Updated evidence-based medicine of luteal support Dydrogesterone in assisted reproduction

Prof. Ph.D. Le Hoang

Vice Director of National Obstetrics and Gynecology Hospital,

National Center for Assisted Reproduction.

Current infertility rate

- **World:**
  - ✓ *Fast increase in two current decades (average of 6 – 12%)*
  - ✓ *Difficult conception takes one-fourth of couples wanting a baby*
- **Vietnam:**
  - ✓ *Infertility rate per childbearing age couple of 7.7% (700,000 to 1 million infertile couples)*
  - ✓ *Primary infertility: 3.9%*
  - ✓ *Secondary infertility: 3.8%*
  - ✓ *50% of infertile couples under the age of 30*

Nationwide study by the National Obstetrics and Gynecology Hospital and Hanoi Medical University

Success rate when applying IVF/ ICSI technique

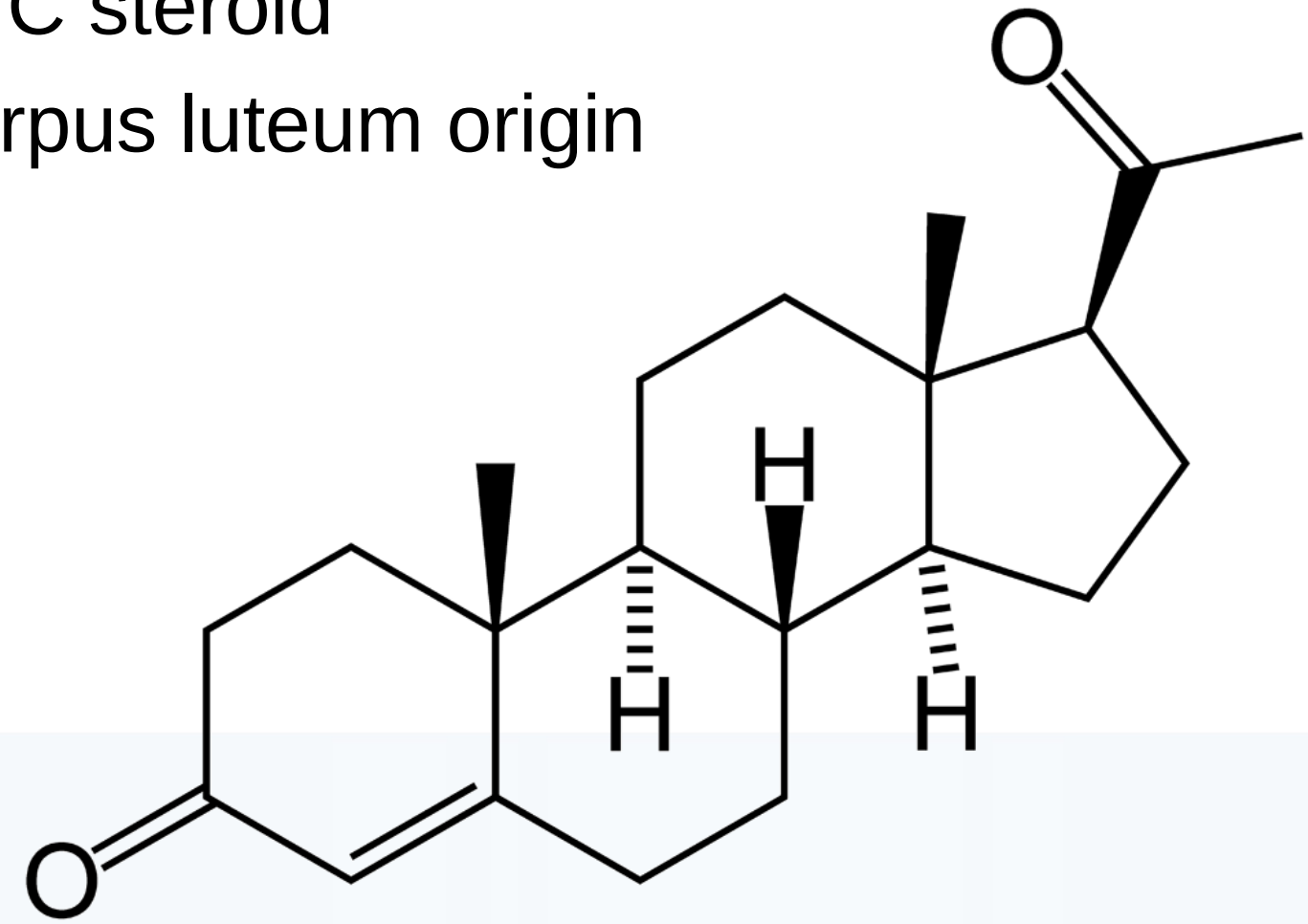
- **24,7%** success rate on clinical pregnancies of all women who undergo IVF treatment.
- **50%** of all embryos cultured *in vitro* reached blastocyst stage by day 6.
- Around **15%** of embryo transfer (ET) develop into fetus

