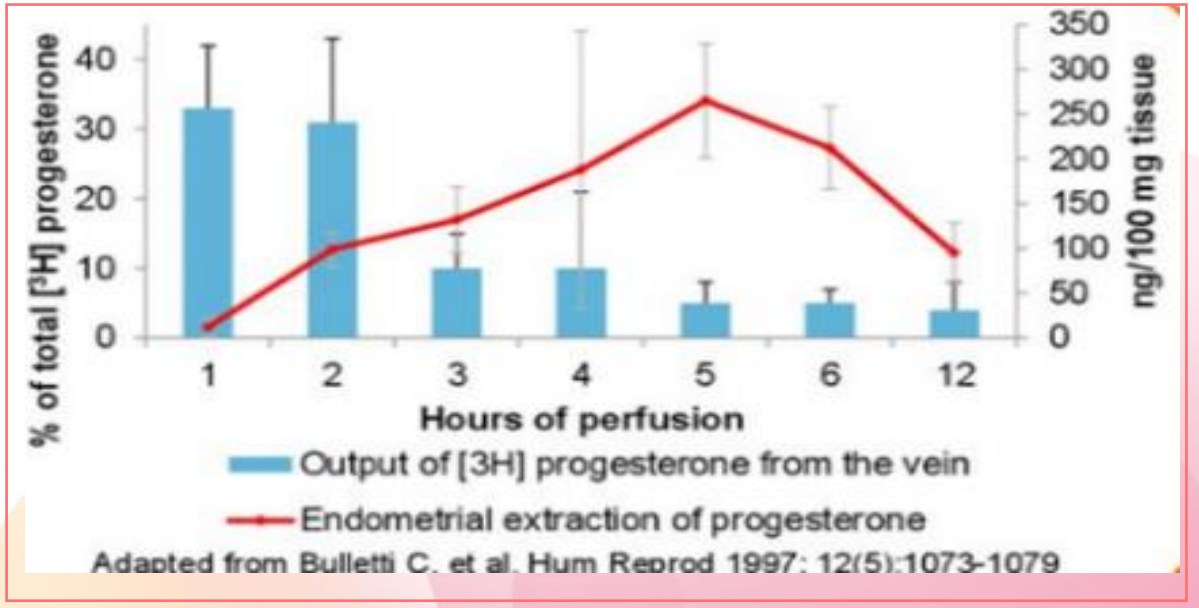
Vaginal route of administration



Different mechanisms can be advocated

- Direct diffusion through tissues: this "uterine first-pass effect" avoids first-pass liver metabolism with a potential for less stimulation of the liver proteins (***Bulletti et al***, 1997***)***

- Counter-current transfer between utero-vaginal veins or lymph vessels and arteries (***Einer-Jensen et al***, 1993***)***
- Intraluminal passage from the vagina to the uterus (***Wildt et al,*** 1998***)***
- Venous or lymphatic circulatory systems (***Magness et al,*** 1983***)***

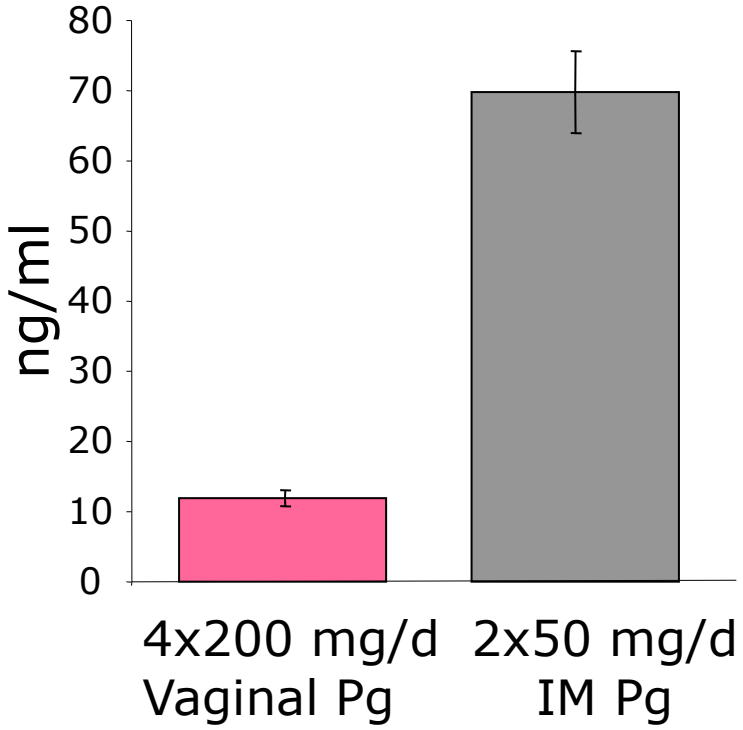


1. **Cicinelli E**, et al. *Hum Reprod Update* 1999; 5; 365–372 2. **Fanchin R,** *et al. Obstet Gynecol* 1997; **90**;396–401 3. **Cicinelli E,** *et al. Fertil Steril* 2000; 69, 471–3.

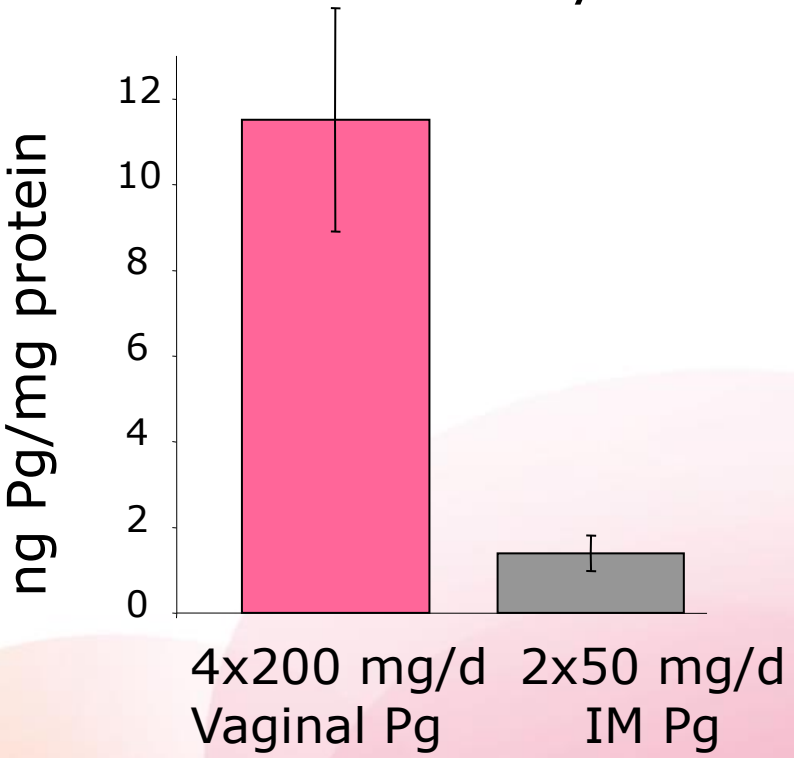
USE OF EXOGENOUS PROGESTERONE (P4)

Pharmacokinetics data: **vaginal route**

Plasma progesterone concentrations in steady state



Progesterone concentrations in uterine tissue in steady state

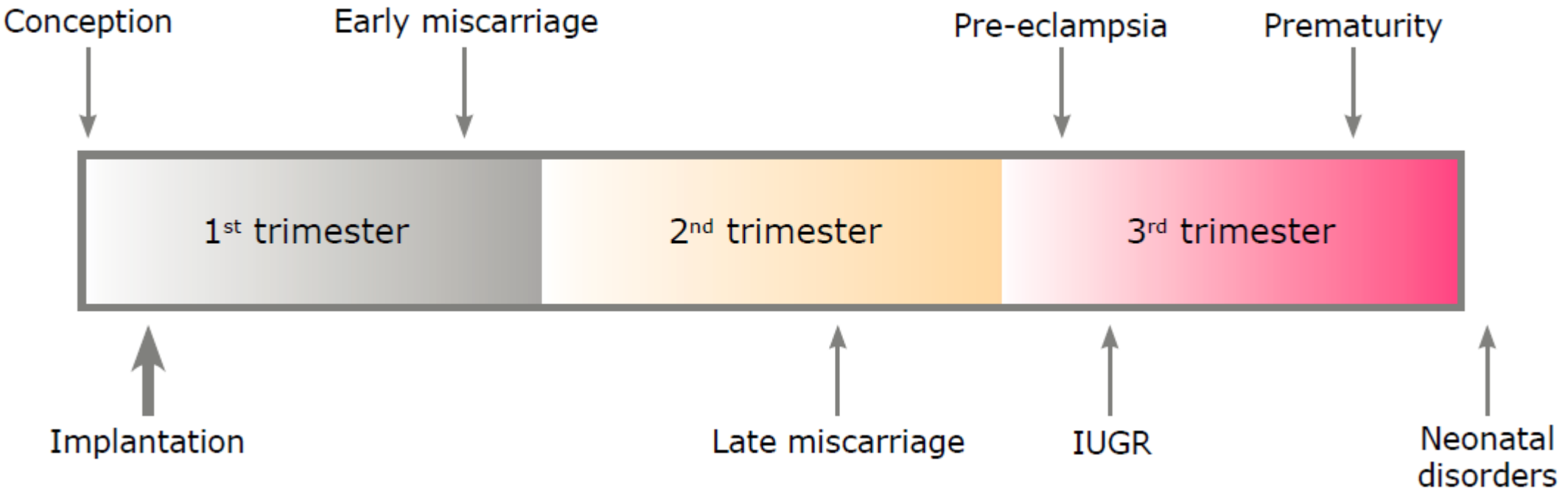


Miles A et al, *Fertil Steril 1994;* ***62****: 485-90*

Indication for Progesterone in Pregnancy Maintenance

- **Threaten and Recurrent Miscarriage**
- Prevention of Preterm Birth

Why progesterone is so important during the all pregnancy?



