THE 18TH VIETNAM - FRANCE - ASIA - PACIFIC CONFERENCE
ON OBSTETRICS & GYNECOLOGY

Prof. GIAN CARLO DI RENZO

Honorary Secretary of International Federation of Gynecology and Obstetrics (FIGO)
Director of Reproductive Health Center - Perugia - Italy

ROLE OF PROGESTERONE IN PREGNANCY:

in which cases it improves pregnancy outcome and how?

G C DI RENZO, MD PhD FRCOG (hon) FACOG (hon) FICOG (hon)
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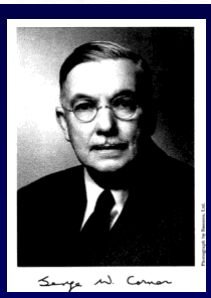
PHYSIOLOGY OF THE CORPUS LUTEUM

II. PRODUCTION OF A SPECIAL UTERINE REACTION (PROGESTATIONAL PROLIFERATION) BY EXTRACTS OF THE CORPUS LUTEUM

GEORGE W. CORNER AND WILLARD M. ALLEN

From the Department of Anatomy, University of Rochester, School of Medicine and Dentistry

Received for publication December 19, 1928



George W. Corner

Willard M. Allen

Corner GW and Allen WM Am J Physiol 1929;88:326-39.

Classic Replacement Experiment

- Extracted material from Corpus Luteum of pigs (alcoholic extract)
- Administered to pregnant rabbits which had been ovariectomized
- Result: changes in endometrium consistent with pregnancy maintenance
- Conclusion: "Corpus Luteum" has a substance capable of sustaining pregnancy…..

American Journal of Physiology 1930:326-339.

Science August 16, 1935

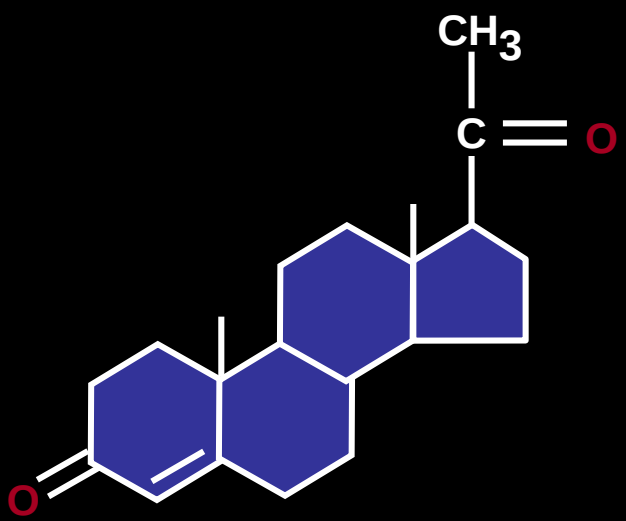
NOMENCLATURE OF CORPUS LUTEUM HORMONE

During the past year the progestational hormone has been isolated from the corpus luteum in pure form and its constitution established. Heretofore two different names have been used for this hormone in the literature (progestin, luteosterone). For the sake of international uniformity we agree to use hereafter in the scientific literature only the name *progesterone* for the pure hormone. As is known, the pure hormone exists in two different forms, one melting at 128° (uncorr.) and the other at 121° (uncorr.). The higher melting form (Compound B of Wintersteiner and Allen (1934)[2] and Compound C of Slotta, Ruschig and Fels (1934)[1]) will be known as α progesterone and the lower melting form (Compound C of Wintersteiner and Allen and Compound D of Slotta, Ruschig and Fels) as β progesterone. We hope that these names will be generally accepted in the scientific literature.

W. M. Allen
A. Butenandt
G. W. Corner
K. H. Slotta

Breslau, Germany;
Danzig-Langfuhr;
Rochester, N. Y.

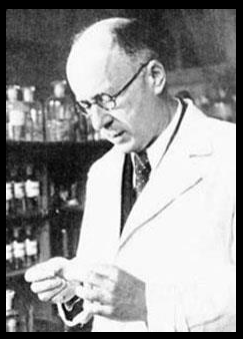
Progesterone



Isolation of Progesterone
Nobel Prize for Chemistry 1939

Adolf Butenandt

Germany
1903-1995



Leopold Ruzicka

Croatia/Switzerland
1887-1976

www.nndb.com

Progesterone

20 mgs

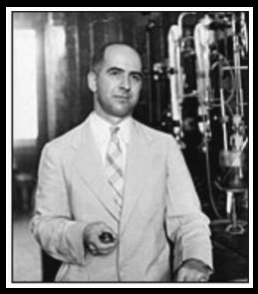
=

50,000 Pigs

www.tannadicefarms.com

Russell Marker (1940) =

Synthesis of progesterone from the plant steroid *diosgenin* from the wild Mexican yam (*Dioscorea mexicana)*



Natural micronized Progesterone Source

Plant Mexican Chinese

DIASCOREA (« Wild Yam »)