HFEA 2011

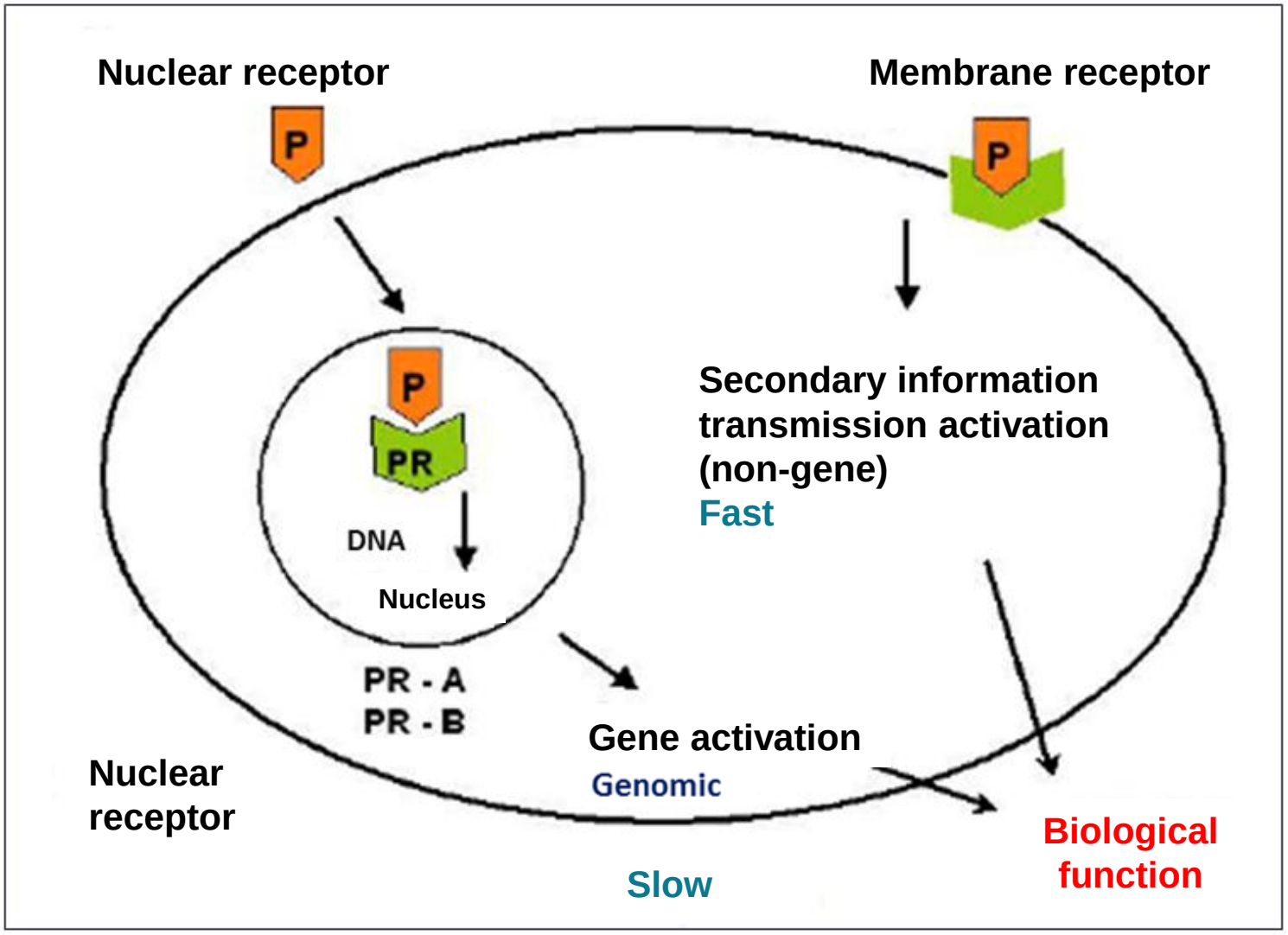
MECHANISM OF PROGESTERONE IN ASSISTED REPRODUCTION

Progesterone = Pro-ges-(s)ter-one
Steroid of pregnancy

- 21 C steroid
- Corpus luteum origin



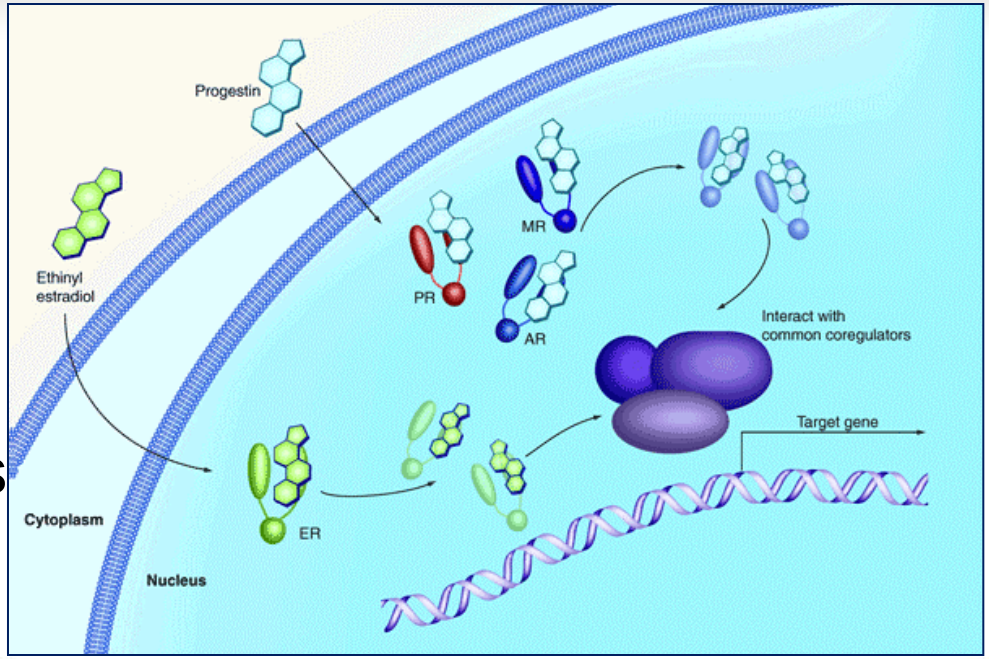
Gene effect
Non-gene effect

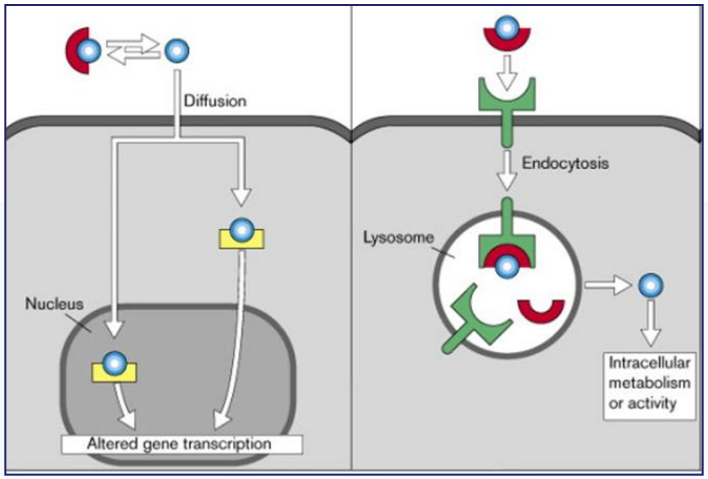


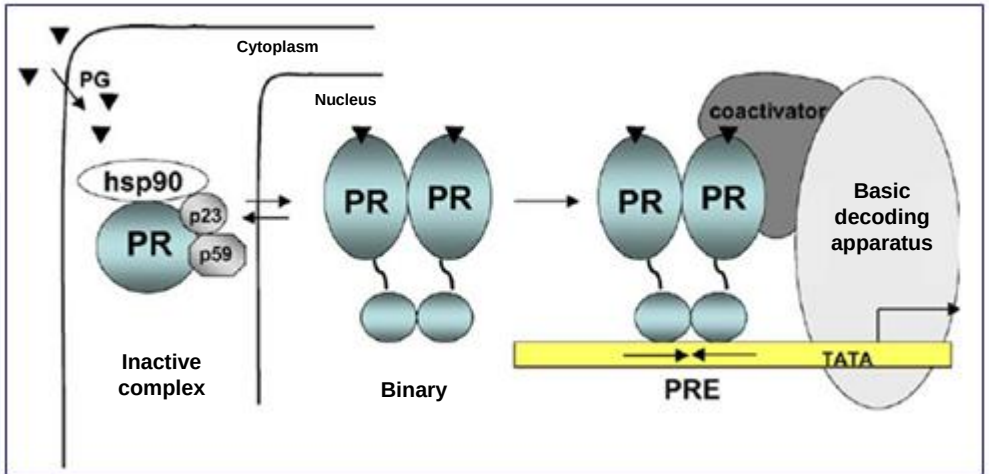
Genomic effect:

gene is activated by PR-A, PR-B hormone complex and Co-activator

- Through membrane
  - Active
  - Diffusive
- At cell nucleus
  - PR-A, PR-B receptors
  - Co-activator

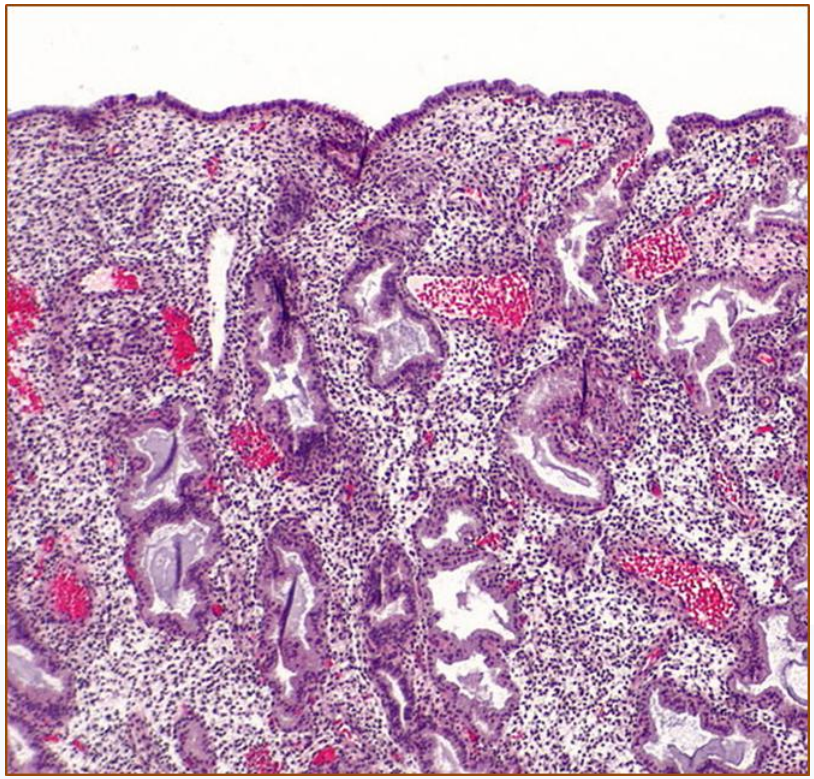




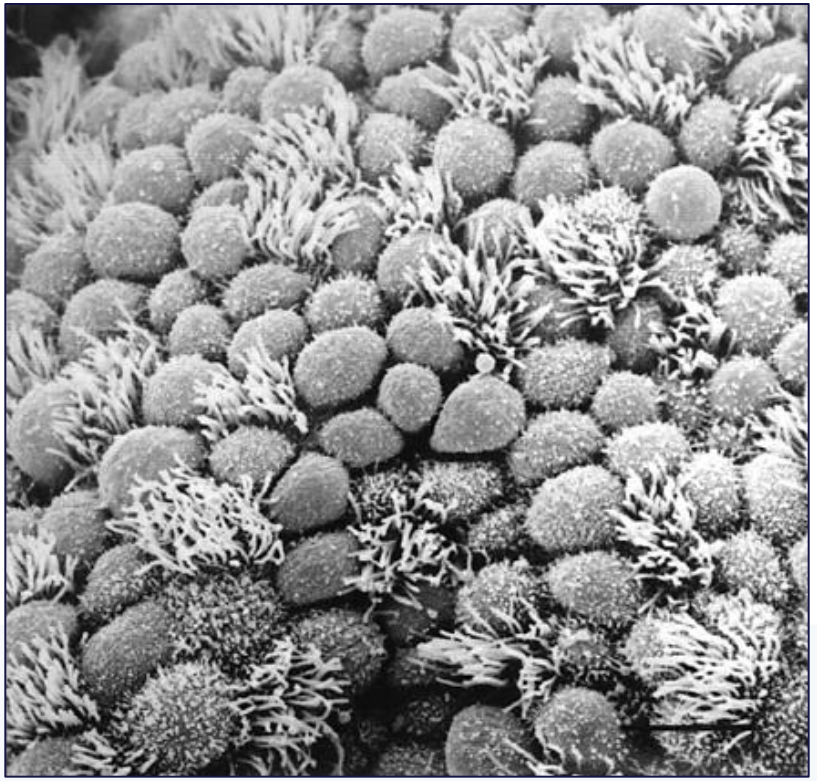


Genomic effect prepares for implantation process Endometrial secretion and appearance of pinopodes