- Miscarriage (M) is spontaneous loss of pregnancy before the fetus has reached viability, from the time of conception until 20 to 24 weeks of gestation.[1,2]
- TM is defined by vaginal bleeding (and pain) in a woman with a confirmed pregnancy.[1]
- Recurrent miscarriage is defined as three or more consecutive pregnancy losses, although many clinicians define it as 2 or more losses.[2]

1. **Rai R** *et al. Lancet* 2006; **368**: 601-611.
2. **Griebel CP** *et al. Am Fam Physician* 2005 Oct 1; **72(7)**: 1243-1250.

Miscarriages

Miscarriage is the loss of pregnancy in the **first 23 weeks**

Around **1 in 6** pregnancies end in miscarriage

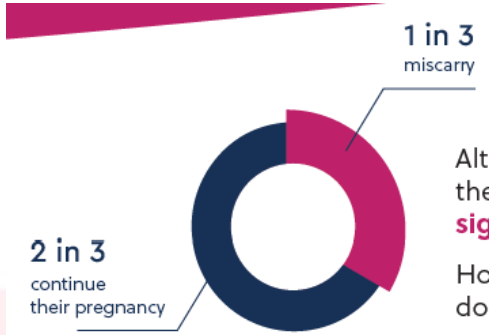
1/2 of early miscarriages have an underlying cause that could be prevented

1 in 5 women who miscarriage have **anxiety** levels similar to those seen in psychiatric outpatient services

1 in 3 women attending miscarriage clinics are clinically **depressed**

20% OF WOMEN

Bleeding before 12 weeks can happen for about **20% of pregnant women.**



Although women are often worried at the sight of blood, **it is not always a sign of a problem**.

However, bleeding in early pregnancy does increase the risk of miscarriage.

https://www.tommys.org/baby-loss-support/miscarriage-information-and-support/miscarriage-statistics

Progesterone has a unique pharmacodynamics profile for preventing miscarriage

Contents lists available at ScienceDirect
Best Practice & Research Clinical Obstetrics and Gynaecology
journal homepage: www.elsevier.com/locate/bpobgyn

The pharmacodynamics and safety of progesterone

Paul C.M. Piette, PharmD, Consultant

Modulates of maternal immune responses (protection of the semiallogenic fetus) [1,2]

Endometrium secretory changes, decidualization, vasodilation (↘apoptosis [7]), promotes extravillous trophoblasts (EVTs) Invasion in the maternal decidua remodeling the local vasculature [9]

Improves the utero-placental circulation [3]

Suppression of fetal immunoplacental inflammatory response [4]

Progesterone and metabolites

↓

Activation of PRs (PRA, PRB,…) and/or mPRs

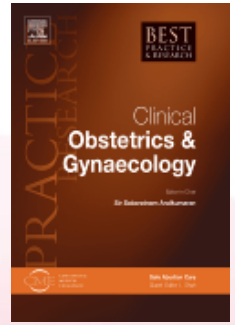
Uterine quiescence (+)

Cervix integrity [8] (+)

Reduce uterine contractility antagonizing oxytocine rec. [5,6]

Cervix ripening (−)

CRH → Prostaglandin (+)



1. **Norwitz ER**, et al. *N Engl J Med*. 2001;345:1400-1408.
2. **Druckmann R**, et al *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.
8. **Iams JD**, et al. Lancet. 2008;371:164-175
9. **Vondra S**, et al. *J Lip Res* 2019; 20:1922-1934..

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

Taylor & Francis
Taylor & Francis Group

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

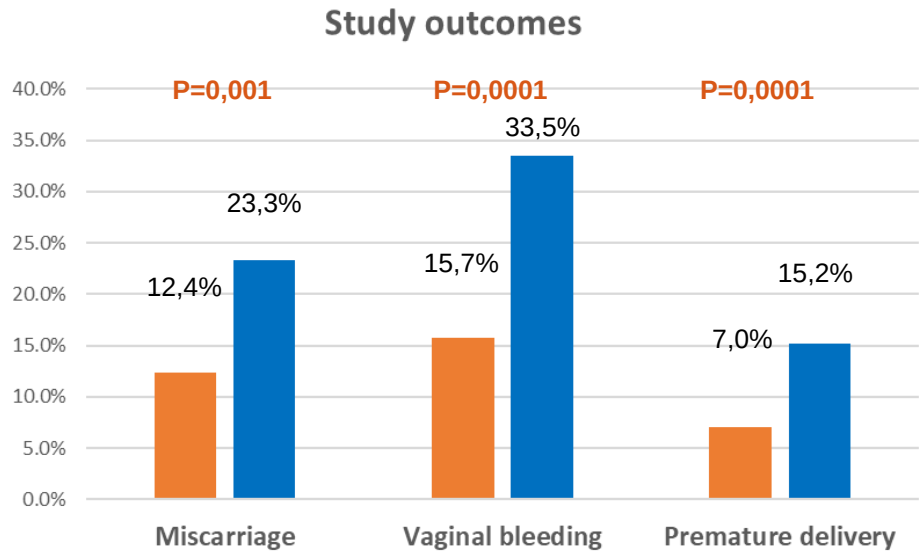
POPULATION	Women with unexplained recurrent miscarriages
INTERVENTION	400 mg progesterone taken vaginally twice daily, started in the luteal phase and continued to 28 weeks
COMPARISON	Placebo
OUTCOMES	Miscarriage

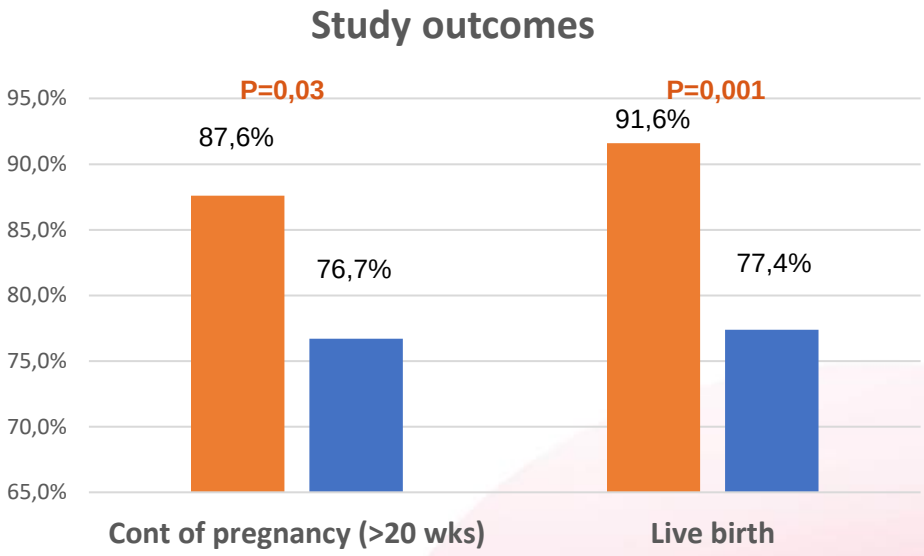
Ismail AM et al. *J Matern Fetal Neonatal Med* 2017; **15**: 1-7.

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**

Conclusion: Supplementation of vaginal micronized progesterone from the luteal phase and during gestation significantly reduces the rate of miscarriages and increases the frequency of pregnancy in patients with recurrent miscarriage.

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

Latest update – based on findings in PROMISE & PRISM Trial

Expert Review ajog.org

Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence

Arri Coomarasamy, MD, MRCOG; Adam J. Devall, PhD; Jan J. Brosens, PhD; Siobhan Quenby, MD, FRCOG; Mary D. Stephenson, MD; Sony Sierra, MD; Ole B. Christiansen, MD; Rachel Small, BSc; Jane Brewin, BSc; Tracy E. Roberts, PhD; Rima Dhillon-Smith, PhD, MRCOG; Hoda Harb, PhD; Hannah Noordali, PhD; Argyro Papadopoulou, BSc; Abey Eapen, PhD, MBBS; Matt Prior, MRCOG; Gian Carlo Di Renzo, MD; Kim Hinshaw, MBBS, FRCOG; Ben W. Mol, MD, PhD; Mary Ann Lumsden, MD, FRCOG; Yacoub Khalaf, MD, FRCOG; Andrew Shennan, MD, FRCOG; Mariette Goddijn, MD, PhD; Madelon van Wely, PhD; Maya Al-Memar, PhD, MRCOG; Phil Bennett, PhD, FRCOG; Tom Bourne, PhD, FRCOG; Raj Rai, MD, MRCOG; Lesley Regan, MD, FRCOG; Ioannis D. Gallos, MD, MRCOG

A key finding, first observed in the PROMISE trial, and then replicated in the PRISM trial, was that *treatment with vaginal micronized progesterone 400 mg twice daily was associated with increasing live birth rates according to the number of previous miscarriages*

Prespecified PRISM trial subgroup analysis in women with the dual risk factors of *previous miscarriage(s) and current pregnancy bleeding*