Alcaloid extraction

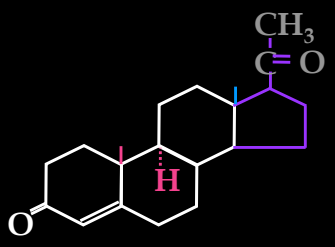
DIOGENIN

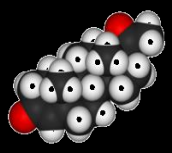
Hemi synthesis

P4

Characteristics of MP versus synthetic Progestins

- Bio-identical to progesterone of ovarian origin
- Synthesized from a naturally precursor extracted from wild yams (*Diascorea sp*)
- Optimal bioavailability is obtained by micronisation and oil suspension





- Importance of the size of the particles (10 µm)
- Importance of the nature of the oily excipients

"Natural" Progesterones

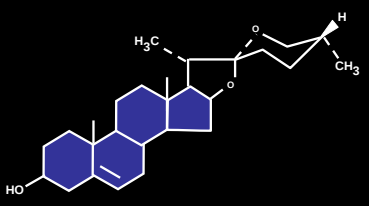
Mexican Yam

http://botit.botany.wisc.edu/images

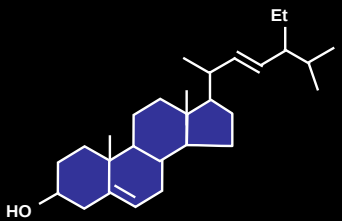
Soy Bean

http://www.organicindia.com

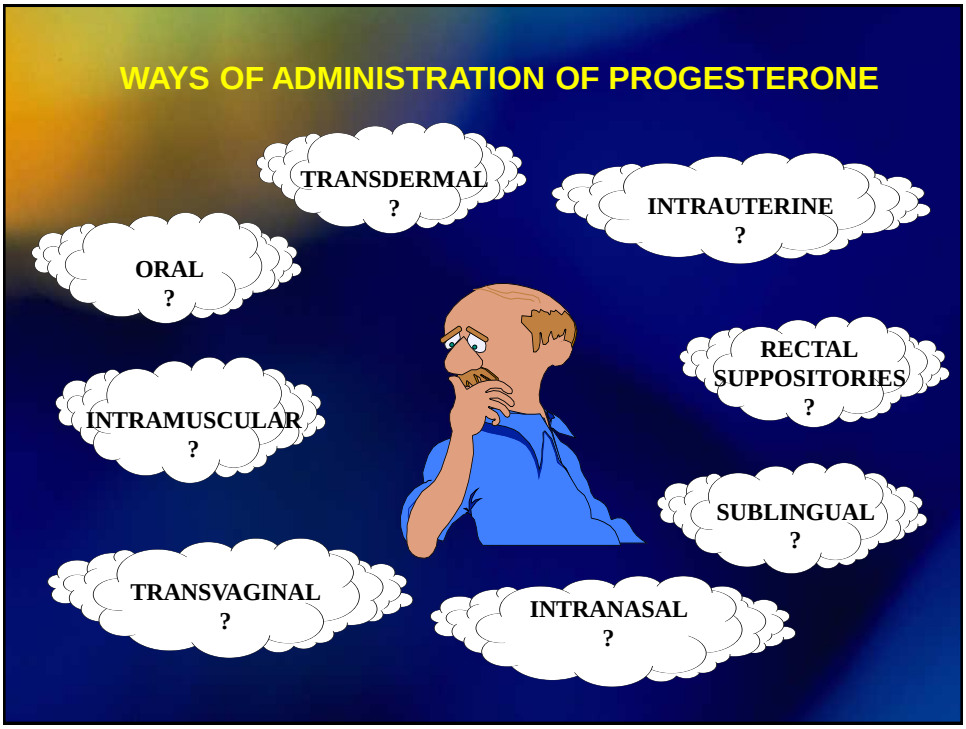
Diosgenin



Stigmasterol



WAYS OF ADMINISTRATION OF PROGESTERONE



What is the problem with natural Progesterones ?

Poorly soluble

Limited absorption in the intestine

Rapid hepatic metabolism

Solution to poor oral absorption

Non-oral administration

- Vaginal (progesterone)
- Intramuscular "Micronization" of natural progesterone

Synthetic compounds

- Medroxyprogesterone acetate (MPA)
- 17 OH progesterone caproate

Micronization of progesterone

- Add small progesterone crystals to long chain fatty acids
- Improves absorption and bioavailability due to increased surface area in contact with mucosal surfaces
- Initially used to increase plasma concentrations with oral administration
- Oral intake of capsules – concentrations not high vaginally

Metabolization of oral Natural Progesterone

Oral–administered progesterone undergoes several successive metabolisation steps:

- in the gut (bacteria with 5b-reductase activity)
- in the intestinal wall (5a-reductase activity)
- in the liver (5b-reductase, 3a-and 20a-hydroxylase activities)

↓

5a-pregnanolone and 5b-pregnanolone (GABA $_A$)
5a-pregnanedione and 5b-pregnanedione (anti-mitotic, tocolytic)

Transvaginal administration of progesterone
First Uterine Pass Effect

Women deprived of ovarian function received three different doses of vaginal gel of progesterone.

Serum gonadotropins and steroids were measured and endometrial biopsies were performed.

Transvaginal administration of progesterone induced normal secretory transformation of the endometrium despite low plasma levels, suggesting a direct transit into the uterus or “first uterine pass effect”.