- Result of genomic effect is gene regulation
- Gene expression by protein biosynthesis



Endometrial secretion

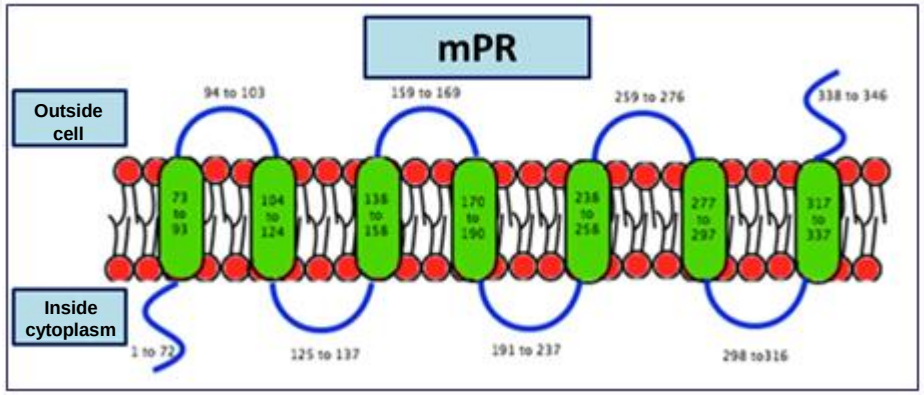


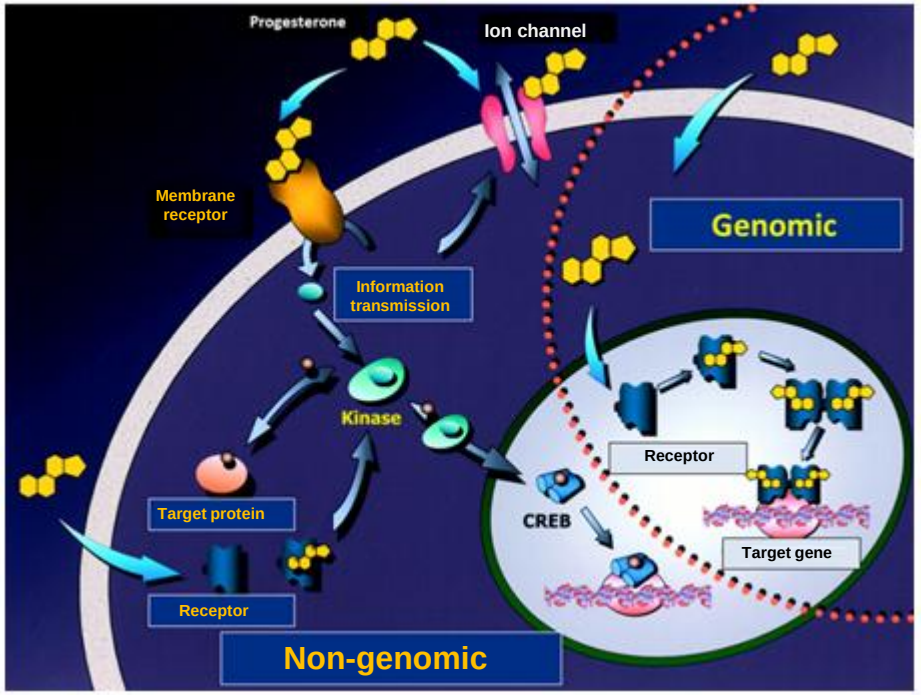
Implantation window opening

None-gene effect

Unspecific membrane receptor

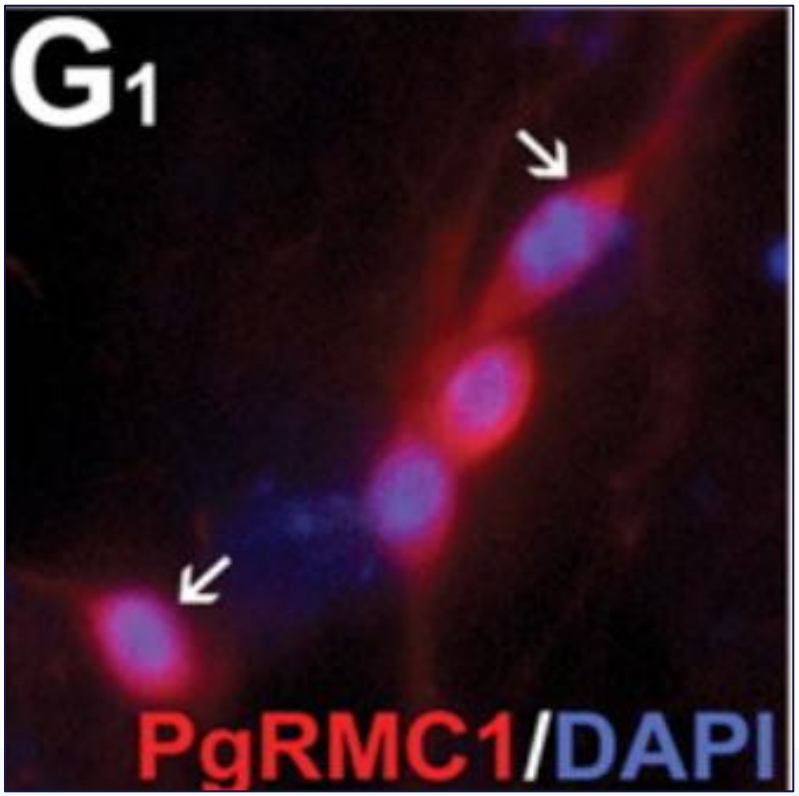
- Effect through
  - mPR membrane receptor
  - Ion channel
  - Cytoplasmic receptor
- Cascade activation
  - Diverse response
  - Change by
    - Target organ type
    - mPR type: α or β





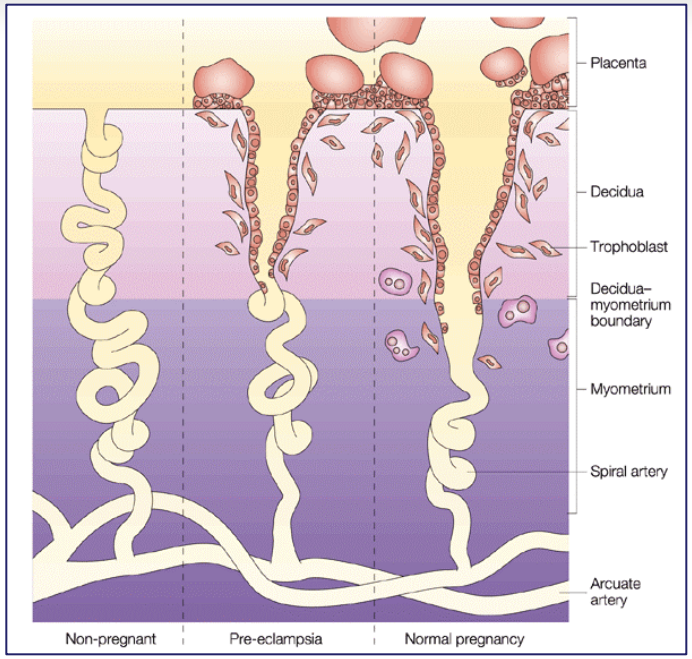
Non-genomic effect inhibits hypothalamus and lyses corpus luteum

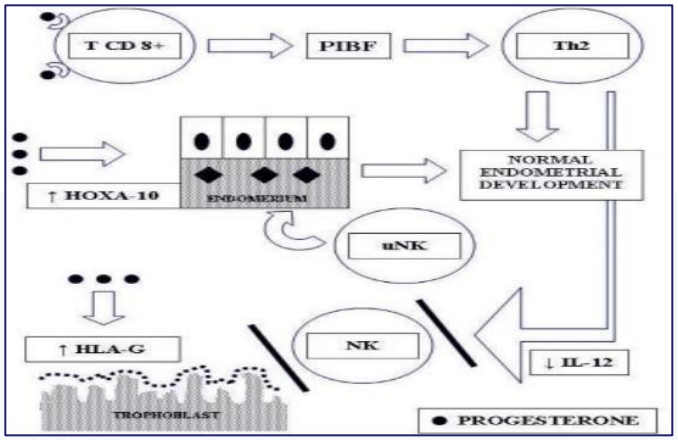
- Anti-hypothalamus effect
  - GnRH impulse frequency reduction
  - Pituitary LH reduction
  - Corpus luteum physiologically lysis