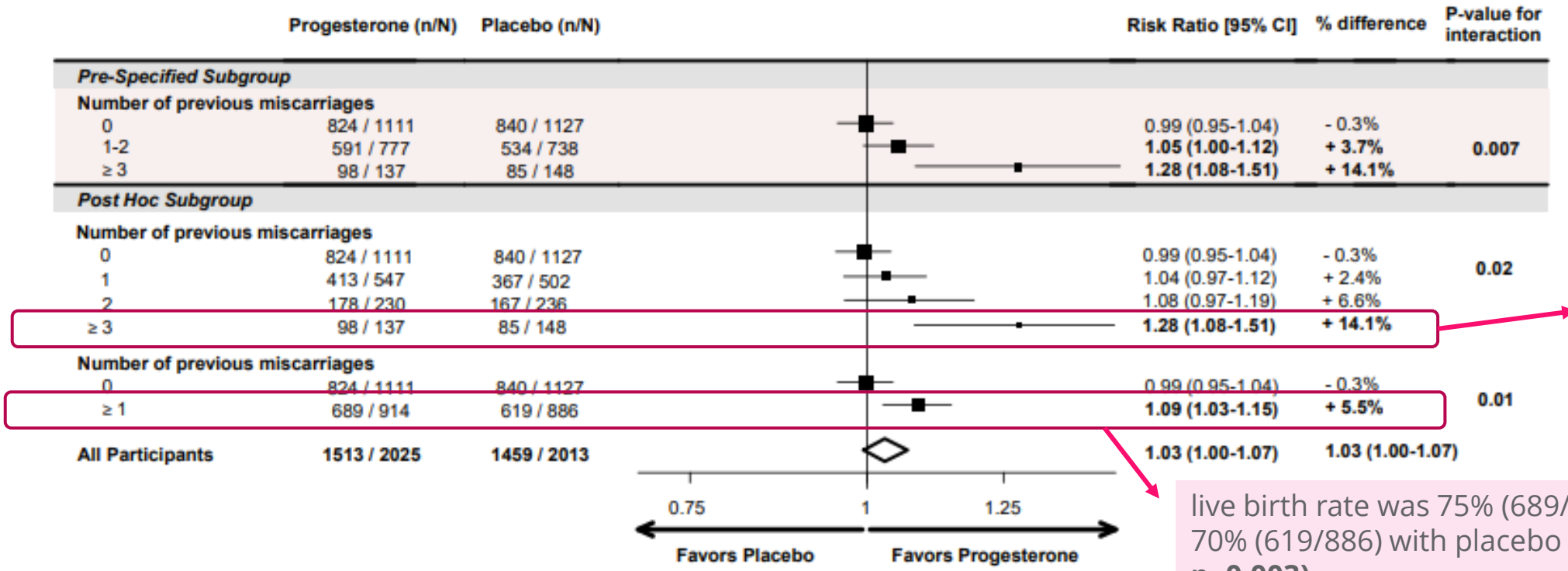
Coomarasamy et al, *Am J Obstet Gynecol* 2020;223(2): 167

PRISM: Result of sub-analysis

The benefit was greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding

FIGURE 2

PRISM trial data on live birth >34 weeks by the number of previous miscarriages



live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (**rate difference 15%), p=0.004**

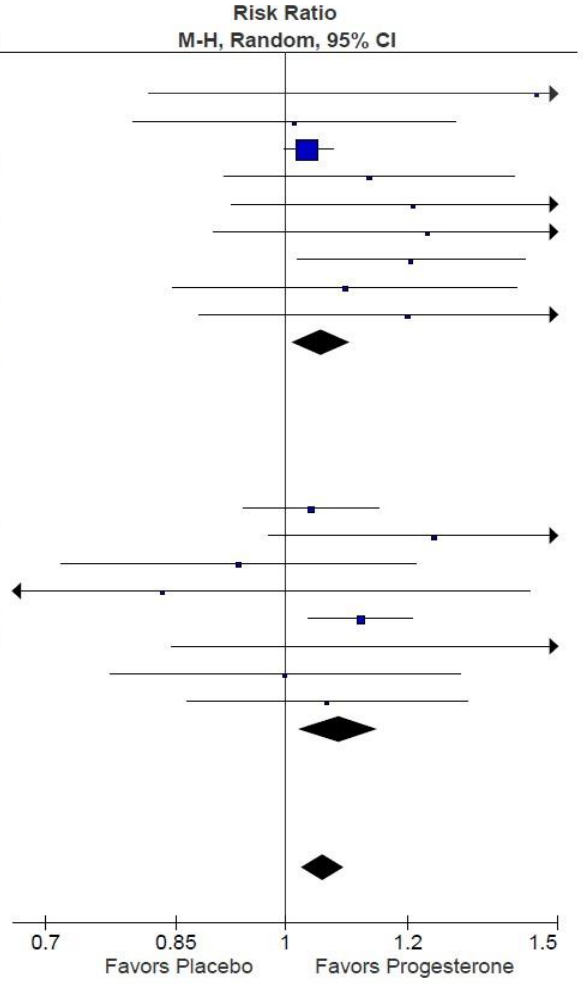
live birth rate was 75% (689/914) with progesterone vs 70% (619/886) with placebo (**rate difference 5%; p=0.003)**

CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage.

Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.

Meta-analysis of all studies for the outcome of live birth or ongoing pregnancy

Study or Subgroup	Progesterone Events	Progesterone Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Threatened miscarriage						
Akhtar 2012 (a)	16	30	11	30	0.3%	1.45 [0.82, 2.59]
Alimohamadi 2013 (b)	47	72	47	73	1.5%	1.01 [0.80, 1.29]
Coomarasamy 2019 (c)	1513	2025	1459	2013	61.3%	1.03 [1.00, 1.07]
El-Zibdeh 2009 (d)	65	86	40	60	1.8%	1.13 [0.91, 1.41]
Gerhard 1987 (b)	23	26	19	26	1.1%	1.21 [0.92, 1.59]
Palagiano 2004 (e)	21	25	17	25	0.8%	1.24 [0.90, 1.70]
Pandian 2009 (b)	78	96	64	95	2.9%	1.21 [1.02, 1.43]
Turgal 2017 (f)	26	32	26	35	1.3%	1.09 [0.85, 1.41]
Yassaee 2014 (b)	24	30	20	30	0.9%	1.20 [0.88, 1.64]
Subtotal (95% CI)		2422		2387	71.8%	**1.06 [1.01, 1.10]**
Total events	1813		1703			
Heterogeneity: Tau² = 0.00; Chi² = 8.16, df = 8 (P = 0.42); I² = 2%						
Test for overall effect: Z = 2.62 (P = 0.009)						
Recurrent miscarriage						
Coomarasamy 2015 (g)	262	398	271	428	8.2%	1.04 [0.94, 1.15]
El-Zibdeh 2005 (d)	64	82	30	48	1.4%	1.25 [0.98, 1.60]
Goldzieher 1964 (h)	18	23	26	31	1.2%	0.93 [0.72, 1.22]
Klopper 1965 (i)	10	18	10	15	0.3%	0.83 [0.48, 1.44]
Kumar 2014 (e)	163	175	144	173	13.8%	1.12 [1.04, 1.21]
Le Vine 1964 (j)	11	15	7	15	0.2%	1.57 [0.84, 2.92]
MacDonald 1972 (e)	17	20	17	20	1.2%	1.00 [0.77, 1.30]
Swyer 1953 (b)	47	60	39	53	1.9%	1.06 [0.86, 1.31]
Subtotal (95% CI)		791		783	28.2%	**1.08 [1.03, 1.14]**
Total events	592		544			
Heterogeneity: Tau² = 0.00; Chi² = 6.53, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 2.88 (P = 0.004)						
Total (95% CI)		3213		3170	100.0%	**1.06 [1.03, 1.09]**
Total events	2405		2247			
Heterogeneity: Tau² = 0.00; Chi² = 15.61, df = 16 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						



Synthesis of external evidence: The studies were broadly consistent in showing a benefit on live birth or ongoing pregnancy rate from the first-trimester use of progesterone or progestogens

Coomarasamy et al, *Am J Obstet Gynecol* 2020;223(2): 167

Drug Safety

The NEW ENGLAND JOURNAL of MEDICINE

Level 1 of evidence

- The use of micronized progesterone until 16th week of gestation at a dose of 800 mg / day **confirmed its safety for mother, including obese women and for fetus**
- The incidence of congenital anomalies was not different in the vaginal progesterone group and placebo
- No short-term safety concerns were identified from the PROMISE and PRISM trials. Therefore, women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronized progesterone.

PROMISE

	Progesterone	Placebo	RR (95% CI)
Congenital abnormalities	8/266	11/276	0.75 (0.31, 1.85) p=0.54

Coomarasamy et al, PROMISE trial
N Engl J Med 2015;373:2141-2148

PRISM

	Progesterone	Placebo	RR (95% CI)
Termination of pregnancy	34/2025	36/2013	0.94 (0.59, 1.50) p=0.81
Congenital abnormalities	53/1574	51/1551	1.00 (0.69, 1.47) p=0.99

Coomarasamy et al, PRISM trial
N Engl J Med 2019; 380:1815-1824

Coomarasamy et al, *Am J Obstet Gynecol* 2020;223(2): 167-

Cochrane: Vaginal micronized progesterone

Cochrane Library

Cochrane Database of Systematic Reviews

Progestogens for preventing miscarriage: a network meta-analysis (Review)

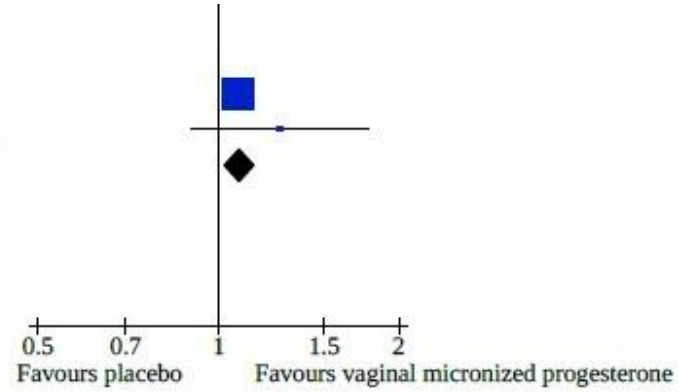
Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID

1.8.2 One or more previous miscarriages and early pregnancy bleeding						
Coomarasamy 2019	689	914	619	886	98.3%	1.08 [1.02 , 1.14]
Gerhard 1987	13	14	11	15	1.7%	1.27 [0.90 , 1.78]
Subtotal (95% CI)		**928**		**901**	**100.0%**	**1.08 [1.02 , 1.14]**
Total events:	702		630			

Heterogeneity: $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0\%$

Test for overall effect: Z = 2.75 (P = 0.006)

Test for subgroup differences: $Chi^2 = 5.03$, df = 1 (P = 0.02), $I^2 = 80.1\%$



For women with one or more previous miscarriages and early pregnancy bleeding, vaginal micronized progesterone increases the live birth rate compared to placebo: RR 1.08, 95% CI 1.02 to 1.15, high-certainty evidence

Devall AJ, PapadopoulouA, PodesekM, HaasDM, PriceMJ, CoomarasamyA, GallosID. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD013792. DOI: 10.1002/14651858.CD013792.pub2.