Fanchin, Obstet Gynecol, 1997

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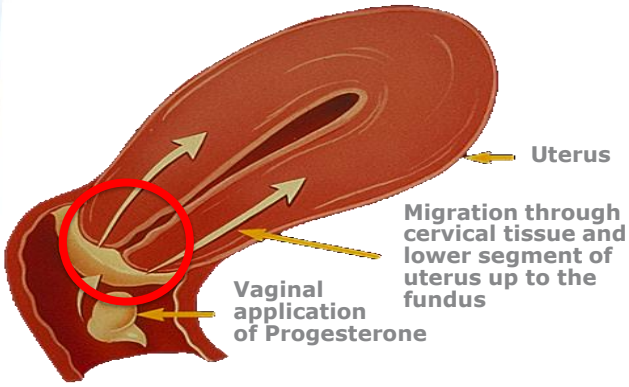
Vaginal administration (route)



First uterine pass effect / targeted delivery

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

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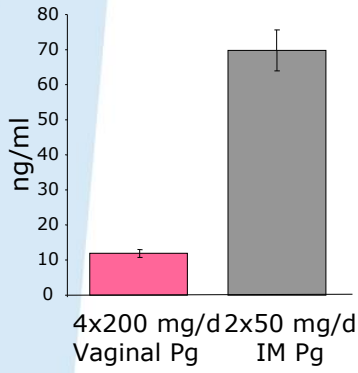
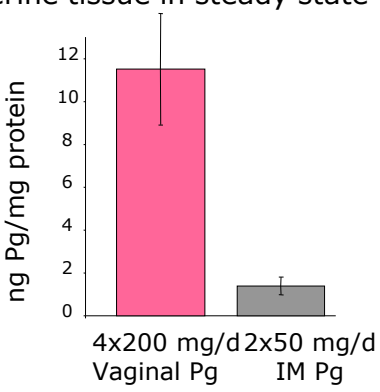
Pharmacokinetics data: **vaginal route vs IM**

Plasma progesterone concentrations in steady state



Progesterone concentrations in uterine tissue in steady state



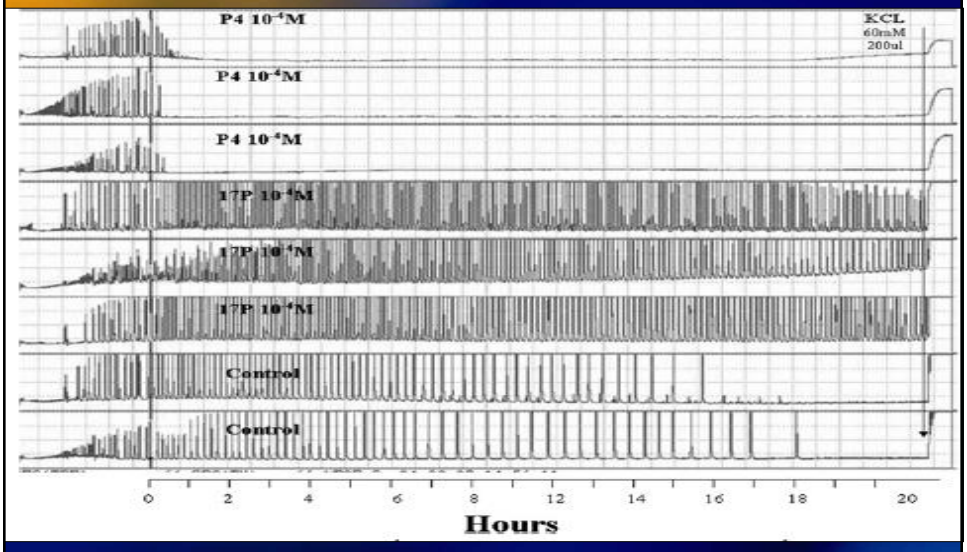
Miles A et al, *Fertil Steril 1994;* **62**: *485-9*

Metabolization of vaginal Natural Progesterone

- Normal vaginal bacteria and mucosa seem devoid of 5a-and 5b-reductases
- After vaginal, only a small increase in 5a-pregnanolone observed and 5b-pregnanolone levels were not affected