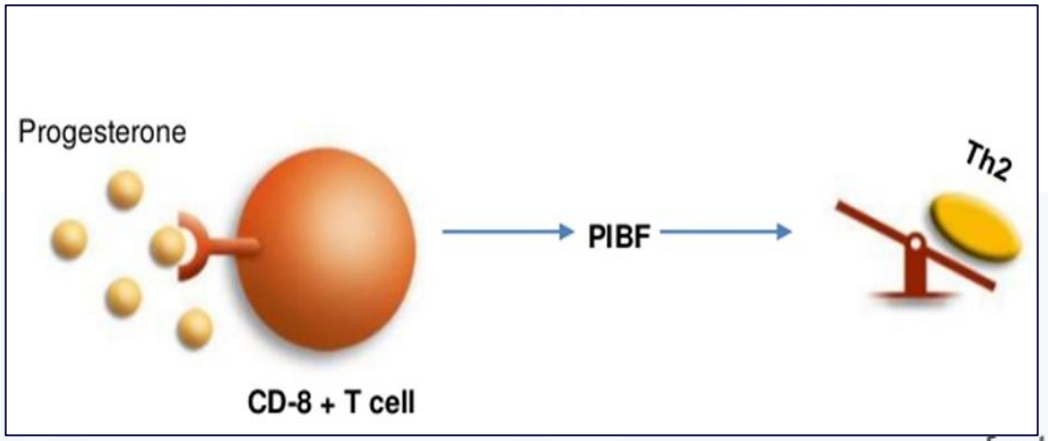


Non-genomic effect on CD8+ T cell, through Progesterone Induced Blocking Factor (PIBF) to Th2

- On CD8+ T cell
  - Through PIBF
  - Causing bias toward Th2
  - Tolerating semi-heterograft
- Inhibiting Natural Killer cell
  - Reducing NKc forming differentiation
  - NKc activity is inhibited

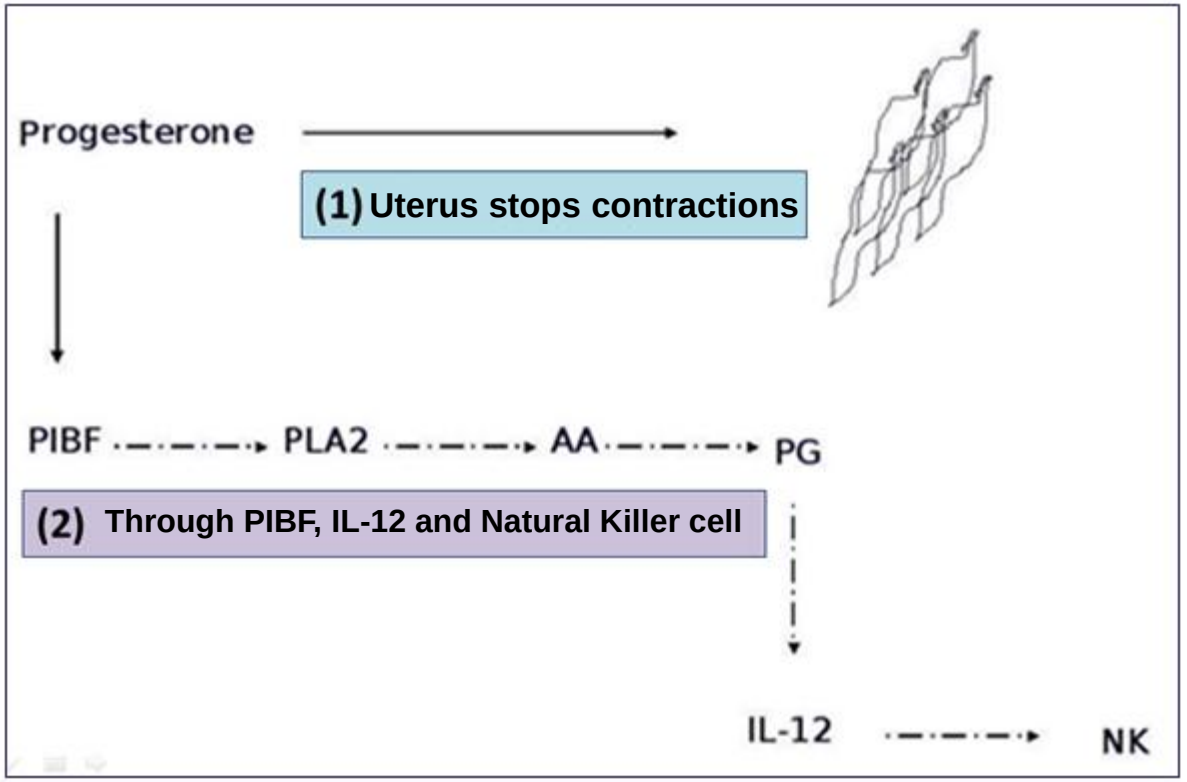






Maintaining pregnancy during late stage of pregnancy
Non-genomic effect plays an important role

- Dual mechanism, both non-genomic
  - Relaxing uterine muscle
  - Inhibiting Th1



Progesterone affects outcomes through both genomic and non-genomic effects

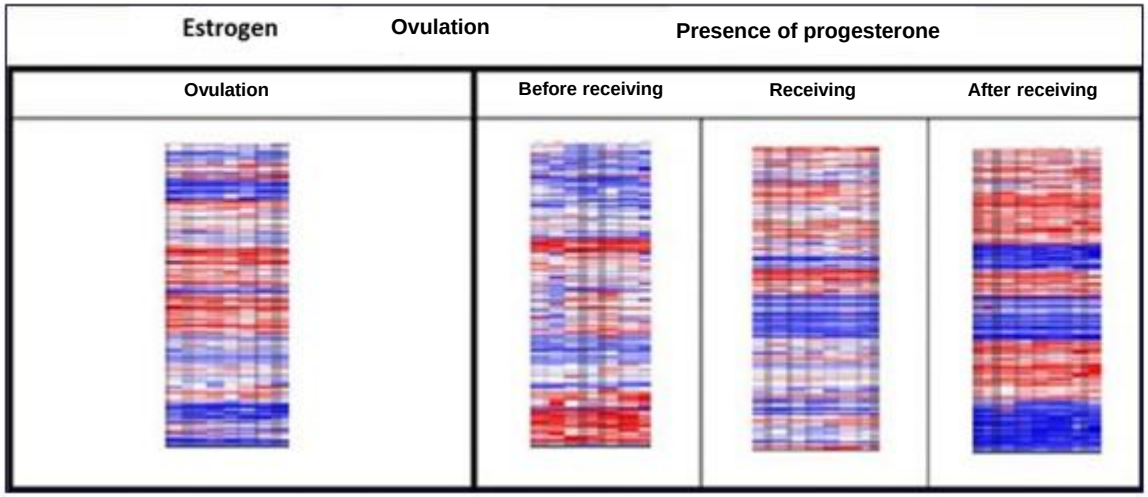
- On gene regulation
  - Opening and closing implantation window at suitable time
- On semi-heterograft tolerance
  - Stimulating PIBF, facilitating Th2 response
- On trophoblast penetration
  - Through PIBF, facilitating T2 response, helping pseudo-vascularization reaction to occur completely
- On pregnancy
  - Through PIBF, prevention of premature delivery in population at high risk of premature delivery

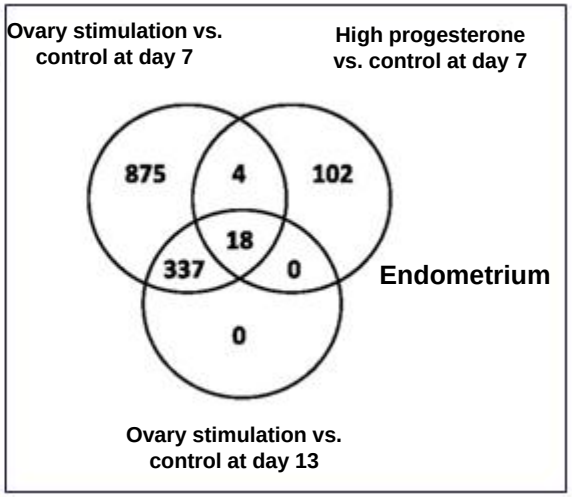
IVF is a process that produces endocrine and "non-physiological" environmental conditions

- Derived from
  - Increase of number of follicles and increase of number of corpus luteum
    - Estrogen-progesterone imbalance
  - Retrieval
    - Loss of granular cells
  - Extrinsic hormones in many different stages
    - Ovary stimulation
    - Implantation
    - Pregnancy
- Causing serious changes
  - Gene expression