NICE Guideline NG126: 24 November 2021

November 2021, 24th

BBC Sign in | Home | News | Sport | Reel | Worklife | Travel

NEWS

Home | Coronavirus | Climate | Video | World | UK | Business | Tech | Science | Stories | Entertainment & Arts

Health | Coronavirus

Progesterone recommended to prevent early miscarriage

By Tulip Mazumder
Global health correspondent

1 hour ago

NICE National Institute for Health and Care Excellence

Ectopic pregnancy and miscarriage: diagnosis and initial management

NICE guideline
Published: 17 April 2019
www.nice.org.uk/guidance/ng126

1.5 Management of miscarriage

Threatened miscarriage

1.5.1 Advise a woman with a confirmed intrauterine pregnancy with a fetal heartbeat who presents with vaginal bleeding, but has no history of previous miscarriage, that:

- if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment
- if the bleeding stops, she should start or continue routine antenatal care. **[2012, amended 2021]**

NICE guideline

Offer vaginal micronised progesterone 400 mg twice daily to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage. **[2021]**

1.5.3 If a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy. **[2021]**

In November 2021, this was an off-label use of vaginal micronised progesterone. See NICE's information on prescribing medicines.

ESHRE Recommendation 2022 on Recurrent Pregnancy Lost

Vaginal progesterone may improve live birth rate in women with 3 or more pregnancy losses and vaginal blood loss in a subsequent pregnancy	Conditional	⊕⊕⊕■	Vaginal progesterone during early pregnancy may have beneficial effects in women with unexplained RPL with vaginal bleeding. There is some evidence that oral dydrogesterone initiated when fetal heart action can be confirmed may be effective, but more trials are needed.	UPDATED (2022)

Only vaginal micronized is recommended for RPL

Dydrogesterone is not recommended, more trials are needed to confirm the efficacy

Why Dydrogestrogesterone is not recommended?

- ***El-Zibdeh study does not meet standard criteria for valid RCT*** study (the treatments were not blinded, no placebo was given→ introduce performance bias
- ***Kumar study is retracted***→ due to late inclusion of patients in the study
- ***Meta-analysis by Howard Carp*** is just combined analysis of El-Zibdeh study & Kumar study + 1 very small non-RCT→ ***adds nothing to literature***
- Other publication of Dydrogesterone for RPL: Haas 2019, Saccone 2017, are ***flawed by the quality of older included study***

BESINS HEALTHCARE
Innovating for Well-being

ESHRE Recurrent Pregnancy Loss Guideline Development Group. Recurrent Pregnancy Loss: Guideline of European Society of Human Reproduction and Embryology. 2022. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss

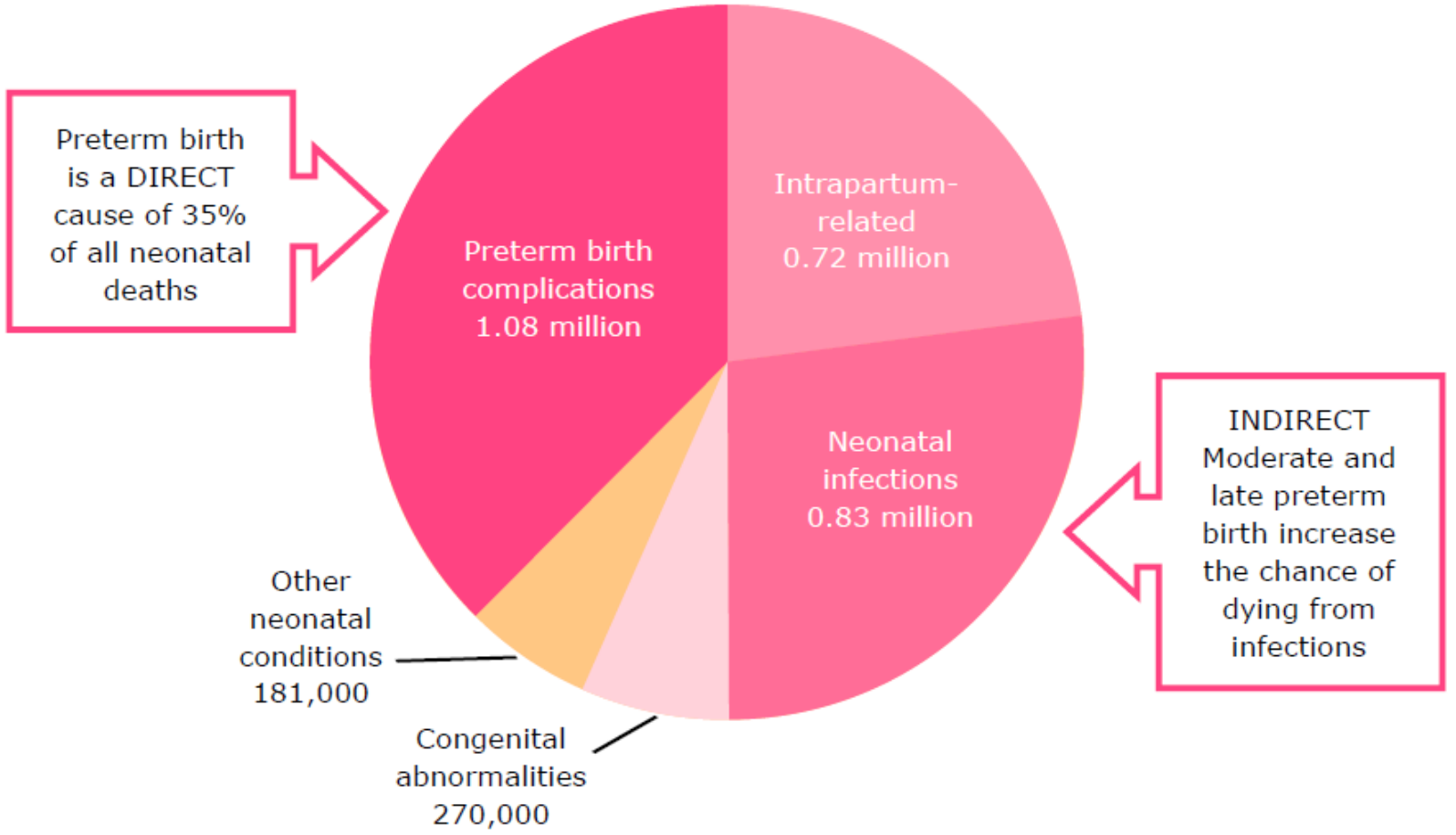
UTROGESTAN®
Natural micronised progesterone