Progesterone activities on CNS can be modulated by the route of administration

Changes in contractility in control and P4-treated tissues



Ruddock NK et al *Am J Obstet & Gynecol* 2008

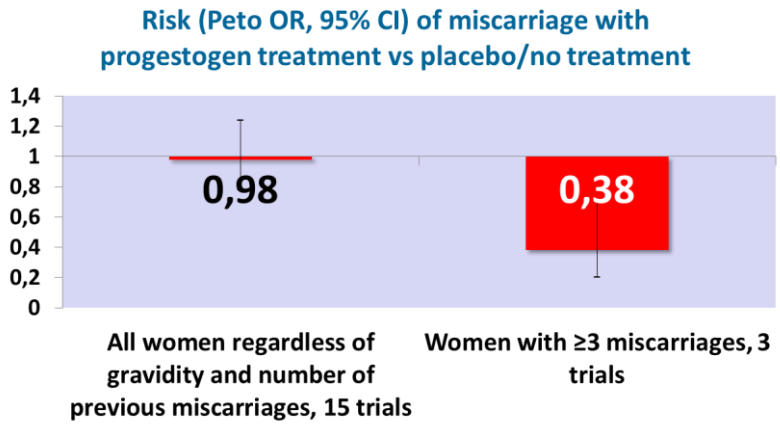
Progesterone: Maintains pregnancy

1	**Modulates maternal immune response** Druckmann R, et al. J Steroid Biochem Mol Biol. 2000 Szekeres-Bartho J, et al. Int Immunopharmacol. 2001 Di Renzo GC, et al. Gynec Endocrinol. 2012
2	**Suppresses inflammatory response** Schwartz N, et al. Am J Obstet Gynecol. 2009
3	**Reduces uterine contractility** Fanchin R, et al. Hum Reprod. 2000 Perusquía M, et al. Life Sci. 2001 Chanrachakul B, et al. Am J Obstet Gynecol. 2005
4	**Improves utero-placental circulation** Liu J,et al. Mol Hum Reprod. 2007 Czajkowski K, et al. Fertil Steril. 2007

PART 1: MANAGEMENT OF MISCARRIAGE

Progestogen reduced miscarriage rates in women with recurrent miscarriages

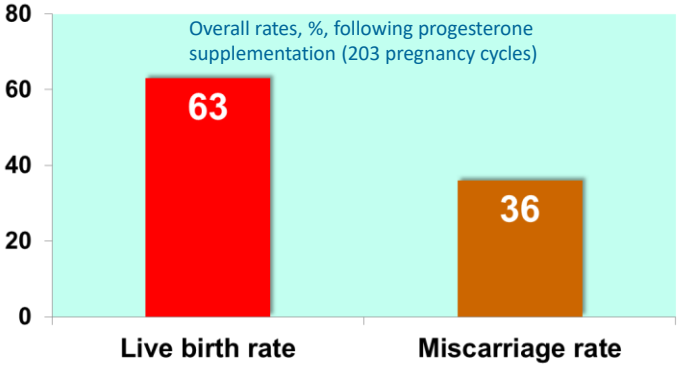
Meta-analysis of 15 trials involving 2118 women



Haas DM, Ramsey PS. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD003511.

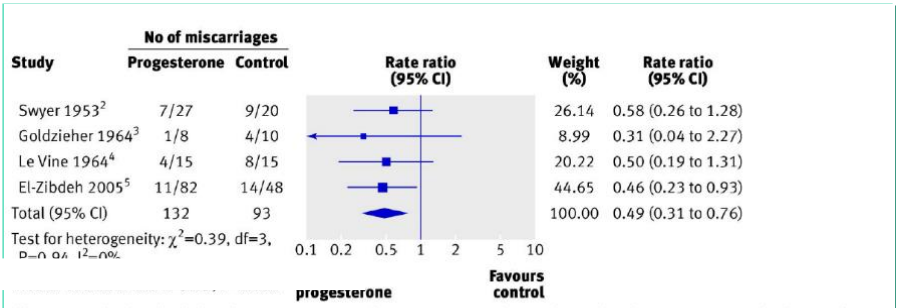
Progesterone supplementation beneficial in women with otherwise unexplained recurrent miscarriages

Women with ≥3 recurrent miscarriages and inadequate endogenous progesterone secretion treated with natural progesterone vaginal pessaries 400 mg 12-hour hourly until 12 weeks gestation



Hussain M, et al. J Hum Reprod Sci. 2012 Sep;5(3):248-51.

Meta-analysis of trials of progesterone



Meta-analysis of trials of progesterone in recurrent miscarriage for the outcome of miscarriage

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

Women with a history of ≥ 3 consecutive miscarriages

In a subgroup analysis of **four trials** involving women who had recurrent miscarriages,

✓≥ 3 consecutive miscarriages

✓4 trials

✓225 women

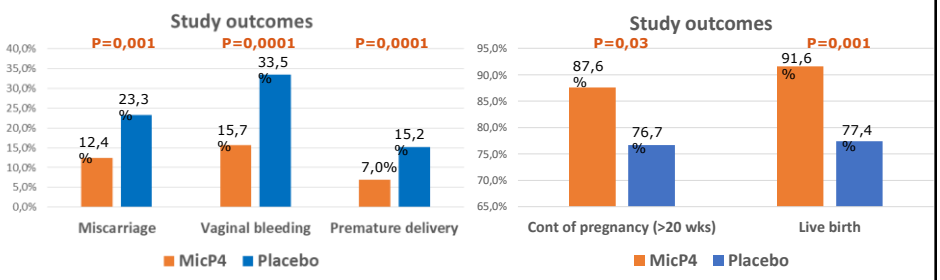
progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment

OR 0.39; 95% CI 0.21 to 0.72

Cochrane Database Syst Rev 2013

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

MicP4*: N=340
Placebo: N=335



* MicP4= vag.micronised progesterone 400 mg BID

UNIVERSITY OF BIRMINGHAM | COLLEGE OF MEDICAL AND DENTAL SCIENCES

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

Micronized progesterone use to prevent recurrence pregnancy loss

- Nuclear Ciclyn E (nCiclynE) is a cell cycle regulator, which expression changes during the menstrual cycle
- Abnormal nCiclynE expression in endometrial glands (defined as >20% after day 20 of menstrual cycle) correlates with RPL

- (Dubowy RL, Feinberg RF, Keefe DL, Doncel GF, Williams SC, McSweet JC, et al. Improved endometrial assessment using cyclin E and p27. Fertil Steril 2003;80:146–56).