"Non-physiological" environment causes abnormalities in gene expression

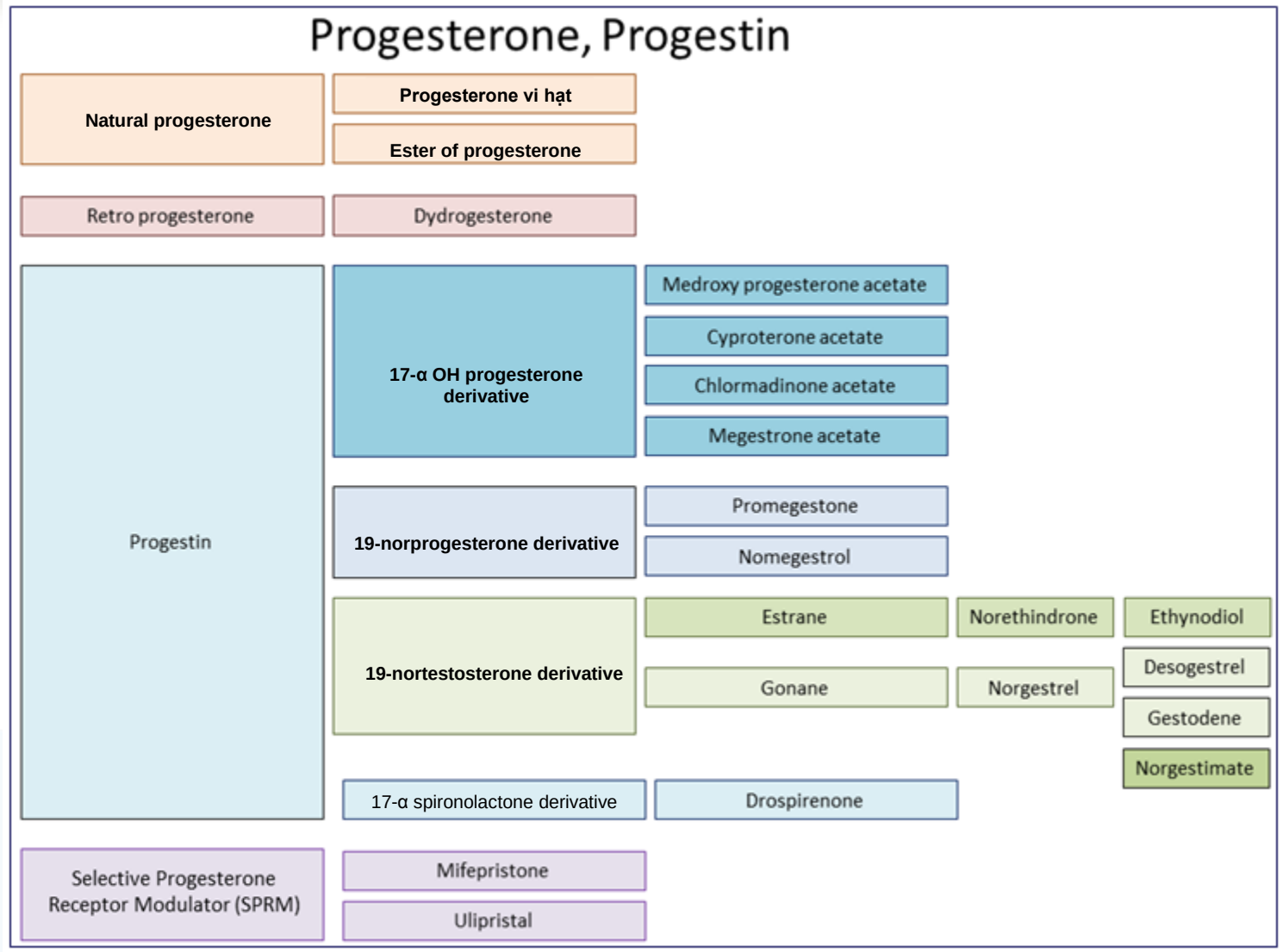
- Genes are abnormally regulated due to:
- Abnormal estrogen-progesterone correlation
  - Duration of exposure to hormones
  - Time of exposure to hormones
  - Level of exposure to hormones





Progesterone is needed

Which progesterone?

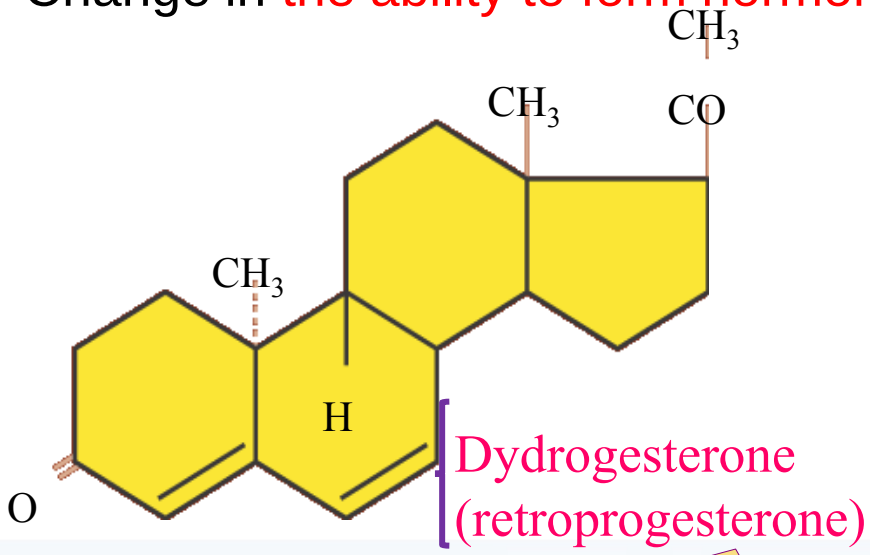


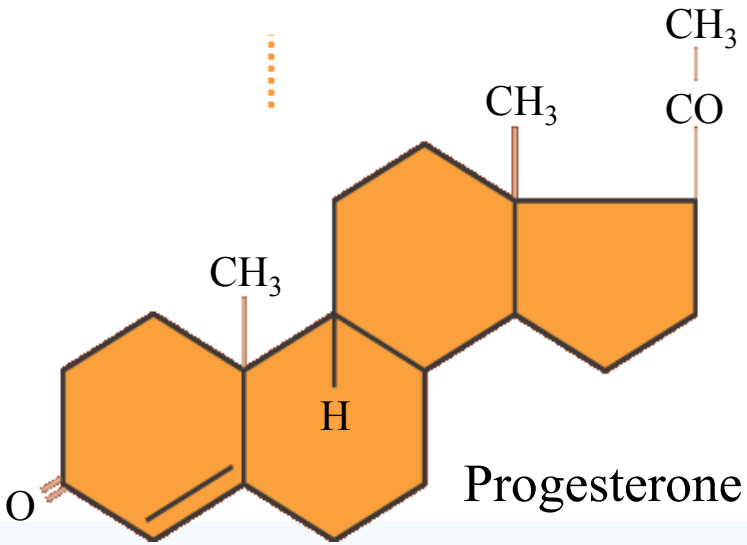
CHEMICAL STRUCTURE OF

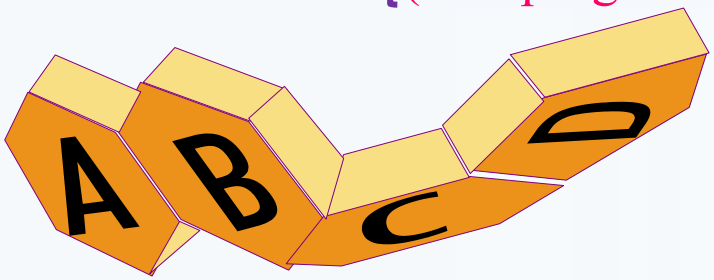
Dydrogesterone and Progesterone

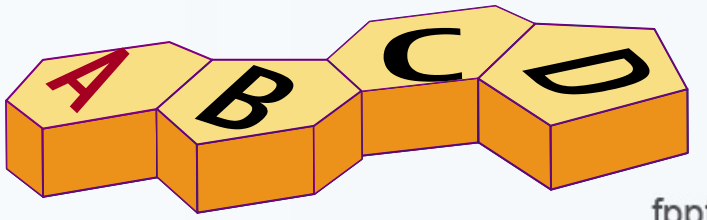
Micronized progesterone vs. Retro-progesterone: Changes of spatial structure due to the addition of a double bond

- Change of spatial structure due to the addition of a double bond in B ring
- Change in the ability to form hormone-receptor-co-activator complex









Origin of Dydrogesterone

Diosgenin from Yams or Soy

Progesterone

Dydrogesterone

UV-irradiation

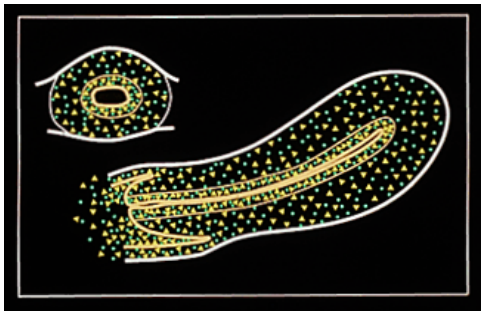
Oral progesterone

- Having biological effect only in fine form
- Unstable serum concentration
- Fast metabolism
- First pass of large steroid load
- Overload of non-progestogenic metabolite

Dydrogesterone:

- having oral bioavailability
- small steroid load
- progestogenic metabolite

Micronized progesterone and Dydrogesterone Pharmacokinetics



- **Micronized progesterone**
  - Vaginal and oral routes
    - Vaginal route appears to be better
  - Direct effect
    - Giving local non-genomic effect
- **Dydrogesterone**
  - Oral availability
  - Effect via systemic route
    - No difference in genomic effects
    - Having a difference in systemic non-genomic effects

Both genomic and non-genomic effects are affected by structural changes

- Affinity
- Gene regulation
- Non-genomic cascades

	Progesto-genic	Anti-hypothala mus-pituitary	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgen	Gluco-corticoid	Anti-mineralo-corticoid
Progesterone	+	+	+	-	-		+	+
Dydrogesterone	+	-	+	-	-		-	+

Comparison of biological effects between 2 types of progesterone

Table 2
Biological activities of natural progesterone and synthetic progestins

Progestin	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Gluco-corticoid	Anti-mineralo-corticoid
Progesterone	+	+	+	–	–	±	+	+
Dydrogesterone	+	–	+	–	–	±	–	±