Indication for Progesterone in Pregnancy Maintenance

- Threaten and Recurrent Miscarriage
- **Prevention of Preterm Birth**

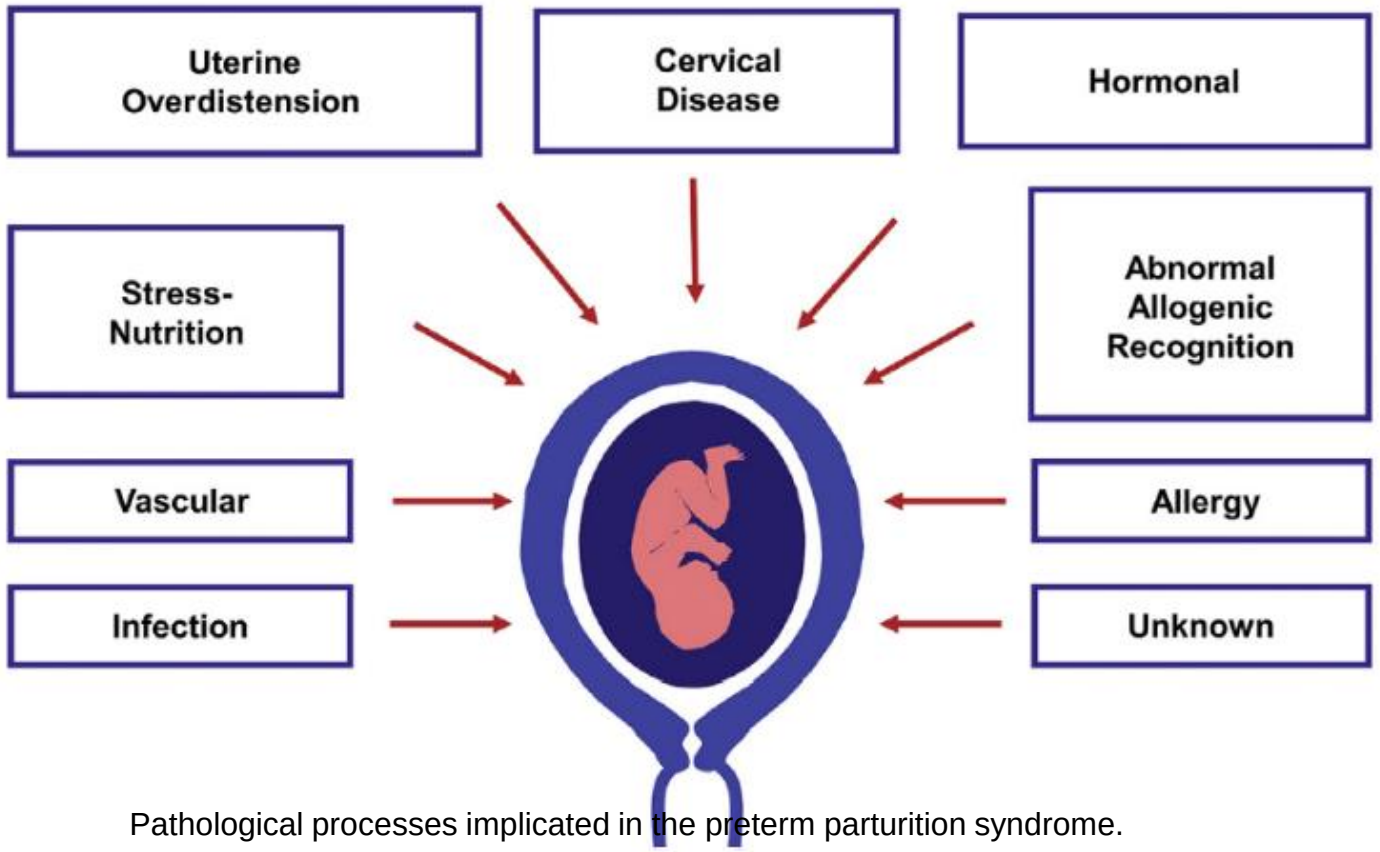
Preterm Birth and Mortality

- Leading cause of child death in high- and middle income countries.[1]
- Risk factor for neonatal and post-neonatal deaths in at least 50% of all neonatal deaths.[2]
- Economic costs of about $5-6 billion annually in the United States.[3]



1. Liu L et al. , *Lancet* 2012; 379(9832):2151-2161.
2. Lawn JE, et al. *Semin Perinatol* 2010; 34(6): 371–386.
3. Challis JRG. *Obstet Gynecol Surv*. 2000;55(10):650-660.

Preterm Parturition Syndrome



Pathological processes implicated in the preterm parturition syndrome.

Romero R, Espinoza J, Mazor M, Chaiworapongsa T. The preterm parturition syndrome. In: Critchely H, Bennett P, Thornton S, editors. Preterm Birth. London: RCOG Press; 2004.

Challenges in preterm delivery prevention and management

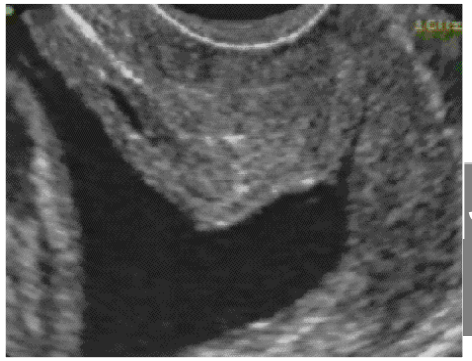
Identification of risk factors

Prior history of preterm birth

Twin pregnancy

Short cervix at scan

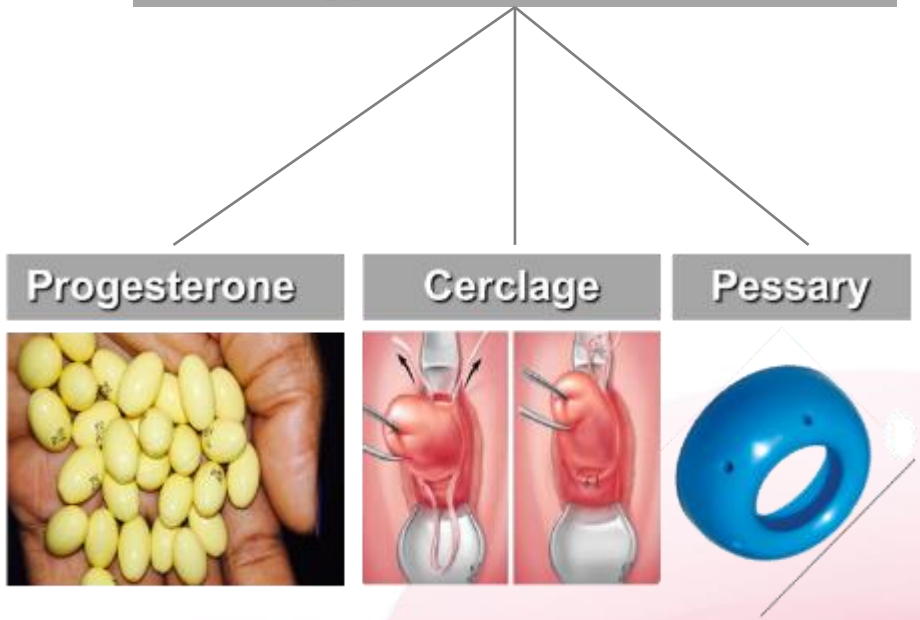
TVS-cervical length is the single most powerful predictor for PTD in the index pregnancy.



Short cervix at scan

<25 mm

Strategy in the prevention



Prevention of Preterm Birth

Women with history of preterm delivery

Women with short cervical length on transvaginal sonography

↓

Prophylactic use of progesterone

↓

Incidence of preterm delivery significantly reduced

Effect of vaginal progesterone on preterm birth ≤ 33 weeks of gestation

Reports of Major Impact ajog.

Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data

Roberto Romero, MD, DMedSci; Agustin Conde-Agudelo, MD, MPH, PhD; Eduardo Da Fonseca, MD; John M. O'Brien Elcin Cetingoz, MD; George W. Creasy, MD; Sonia S. Hassan, MD; Kypros H. Nicolaides, MD

Meta-analysis of 5 RCTs

to determine whether vaginal progesterone prevents preterm birth and improves perinatal outcomes in asymptomatic women with a singleton gestation and a midtrimester sonographic short cervix (≤ 25 mm)

TABLE 2
Studies included in the meta-analysis of individual patient data

Study	Trial enrollment	Participants randomly assigned in original trial	Participants eligible for IPDMA	Treatment groups	Compliance ≥80%
Fonseca et al,[69] 2007	8 Centers in United Kingdom, Chile, Brazil, and Greece	250 with singleton or twin gestation and cervical length ≤15 mm	226	Vaginal progesterone 200 mg/d or placebo from 24–33 6/7 wk of gestation	92% for vaginal progesterone group and 94% for placebo group
O'Brien et al,[70] 2007	53 Centers in United States, South Africa, India, Czech Republic, Chile, and El Salvador	659 with singleton gestation and previous spontaneous preterm birth	31	Vaginal progesterone 90 mg/d or placebo from 18–22 to 37 0/7 wk of gestation, rupture of membranes or preterm delivery, whichever occurred first	100% for vaginal progesterone group and 95% for placebo group
Cetingoz et al,[71] 2011	Single Center in Turkey	160 with twin gestation, or singleton gestation with previous spontaneous preterm birth, or uterine malformation	8	Vaginal progesterone suppository 100 mg/d or placebo from 24–34 wk of gestation	100% for both study groups
Hassan et al,[72] 2011	44 Centers in United States, Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, and Ukraine	465 with singleton gestation and cervical length between 10–20 mm	458	Vaginal progesterone 90 mg/d or placebo from 20–23 6/7 to 36 6/7 wk of gestation, rupture of membranes or preterm delivery, whichever occurred first	89% for vaginal progesterone group and 93% for placebo group
Norman et al,[54] 2016	66 Centers in United Kingdom and Sweden	1228 with singleton gestation and previous spontaneous preterm birth, or cervical length ≤25 mm, or positive fetal fibronectin test combined with other clinical risk factors for preterm birth	251	Vaginal progesterone 200 mg/d or placebo from 22–24 to 34 wk of gestation or preterm delivery, whichever occurred first	63% for vaginal progesterone group and 69% for placebo group