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

Oral micronized progesterone and prevention of recurrent spontaneous preterm delivery:

- Still scarcity of relevant research on the use of oral progesterone (OP) to prevent spontaneous preterm delivery (SPD) because of:

- Few studies published
- Low size of the analyzed patients groups
- Variable doses of OP used in the published studies
- Variable type of oral progesterone used

The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial

(ASHOUSH S., EL-KADY O., AL-HAWWARY G. & OTHMAN A., Acta Obstet Gynecol Scand. 2017 Dec;96(12):1460-1466)

Table 3. Maternal outcomes of the current pregnancy.

	Progesterone group	Placebo group	*p*-value
Gestational age at delivery (weeks)	35.4 ± 2.7	33.9 ± 2.9	0.01
Mid-trimester miscarriages	7 (6.7)	11 (10.8)	0.46
Admission for tocolysis	12 (12.5)	23 (25.3)	0.03
Mean tocolysis-to-delivery interval (hours)	87 ± 45.5	36 ± 14.2	<0.001
PPROM	36 (37.5)	40 (43.9)	0.27
Preterm delivery	43 (44.7)	58 (63.7)	0.01
Cesarean delivery	69 (71.9)	77 (85.6)	0.05
Instrumental delivery	8 (8.3)	7 (7.6)	0.93
Chorioamnionitis	9 (9.3)	12 (13.1)	0.55
Postpartum hemorrhage	7 (7.3)	11 (12)	0.4
Postpartum sepsis	4 (4.1)	10 (10.9)	0.13

Data are given in mean ± standard deviation or *n* (%).
PPROM, preterm premature rupture of membranes.

The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial

(ASHOUSH S. , EL-KADY O., AL-HAWWARY G. & OTHMAN A., Acta Obstet Gynecol Scand. 2017 Dec;96(12):1460-1466)

Table 4. Fetal and neonatal outcomes of the current pregnancy.

	Progesterone group	Placebo group	*p*-value
Birthweight (g)	2312 ± 77	1878 ± 74	0.03
LBW (<2.5 kg)	29 (33.7)	48 (52.8)	0.003
Admission to NICU	22 (22.9)	42 (46.1)	<0.001
Duration of stay in NICU (days)	15.4 ± 5.5	19.5 ± 5.8	0.008
Neonatal mortality rate	7 (7.3)	23 (25.2)	<0.001
RDS	21 (21.8)	39 (42.8)	0.004
ICH	8 (8.3)	11 (12)	0.55
NEC	5 (5.2)	9 (9.8)	0.36

Data are given in mean ± standard deviation or *n* (%).
ICH, intracranial hemorrhage; LBW, low birthweight; NEC, necrotizing enterocolitis; NICU, neonatal intensive care units; RDS, respiratory distress syndrome.

The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial

(ASHOUSH S. , EL-KADY O., AL-HAWWARY G. & OTHMAN A., Acta Obstet Gynecol Scand. 2017 Dec;96(12):1460-1466)

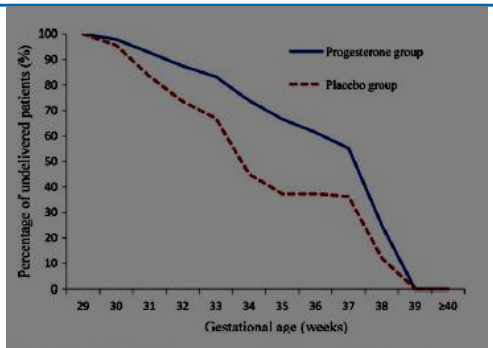


Figure 2. Cumulative percentage of undelivered patients per week, for progesterone and placebo groups. $\chi^2 = 6.09$, $p = 0.01$. [Color figure can be viewed at wileyonlinelibrary.com].

Summary

- **Up-to-date meta-analysis**
  - 10 studies (+1) ⇨ benefit
  - Most studies poor quality
- **PROMISE study**
  - No global effect
  - A possible subgroup effect in those with ≥ 4 miscarriages
- **Micronised progesterone vs dydrogesterone**
  - Evidence unclear – may require a trial
- **Luteal phase (vs first trimester)**
  - Evidence to be confirmed

PART 2: PREVENTION OF PRETERM BIRTH

PREVENTION:
IN WHICH CASES?

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Neonatal and Reproductive Medicine

Strategy in the prevention

Identification of risk factors

Prior history of preterm birth

Twin pregnancy

Short cervix at scan

Women with previous preterm birth

Main results

36 RCTs included — **8523 women**, **12515 infants**

- **Progesterone vs placebo for women with a past history of spontaneous PTB**

Perinatal mortality	6 studies	N =1453	RR 0.50	[95% CI 0.33 to 0.75)]
Preterm birth < 34 weeks	5 studies	N = 602	**RR 0.31**	[95% CI 0.14 to 0.69)]
Preterm birth < 37 weeks	10 studies	N =1750	**RR 0.55**	[95% CI 0.42 to 0.74)]
Infant birth weight < 2500 g	4 studies	N = 692	RR 0.58	[95% CI 0.42 to 0.79)]
Use of assisted ventilation	3 studies	N = 633	RR 0.40	[95% CI 0.18 to 0.90)]
Necrotizing enterocolitis	3 studies	N =1170	RR 0.30	[95% CI 0.10 to 0.89)]
Neonatal death	6 studies	N =1453	RR 0.45	[95% CI 0.27 to 0.76)]
Admission to NICU	3 studies	N = 389	RR 0.24	[95% CI 0.14 to 0.40)]
				Statistically significant reduction
	1 study	N= 148	**MD** 4.47**	[95% CI 2.15 to 6.79)].
		Statistically significant increase in pregnancy prolongation weeks		

No differential effects in terms of route of administration, time of therapy initiation and dose of progesterone for majority of outcomes examined.