Maturitas 46S1 (2003) S7-S16

Comparison of concentration of Progestin types

Progestin	Dose for ovulation inhibition (mg/day P.O)	Conversion dose (mg/cycle)	Conversion dose (mg/day P.O)
Progesterone	300	4200	200 - 300
Dyprogesterone	>30	140	10 – 20

Progestogenic effectivity on the level of the endometrium and antigonadotropic effects (dose for ovulation inhibition) of the different progestins

Maturitas 46S1 (2003) S7-S16

Application areas of progesterone
Each progesterone has its own predominant areas

- Progesterone supplementation during luteal phase outside assisted reproduction
  - In the context of less change in gene regulation
- Progesterone supplementation during luteal phase of assisted reproduction
  - In the context of dramatic changes in gene regulation
  - In the context of dramatic changes in corpus luteum function
- Progesterone in miscarriage caused by corpus luteum failure and consecutive miscarriage
  - In the context of Th1-Th2 imbalance

Current options in assisted reproduction

- **Dydrogesterone**, oral tablet: 10 mg (1 tablet x 2-3 times/day)*
- **Vaginal micronized PRG:**
- **Progendo** (200 mg)
- Utrogestant (100 mg, 200 mg)
- Cyclogest (200 mg, 400 mg, can rectal administration)
- **Intramuscular PRG:** 25 mg
- **17 Beta Estradiol (Valiera),** Estradiol Valerate (Progynova)
- **hCG:** 1000 IU, 1500 IU, 2000 IU, 5000 IU
- **GnRHa:** triptoreline 0.1 mg

(*) not yet indicated in IVF

Pregnancy rate between oral Dyprogesterone and vaginal micronized progesterone

Cochrane Library

Cochrane Review 2015

3 Vaginal/rectal vs oral					
Chakravarty 2005 (17)	109/351	25/79		10.5 %	0.97 [0.58, 1.65]
Friedler 1999 (18)	16/32	10/32		1.9 %	2.20 [0.79, 6.10]
Ganesh 2011 (19)	242/941	121/422		46.1 %	0.86 [0.67, 1.11]
Patki 2007 (20)	70/247	122/308		28.9 %	0.60 [0.42, 0.86]
Pouly 1996 (21)	40/139	36/144		9.4 %	1.21 [0.72, 2.05]
Salehpour 2013 (22)	13/40	10/40		2.5 %	1.44 [0.55, 3.83]
Saucedo 2000 (23)	7/20	3/20		0.7 %	3.05 [0.66, 14.14]
Subtotal (95% CI)	**1770**	**1045**		**100.0 %**	**0.89 [0.75, 1.05]**

Total events: 497 (Treatment A), 327 (Treatment B)

Heterogeneity: $Chi^2 = 12.47$, $df = 6$ ($P = 0.05$); $I^2 = 52\%$

Test for overall effect: $Z = 1.36$ ($P = 0.17$)

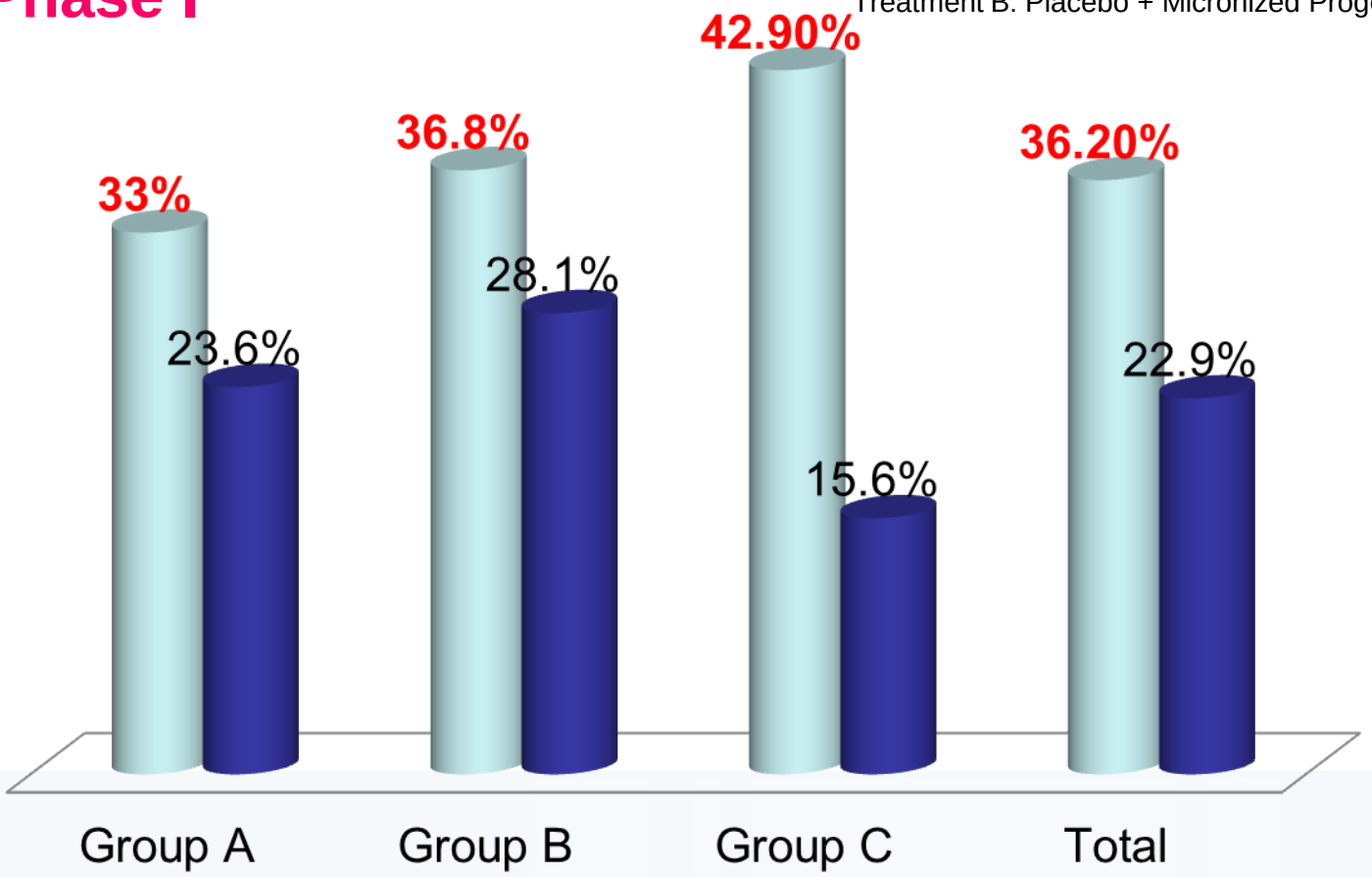
Dyprogesterone + Microproges – oral

Micronized progesterone - vaginal

Pregnancy rate between two routes of administration

Phase I

Treatment A: Oral Dyprogesterone + Micronized Progesterone (vaginal)
Treatment B: Placebo + Micronized Progesterone (vaginal)



P<.001

- Treatment A (n=218)
- Treatment B (n= 280)

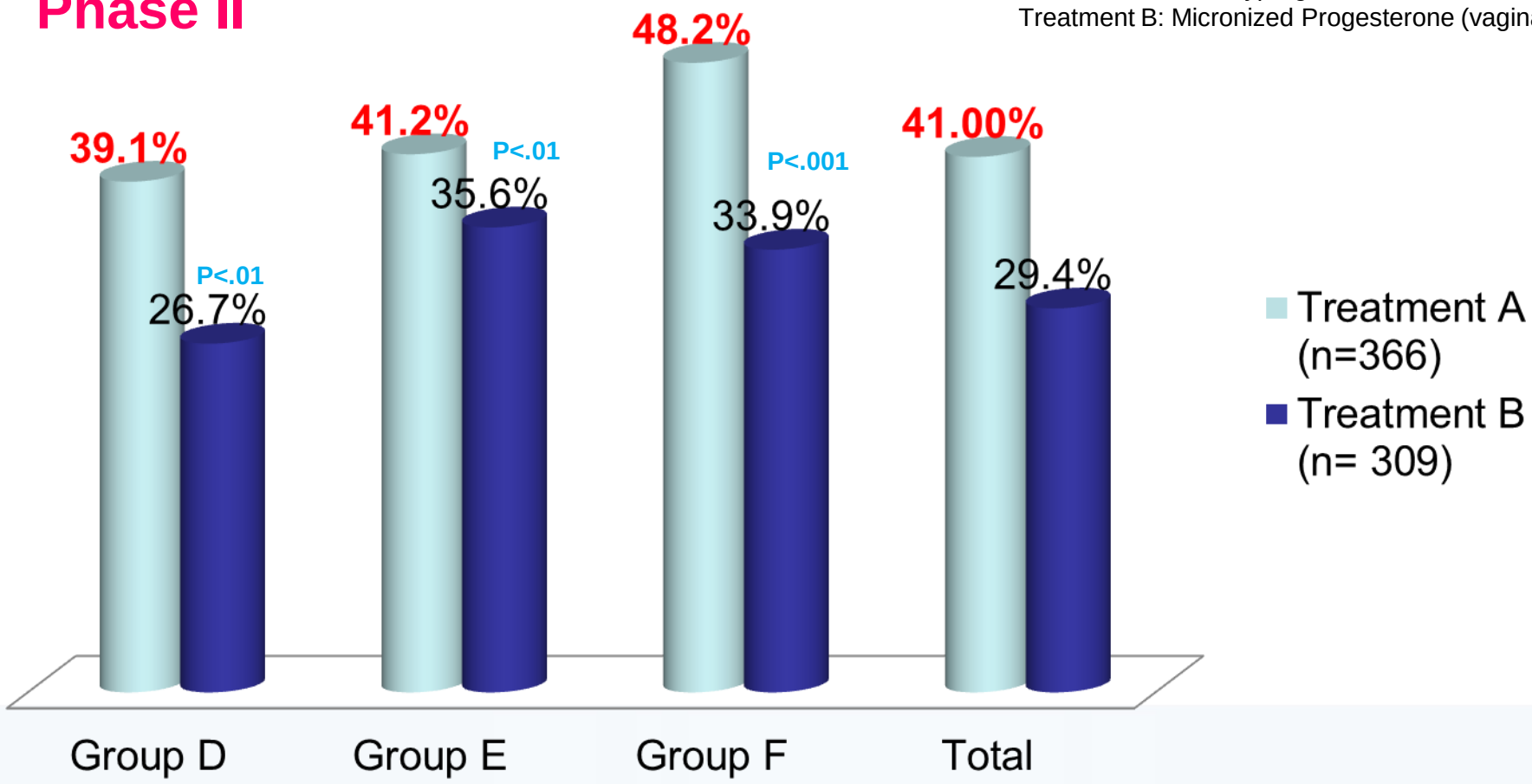
Group A: long protocol, no risk OHSS
Group B: long protocol, risk of OHSS
Group C: donor oocyte program