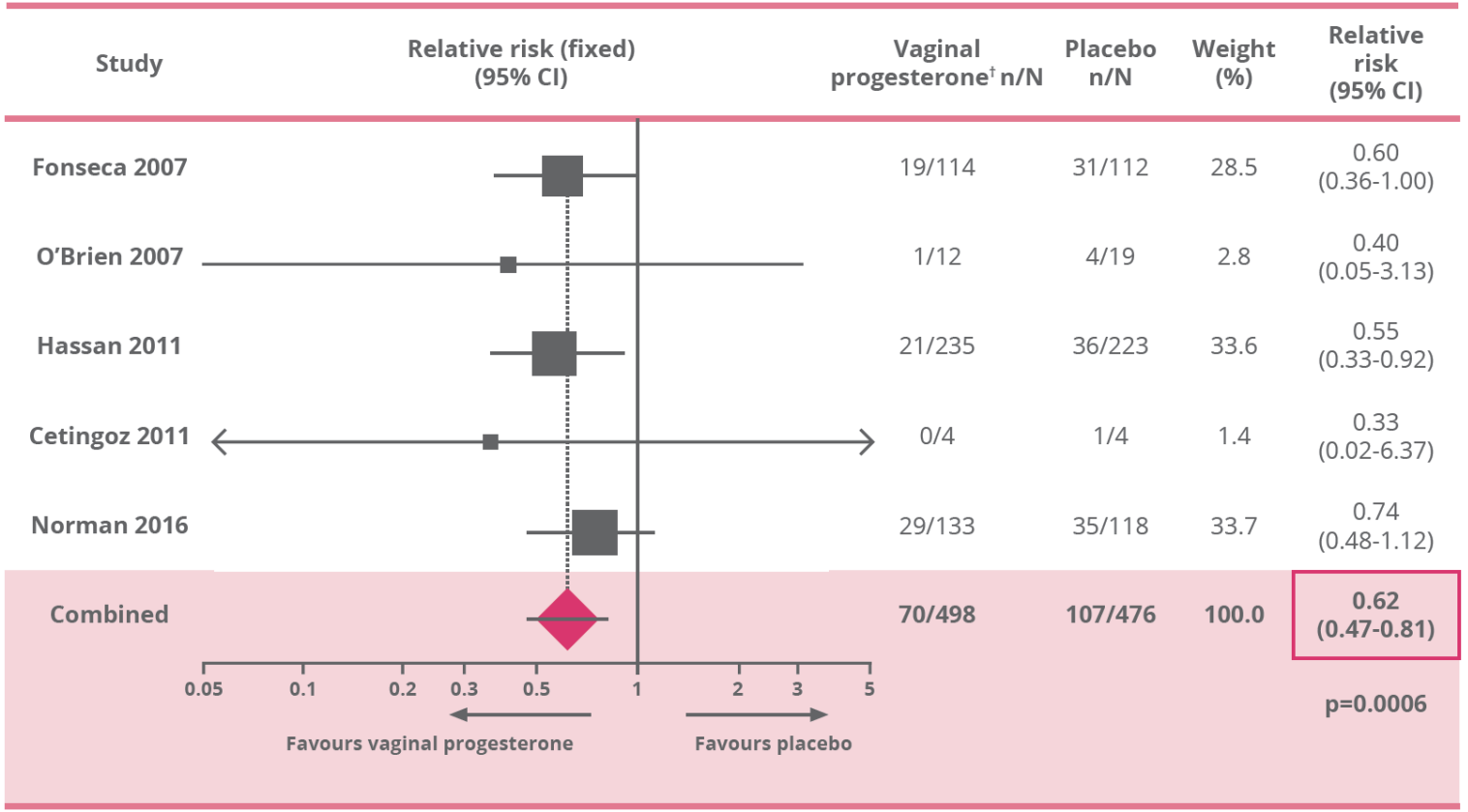
eta-analysis.

Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.

Total: 974 pasien

Romero R et al. *Am J Obstet Gynecol.* 2018**; 218(2)** :161-180.

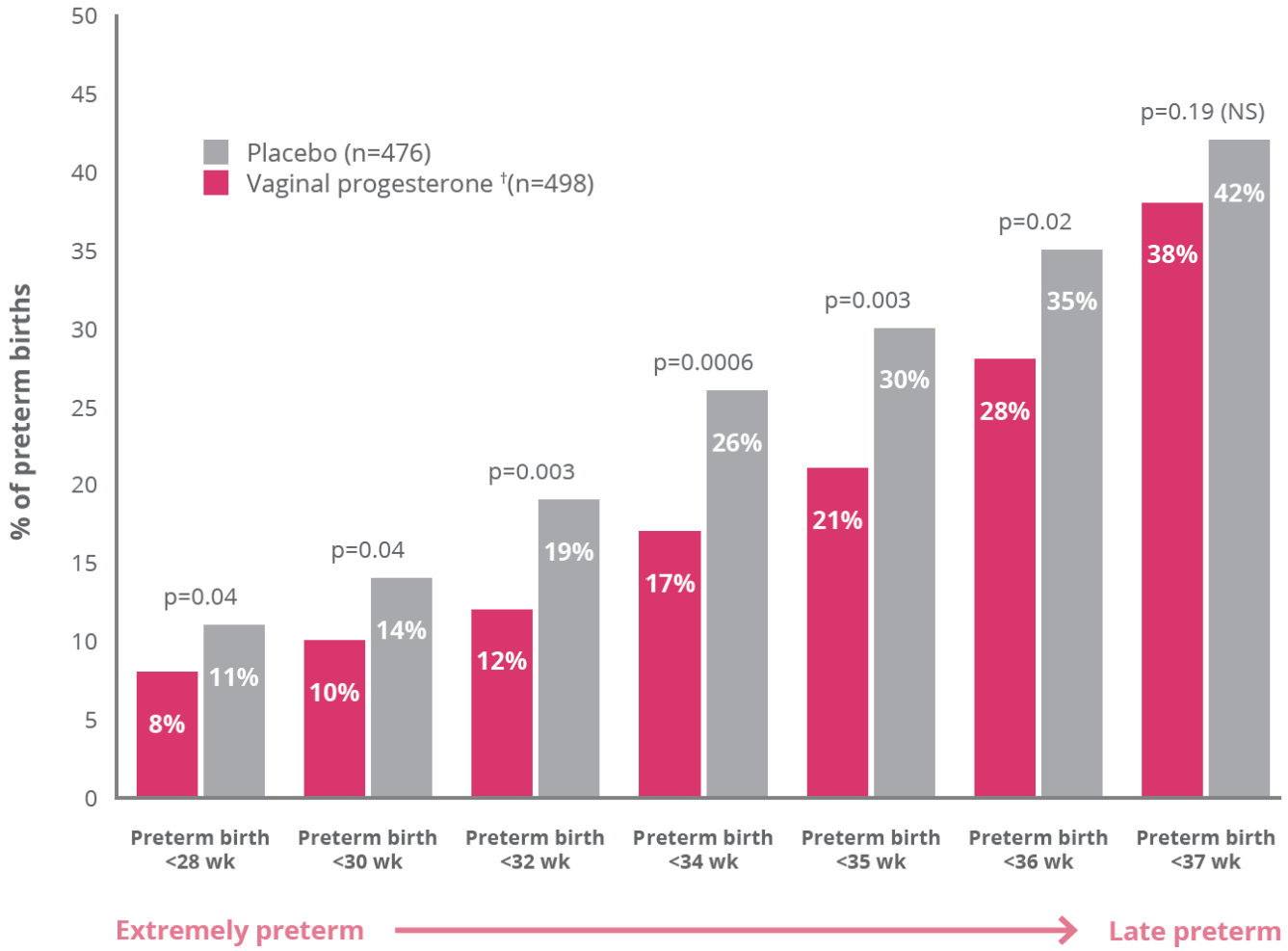
Effect of vaginal progesterone on preterm birth ≤ 33 weeks of gestation



CONCLUSION: Vaginal progesterone administration to asymptomatic women with singleton gestation and a sonographic short cervix decreases the risk of preterm birth ≤ 33 weeks of gestation, and improves perinatal outcomes, without any demonstrable deleterious effects on childhood neurodevelopment.

Romero R et al. *Am J Obstet Gynecol.* 2018**; 218(2)** :161-180.

Vaginal Progesterone's Effect from Extremely Preterm To Late Preterm

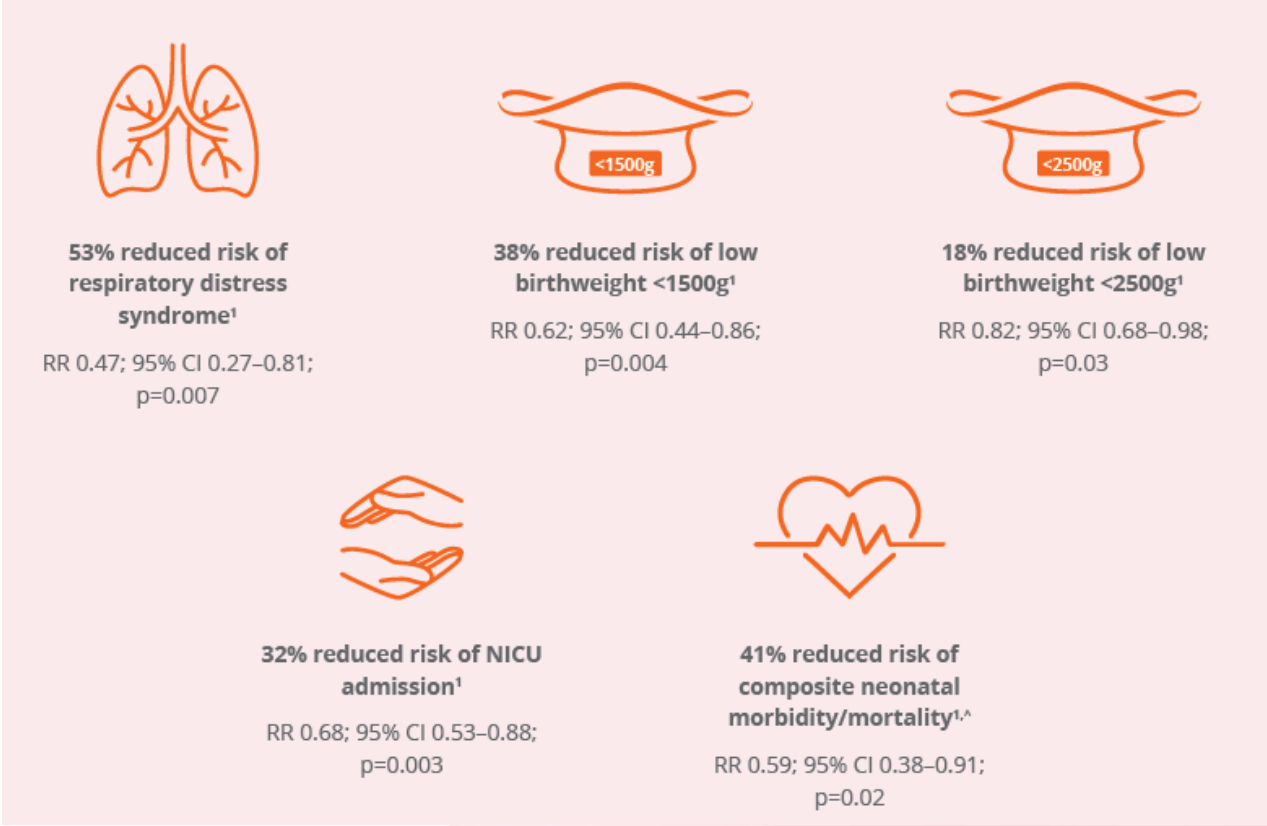


Romero R et al. *Am J Obstet Gynecol.* 2018**; 218(2)** :161-180.