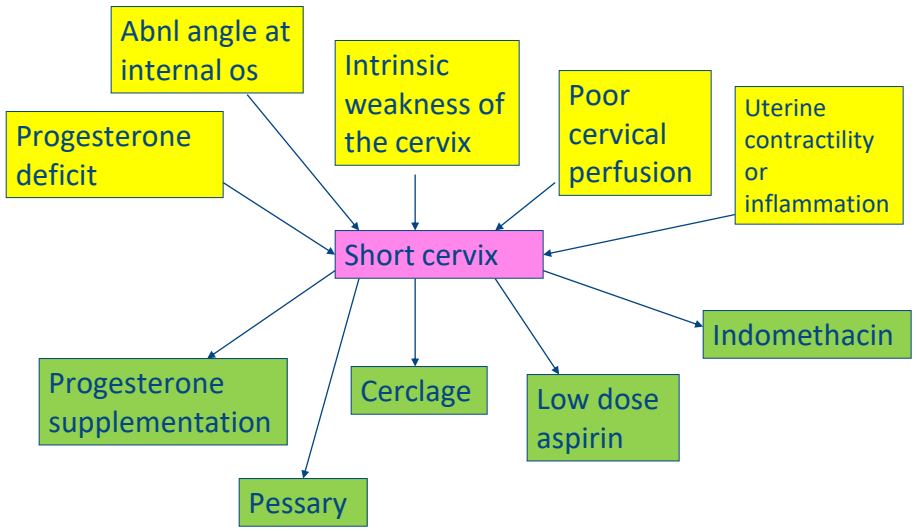
Vaginal progesterone for the prevention of recurrent preterm birth

- More effective than intramuscular progestogen therapy
- Less adverse effects

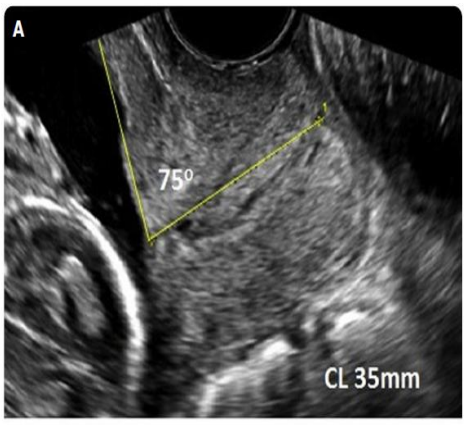
Abdelaziz A, Ellaithy M, Bazeed MF. Acta Obstet Gynecol Scand. 2013;92:215-22.

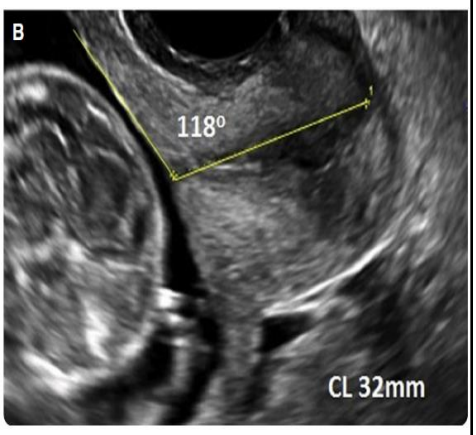
Women with a short cervix

Heterogeneity of causative processes for short cervix



UTERO-CERVICAL ANGLE





ACUTE **OBTUSE**

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Progesterone is given prophylactically to prevent preterm birth among women

- Meis et al, 2003. *N Engl J Med*
- Da Fonseca et al, 2003. *Am J Obstet Gynecol*
- Fonseca et al, 2007. *N Engl J Med*
- O'brien et al, 2007. *Ultrasound Obstet Gynecol*
- DeFranco et al, 2007. *Ultrasound Obstet Gynecol*
- Rai et al, 2009. *Int J Gynecol Obstet*
- Mahji et al, 2009. *J Obstet Gynecol*
- Cetingoz et al, 2009. *Arch Gynecol Obstet*
- Hassan et al, 2011. *Ultrasound Obstet Gynecol*
- Rode et al, 2011. *Ultrasound Obstet Gynecol*
- Maher MA et al, 2013. *Acta Obstet Gynecol Scand*
- Norman J et al, *2016. The Lancet*