Gynecological Endocrinology, October 2007; 23(S1): 68–72

Pregnancy rate between two routes of administration

Phase II

Treatment A: Oral Dyprogesterone
Treatment B: Micronized Progesterone (vaginal)



Group D: long protocol, no risk OHSS
Group E: long protocol, risk of OHSS
Group F: donor oocyte program

Gynecological Endocrinology, October 2007; 23(S1): 68–72

Dydrogesterone versus progesterone for luteal-phase support: systematic review and meta-analysis of randomized controlled trials

W. Martins, M.W. Barbosa, L.R. Silva, P.A. Navarro, R. Ferriani and C.O. Nastri

Fertility and Sterility, 2015-09-01, Volume 104, Issue 3, Pages e345-e346, Copyright © 2015

Study methods

The authors searched the following electronic databases from inception for relevant RCTs: Cochrane CENTRAL, PubMed, Scopus, Web of Science, Clinicaltrials.gov, ISRCTN Registry and WHO ICTRP. Additionally, they hand-searched the reference lists of included studies and related reviews.

Inclusion criteria

- Randomized placebo-controlled studies comparing oral dydrogesterone with progesterone types (oral, intramuscular, vaginal tablet and gel forms) for luteal phase support in women undergoing assisted reproduction (monitored fresh or frozen embryo transfer following IVF/ICSI.

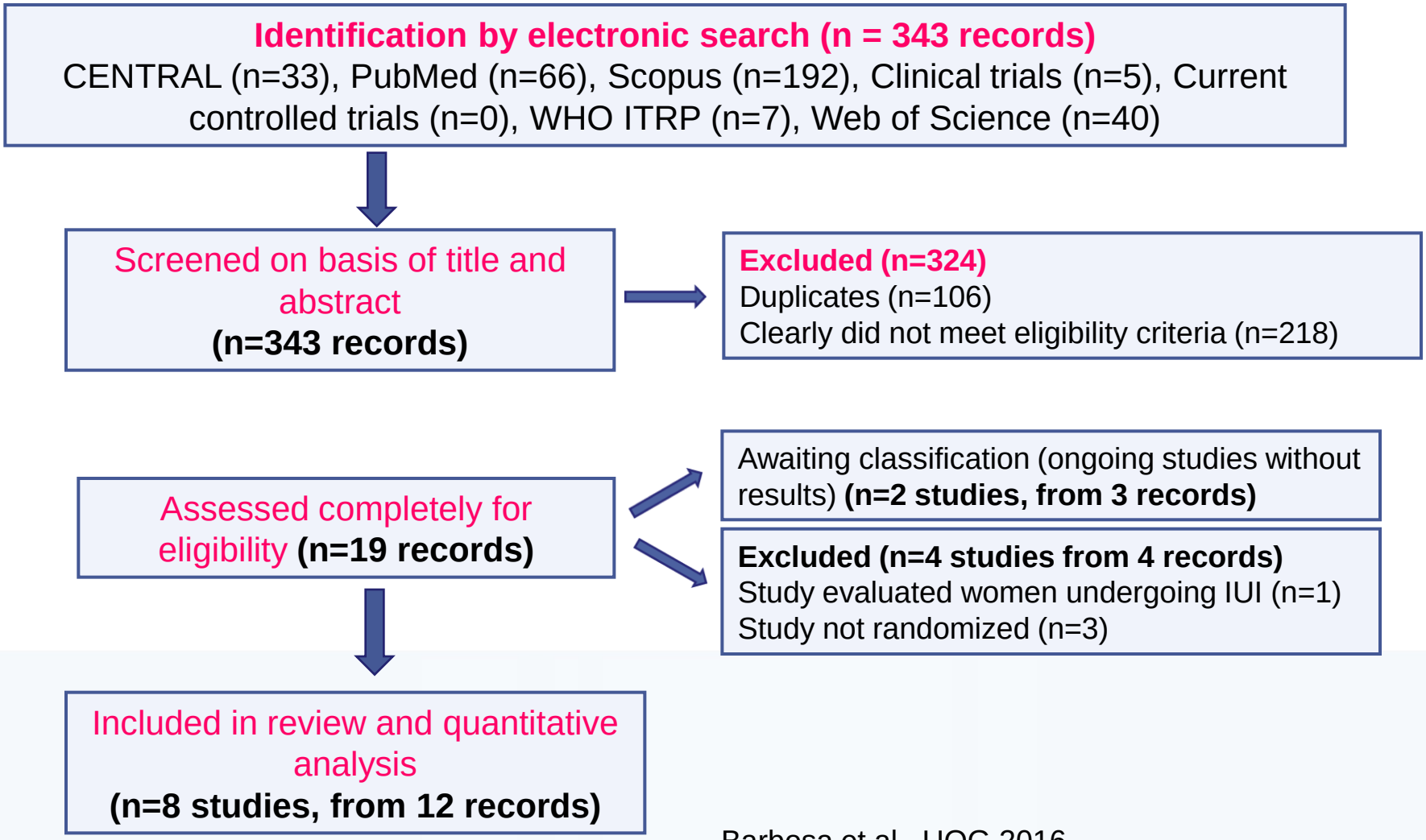
Exclusion criteria

- Quasi index-based or pseudo-randomized studies were discarded as those evaluating Dydrogesterone in assisted reproduction by IUI method.

Results:

- **Main efficacy result:** live birth
- **Main adverse event result:** patient's dissatisfaction with treatment
- **Secondary result:** ongoing pregnancy
- **Other results:** clinical pregnancy, miscarriage rate per pregnancy (1 stillbirth in twin or triplet pregnancy is not considered as miscarriage) and other side effects reports.