Effect of vaginal progesterone on adverse perinatal and neurodevelopmental outcomes

Treatment with vaginal progesterone was also associated with a significant reduction in the risk of

- **RDS,**
- **composite neonatal morbidity and mortality,**
- **birthweight <1500 and <2500 g, and**
- **admission to the NICU** (RRs from 0.47 to 0.82; I2 = 0 for all; high-quality evidence for all).
- The frequency of neonatal death was 1.4% (7/498) in the vaginal progesterone group and 3.2% (15/476) in the placebo group.



Romero R et al. *Am J Obstet Gynecol.* 2018**; 218(2)** :161-180.

Latest study of vaginal progesterone & preterm birth : meta-analysis of Individual Patient Data

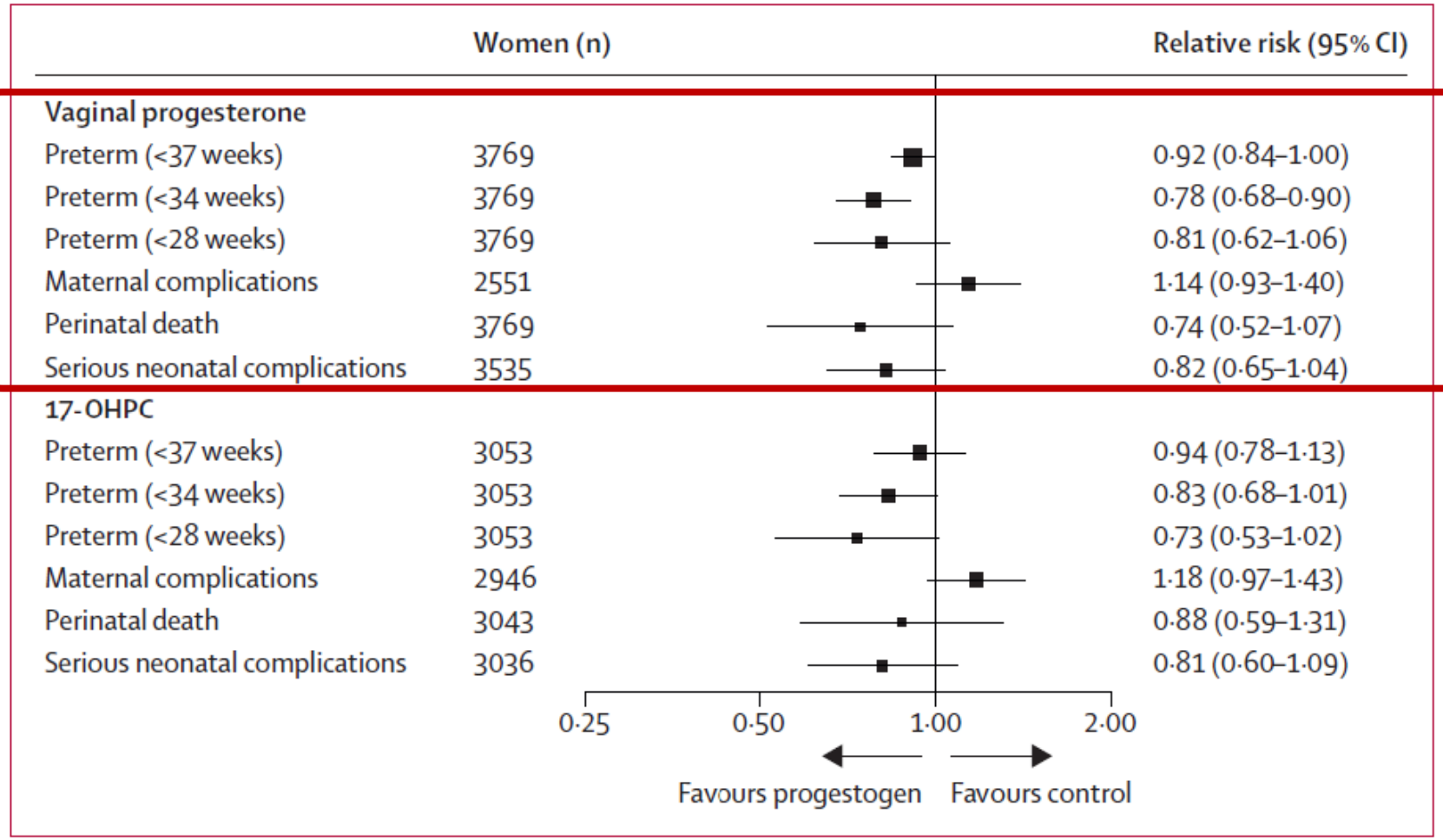
Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials

*The EPPPIC Group**

Interpretation Vaginal progesterone and 17-OHPC both reduced birth before 34 weeks' gestation in high-risk singleton pregnancies. Given increased underlying risk, absolute risk reduction is greater for women with a short cervix, hence treatment might be most useful for these women. Evidence for oral progesterone is insufficient to support its use. Shared decision making with woman with high-risk singleton pregnancies should discuss an individual's risk, potential benefits, harms and practicalities of intervention. Treatment of unselected multifetal pregnancies with a progestogen is not supported by the evidence.

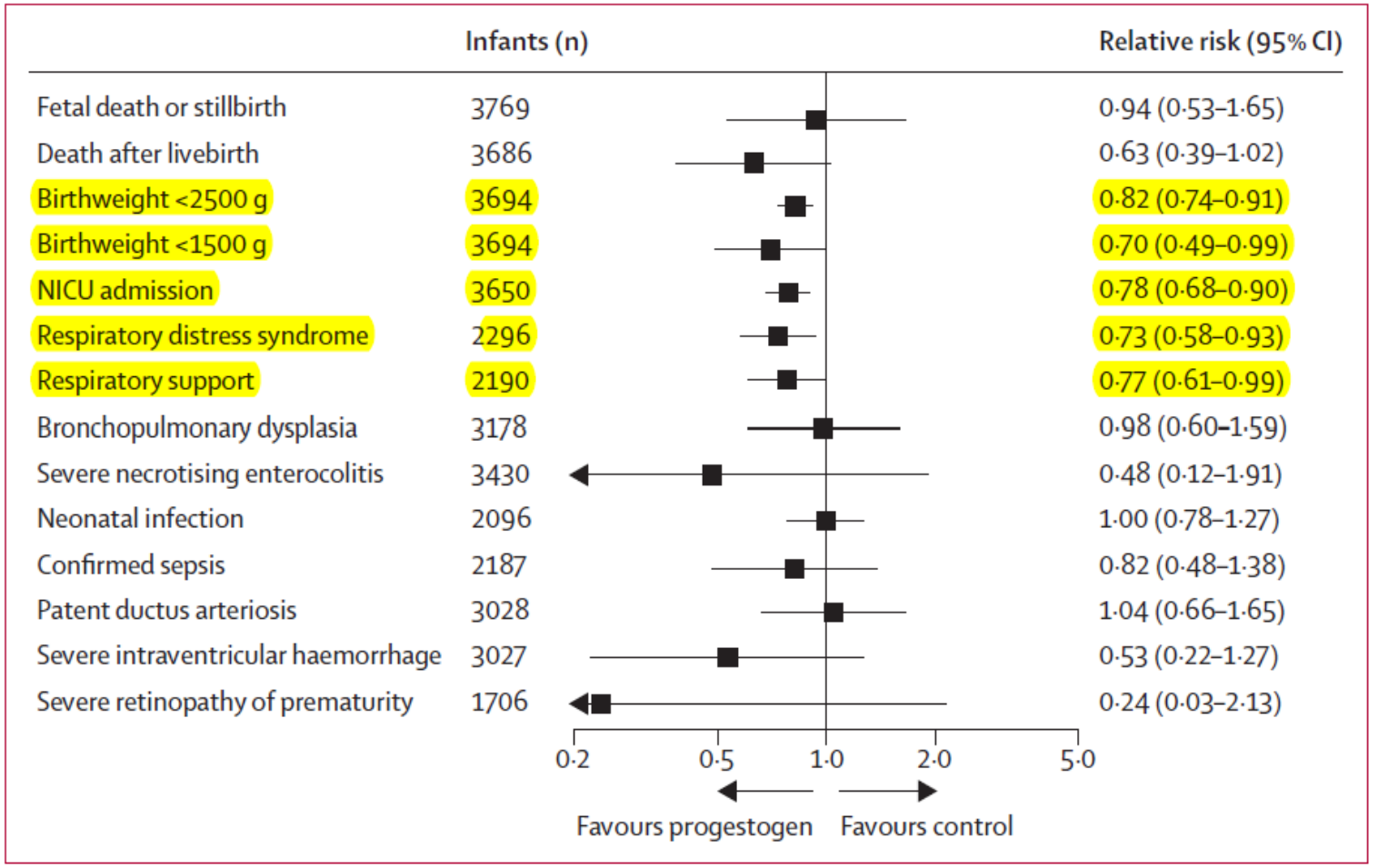
The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. **Lancet 2021; 397: 1183–94.**

Main outcomes of prevention of preterm birth for vaginal progesterone in singleton pregnancies