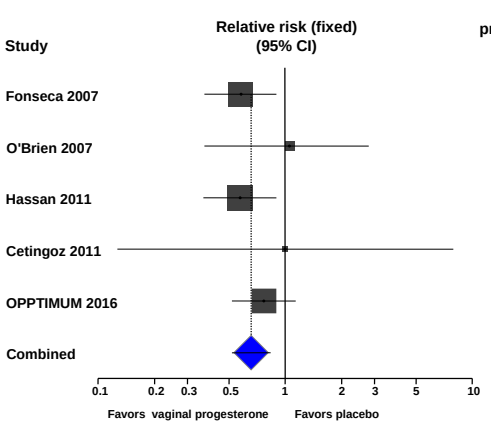
Short cervical length

Vaginal progesterone in women with an aymptomatic short cervix in the midtrimester ultrasound decrease PTD (N=775)

Outcome	No. of trials	No. of events/total no. Vaginal progesterone	Placebo	Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
Respiratory distress syndrome	5	25/411	52/416	0.48 (0.30–0.76)	0	15 (11–33)
Intraventricular hemorrhage	5	6/411	9/416	0.74 (0.27–2.05)	0	–
Neonatal death	5	8/411	15/416	0.55 (0.26–1.19)	43	–
Admission to NICU	5	85/411	121/416	0.75 (0.59–0.94)	0	14 (8–57)
Mechanical ventilation	5	35/411	51/416	0.66 (0.44–0.98)	0	24 (15–408)
Congenital anomaly	7	30/1967	34/1954	0.89 (0.55–1.44)	0	–
Any maternal adverse event	3	86/624	80/595	1.04 (0.79–1.38)	0	–

…and this reduction has been translated to improvement of morbidity and mortality in these babies

METANALYSIS: SHORT CERVIX & VAGINAL NATURAL PROGESTERONE



OBSTETRICS WORLD PREMATURITY DAY

17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm

William A. Grobman, MD, MBA; Elizabeth A. Thom, PhD; Catherine Y. Spong, MD; Jay D. Iams, MD; George R. Saade, MD; Brian M. Mercer, MD; Alan T. N. Tita, MD; Dwight J. Rouse, MD; Yoram Sorokin, MD; Ronald J. Wapner, MD; Kenneth J. Leveno, MD; Sean Blackwell, MD; M. Sean Esplin, MD; Jorge E. Tolosa, MD, MSCE; John M. Thorp Jr, MD; Steve N. Caritis, MD; J. Peter Van Dorsten, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network

CONCLUSION: Weekly IM 17-OHPc does not reduce the frequency of PTB in nulliparous women with a short cervix < 30 mm

Grobman WA et al. Am J Obstet Gynecol. 2012 Nov;207(5):390.e1-8

Women with twin pregnancy

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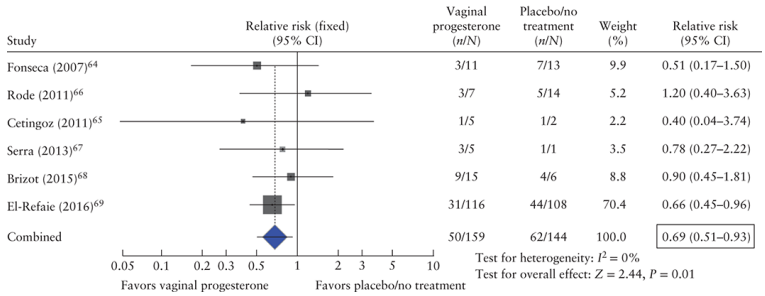
Effect of vaginal progesterone
on preterm birth in twin gestation



CONCLUSION: Administration of vaginal P4 to asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity, without any demonstrable deleterious effects on childhood neurodevelopment.

Romero R et al. *Ultrasound Obstet Gynecol 2017;* **49(3)***: 303-14*

Prevention of preterm birth

Level A evidence

Women with history of preterm delivery

Women with short cervical length on transvaginal sonography

Prophylactic use of progesterone

Incidence of preterm delivery significantly reduced

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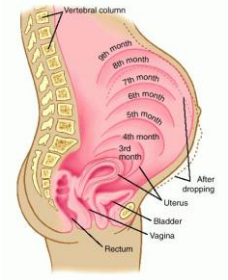
OTHER EFFECTS OF PROGESTERONE

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)

A role for progesterone in human neurodevelopment

Progesterone prophylaxis for preterm birth

- **OPPTIMUM study: significant decrease in brain injury on ultrasound scan.**

Norman (2016) Lancet

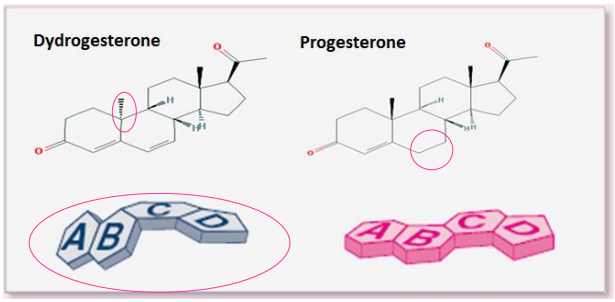
Estradiol + progesterone replacement in extremely preterm infants (outcomes at 5 years)

- **Trends toward improved bone mineral accretion.**
- **Reduced incidence of chronic lung disease.**
- **Improved neurological outcomes.**

Trotter (2012) J Clin Endocrinol Metab 97, 1041

SAFETY ISSUES

Natural progesterone vs Dydrogesterone



Dydrogesterone is a retroprogesterone, a stereoisomer of progesterone:

1. **Progesterone** is a **flat (and not truncated)** molecule
2. **Micronized Progesterone** does not bind same receptors and was **introduced for clinical use by oral route in 1980 and by vaginal route in 1992**
3. Dydrogesterone **was developed in the 1950s and introduced for clinical use in 1961.**

Vaginal progesterone is approved by the FDA in early pregnancy and broadly used in the prevention of preterm deliveries

FDA approved vaginal progesterone for LPS in first trimester of pregnancy

No difference in side effects in group of patients with vaginal progesterone or placebo

No any signal in pregnant patients with short cervix who used progesterone for prevention of PTB (FDA report)

* Roberto Romero et al. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Published Online: May 02, 2013

Safety of vaginal P4 (1)

PLOS ONE

RESEARCH ARTICLE

STOPPIT Baby Follow-Up Study: The Effect of Prophylactic Progesterone in Twin Pregnancy on Childhood Outcome

Helen Christine McNamara[1]*, Rachael Wood[2], James Chalmers[2], Neil Marlow[3], John Norrie[4], Graeme MacLennan[4], Gladys McPherson[4], Charles Boachie[5], Jane Elizabeth Norman[6]

Conclusions

In this cohort of twin children there was no evidence of a detrimental or beneficial impact on health and developmental outcomes at three to six years of age due to in utero exposure to vaginal micronized progesterone.

McNamara HC et al. *PLOS ONE 2015..*

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

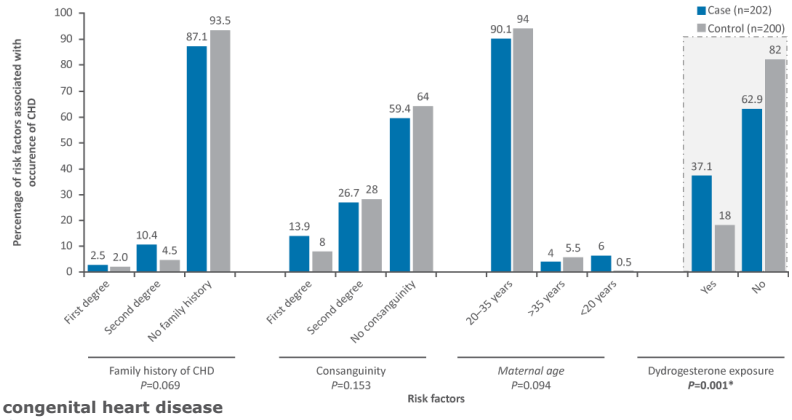
Mahmoud Zaqout, Emad Aslem, Mazen Abuqamar, Osama Abughazza, Joseph Panzer, Daniel De Wolf

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].**

Impact of oral Dydrogesterone during early pregnancy

Significantly more mothers with CHD-affected children were exposed to dydrogesterone during the first trimester of pregnancy compared with controls (37% vs 18% respectively; P= 0.001)

Frequency and univariate analysis of risk factors associated with CHD



CHD, congenital heart disease

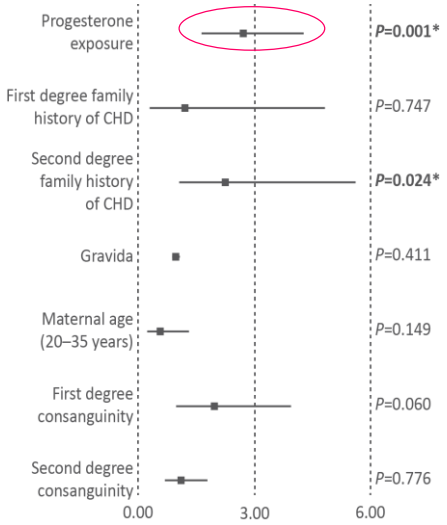
Adapted from Zagout M, *et al. Pediatr Cardiol* 2015

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*)



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I.M. 17 OH-P4 CAPROATE

- **FDA approval** in women with a history of spontaneous singleton preterm birth
- No proven action on uterine contractility
- Injection site pain reported in > 30% of patients
- **Very expensive** weekly injection to be done by healthcare provider
- **Increased risk (x 3) for Gestational Diabetes *(Rebarber 2007, Nelson 2017)***
- Site injection reactions*
  - ✓pain
  - ✓swelling
  - ✓nodule
- ✓Influence of endogenous P4 levels on 17 OHP4 metabolism**

Conclusions

Key role of vaginal P4 in immunology of pregnancy

- Unexplained spontaneous abortion might be attributable to **deleterious immune response** of the mother toward the fetus
- Vaginal Progesterone (P4) might play a **significant role** in establishing an adequate immune environment during the early stages of pregnancy
- There seems to be evidence of **benefit** in women with a history of Recurrent Miscarriage
- **Well-designed randomized studies** are needed to establish the usefulness of any progesterone supplementation in the treatment of RM
- **Safety issues** should be a concern and pharmacodynamics are important in the administration of progestogens

Key role of vaginal P4 in maintainance of pregnancy

- 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.
- Women with **prior history of PTB** or late second trimester abortion should be offered 17 OHP-C weekly injection starting early in the 2nd trimester or vaginal progesterone based on individual benefits/risks evaluation with the patient (increased GDM risk)
- 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


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