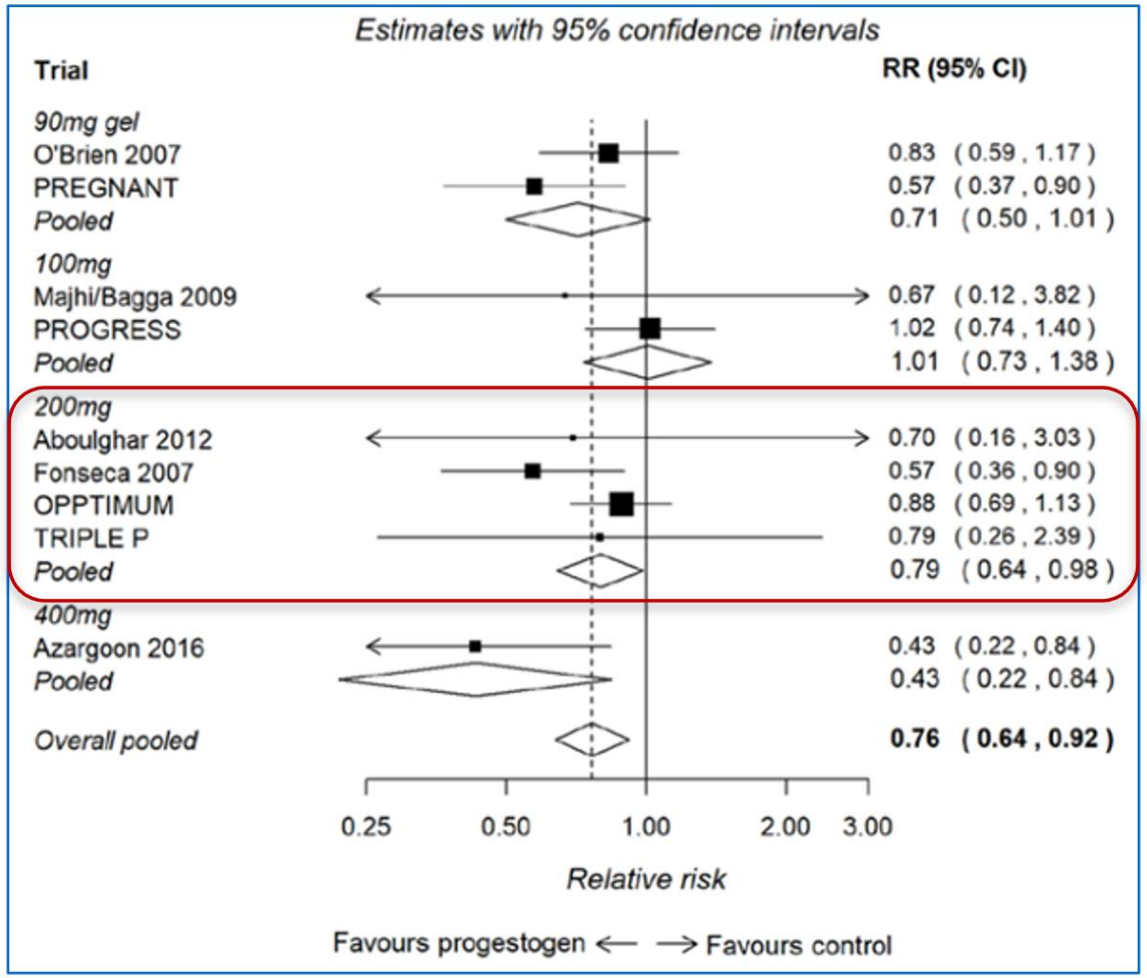


The EPPPIC Group. Lancet 2021; 397: 1183–94.

Safety outcome of prevention of preterm birth for vaginal progesterone in singleton pregnancies



Comparison of Different Vaginal Progesterone Preparations



- Subgroup analysis by planned vaginal progesterone dose in singleton pregnancies, preterm birth before 34 weeks show **significant reduced risk with 200mg with 4 supportive trials** compared to only one for 400mg and two with 90mg gel or 100mg which crossed the line of no effect.

Guideline Recommendations

- Asymptomatic women with a **sonographically short cervix** (≤25 mm) regardless of their obstetrical history should be offered **vaginal progesterone** treatment for the prevention of preterm birth and neonatal morbidity.
- Although there is a **clear benefit on neonatal outcome**, more RCTs are needed before recommending vaginal P4 in **twins** pregnant women with a sonographically short cervix

- SMFM continues to affirm the **use of vaginal progesterone to prevent PTB** in women with a **sonographically short cervix of 20 mm** without a history of a prior spontaneous PTB

EUROPEAN ASSOCIATION OF PERINATAL MEDICINE

Society for Maternal•Fetal Medicine

Di Renzo GC, et al. J Matern Fetal Neonatal Med. 2017 Sep;30(17):2011-2030
Society for Maternal-Fetal Medicine Publications Committee. *Am J Obstet Gynecol 2017.01.022*

Guideline Recommendations

- Women at high risk of preterm birth (either a **previous spontaneous preterm birth** and/or **sonographic short cervix**) with a singleton gestation should be offered **daily vaginal progesterone** or weekly 17-OHPC **treatment to prevent preterm birth**.

Consider prophylactic **vaginal progesterone** for women who have either:

- a **history of spontaneous preterm birth** (up to 34+0 weeks of pregnancy) or mid-trimester loss (from 16+0 weeks of pregnancy onwards) **or**
- results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a **cervical length of 25 mm** or less.

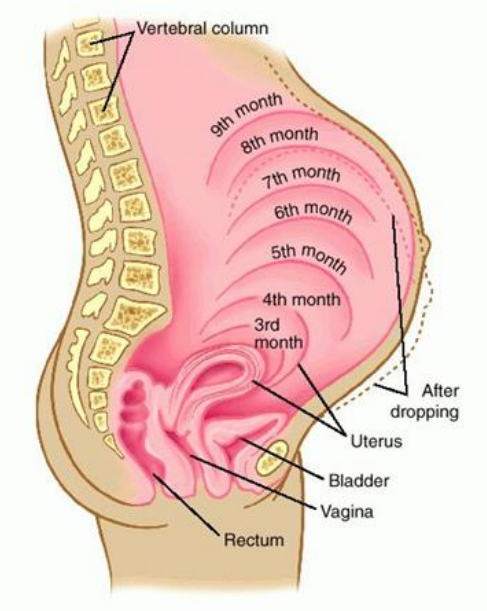
FIGO International Federation of Gynecology and Obstetrics
the Global Voice for Women's Health

NICE National Institute for Health and Care Excellence

Shennan A, Suff N, Leigh Simpson J, Jacobsson B, Mol BW, Grobman WA; the FIGO Working Group for Preterm Birth. FIGO good practice recommendations on progestogens for prevention of preterm delivery. Int J Gynecol Obstet. 2021;155:16–18. https://doi.org/10.1002/ijgo.13852
National Institute for Health and Care Excellence. Preterm labour and birth. 2015. (last updated 2-Aug-2019)Available at: https://www.nice.org.uk

Other effects of progesterone

- Effect
- on uterine
- contractility



Neuroprotection of fetal brain?

- Allopregnanolone (5α pregnane 3 α ol 20 one) = neuroactive steroid
- Modulates GABAergic inbibition
- Control balance fetal behaviour
- Protection of fetal brain from
  - hypoxia
  - ischemia

- *(Hirst JJ et al J Ster Biochem 2014)*

Why should vaginal progesterone be the treatment of choice?

- First uterine pass effect: **high local uterine concentration** with targeted action (available where it is needed) [1-3]
- Induces optimal **endometrial late secretory transformation** (in phase endometrium) [4]
- **Optimal bioavailability** with stable (versus IM or sub cut) and higher plasmatic levels at steady state compared to oral route
- Convenient and **user-friendly** (easy to administrate and provide a scope of self administration) [5]
- Supported by **clinical evidence** of high live birth rates [6]
- Avoidance of first liver and fast pass metabolism with **no side effect or irritation** at gastrointestinal tract. [7]

1. **Devroey P**, et al. *Int J Fertil* 1989; **34**: 188-193 2. **Tavaniotou A** ,et al. *Hum Reprod Update* 2000; **6**: 139-148 3. **Cicinelli E**, et al. *Obstet Gynecol* 2000; **95**: 403–406 4. **Bourgain C,** et al. *Human* Reprod 1990 **5**: 537-543 5. **Bergh C**, et al. *Hum Reprod* 2012; **27**: 3467-76 6. **van der Linden MA**, et al. *Cochrane Database Syst Rev* 2015;7:CD009154 7. **Choudhury A**, et al. *Int J Pharmtech Res* 2011; 3(2): 1033-1044

Originator/Innovator product vs copy product

	Originator/Innovator product	Copy product
Authorization	A pharmaceutical product, which was **first authorized** for marketing (normally as a patented product) with complete evaluation of clinical non-clinical data	A pharmaceutical product, usually intended to be interchangeable with the innovator product, marketed after expiry of the patent or other exclusivity rights
Authorization base	Use **clinical and non-clinical studies** of the said product to get approval	Use **innovator product** as standard comparator to get approval
Study & clinical experience	supported by **many years of evidence from RCTs and extensive clinical experience** in different regions of the world	Usually no RCT, and short clinical experience
	No bioequivalence study required, since it has been supported by clinical studies	Need bioequivalence study as copy product to ensure the quality
Market	Marketed **worldwide**	Marketed in certain country only
Shelf life	**Long shelf-life**	Newly approved copy product has shorter shelf life

Conclusion

Progesterone for Pregnancy Maintenance

- **Efficiency: YES**
- **Safety for mother: YES**
  - Side effects
  - Absence of influence on hemostasis
  - Metabolic neutrality
- **Safety for a fetus: YES**