Study results

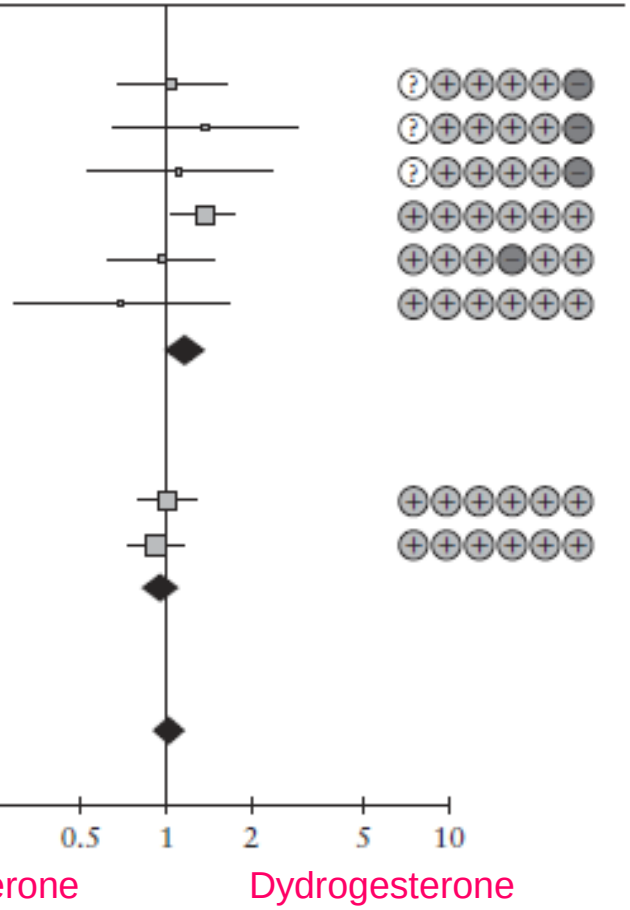


Barbosa et al., UOG 2016

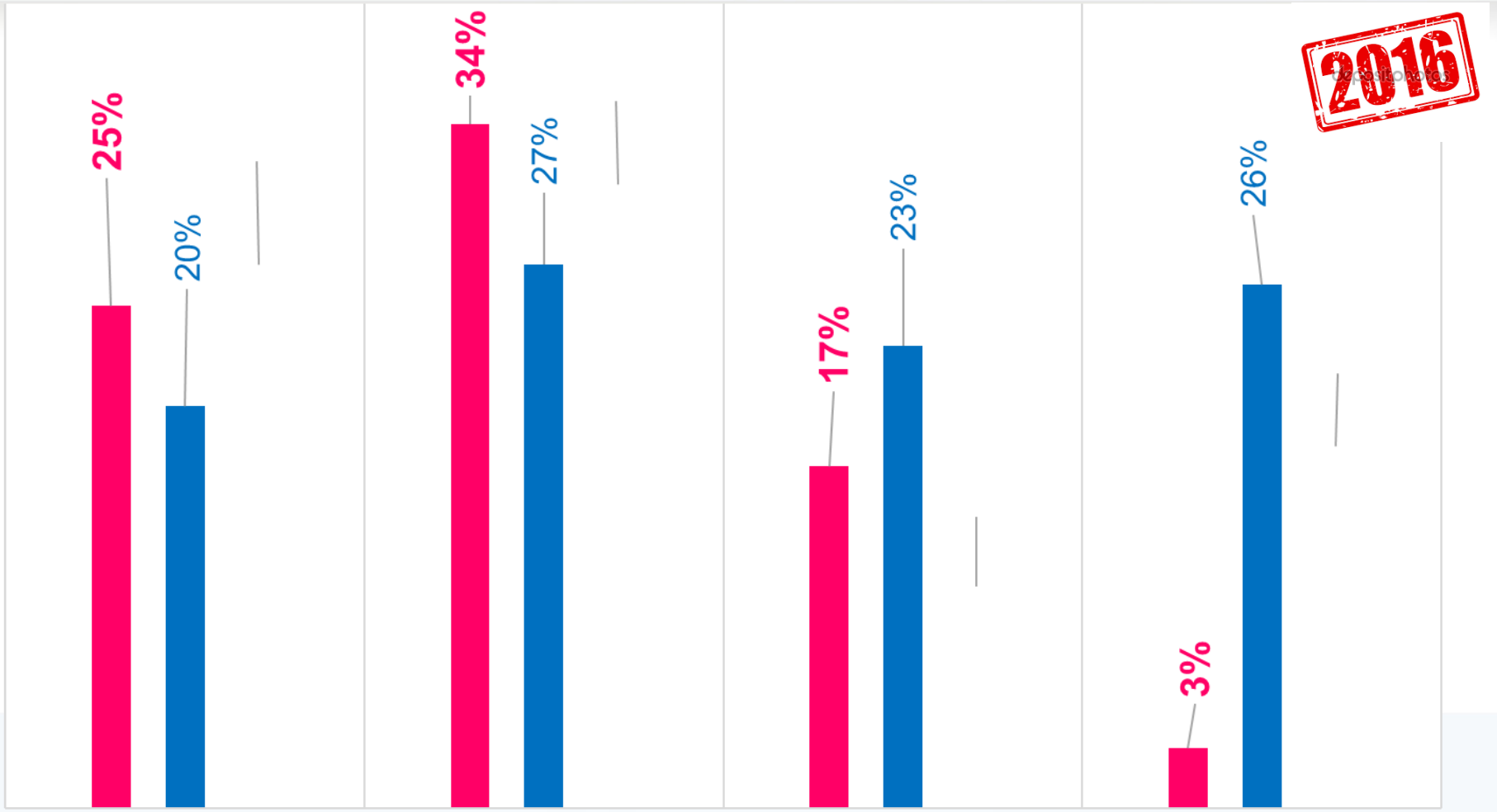
Main study results

No difference between Dydrogesterone vs. MPV in luteal phase support (RR, 1.04 (95% CI, 0.92–1.18); I^2, 0%; 7 RCTs; 3134 women; moderate evidence)

Study or subgroup	Dydrogesterone Events	Dydrogesterone Total	Progesterone Events	Progesterone Total	Weight	Risk ratio M-H, random, 95% CI
Oral dydrogesterone *vs* vaginal progesterone capsules						
Chakravarty (2005a)[33]	19	79	80	351	16.6%	1.06 (0.68, 1.63)
Chakravarty (2005b)[40]	13	55	10	59	5.8%	1.39 (0.67, 2.92)
Chakravarty (2006)[41]	11	50	11	56	5.7%	1.12 (0.53, 2.36)
Ganesh (2011)[42]	107	422	85	459	49.7%	1.37 (1.06, 1.76)
Saharkhiz (2016)[35]	28	96	34	114	17.9%	0.98 (0.64, 1.49)
Salehpour (2013)[36]	7	40	10	40	4.3%	0.70 (0.30, 1.66)
Subtotal (95% CI)	185	742	230	1079	100.0%	1.19 (0.99, 1.42)
Heterogeneity: $I^2 = 0\%$; Test for overall effect: $P = 0.06$						
Oral dydrogesterone vs. vaginal progestserone gel						
Ganesh (2011)[42]	107	422	120	482	46.9%	1.02 (0.81, 1.28)
Tomic (2015)[39]	117	415	126	416	53.1%	0.93 (0.75, 1.15)
Subtotal (95% CI)	224	837	246	898	100.0%	0.97 (0.83, 1.13)
Heterogeneity: $I^2 = 0\%$; Test for overall effect: $P = 0.71$						
All studies						
Subtotal (95% CI)	302	1157	476	1977	100.0%	1.04 (0.92, 1.18)
Heterogeneity: $I^2 = 0\%$; Test for overall effect: $P = 0.53$						
Test for subgroup differences: $I^2 = 29.5\%$, $P = 0.24$						



Efficacy of Dydrogesterone vs. vaginal micronized and gel Progesterone



Barbosa et al., UOG 2016

Live birth rates and safety profile using dydrogesterone for luteal phase support in assisted reproductive techniques

2016

Ravichandran Nadarajah[1], MBBS, MRCOG, Hemashree Rajesh[1], MBBS, MRCOG, Ker Yi Wong[1], BEng, MD, Fazlin Faisal[1], MBBS, Su Ling Yu[1], MMed, FRCOG

[1]Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore

Outcome	No. (%)
Did not achieve pregnancy	686 (65.3)
Achieved pregnancy	364 (34.7)
Live birth	291 (27.7)
Spontaneous miscarriage	62 (5.9)
Ectopic pregnancy	3 (0.3)
Molar pregnancy	1 (0.1)
Termination of pregnancy	7 (0.7)

Type of fetal anomaly	No. (%)
Anencephaly	1 (0.3)
Renal agenesis	1 (0.3)
Arthrogryposis	1 (0.3)
Cleft lip/palate	1 (0.3)
Exomphalos	1 (0.3)
Complex heart disease	1 (0.3)
Sacrococcygealteratoma	1 (0.3)
Total	7 (1.9)

Singapore Med J 2016, 1–11

2016

A comparative study of dydrogesterone and micronized proge for luteal phase support during *in vitro* fertilization (IVF) cycles

Nasrin Saharkhiz[1], Marzieh Zamaniyan[1], Saghar Salehpour[1], Shahrzad Zadehmodarres[1], Sedighe Hoseini[1], Leila Cheraghi[2], Samira Seif[3], and Nafiseh Baheiraei[4]

Table 3. Clinical outcomes, satisfaction and tolerability of patients in two groups.

Variables	Oral dydrogesterone ($N = 96$)	Micronized progesterone ($N = 114$)	p Value
Clinical pregnancy rate (%)	31.0%	33.0%	0.888
Ongoing pregnancy rate (%)	30.0%	30.0%	1.000
Multiple pregnancy rate (%)	5.30%	7.20%	0.394
Miscarriage rate (%)	5.0%	3.0%	0.721

Our results showed that oral dydrogesterone (40 mg/day) is as effective as vaginal micronized progesterone considering its clinical outcomes and patients' satisfaction and tolerability, for LPS among women undergoing IVF.

Efficacy of Dydrogesterone in ART

LOTUS 1 STUDY

human reproduction

ORIGINAL ARTICLE *Infertility*

A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization

Herman Tournaye[1], Gennady T. Sukhikh[2], Elke Kahler[3,*], and Georg Griesinger[4]

[1]Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Brussels, Belgium [2]Research Center for Obstetrics, Gynecology and Perinatology, Akademika Oparina Street, 4, 117497, Moscow, Russia [3]Clinical Development, Established Pharmaceuticals, Abbott Laboratories GmbH, Freundalllee 9A, 30173 Hannover, Germany [4]Department of Gynecological Endocrinology and Reproductive Medicine, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

*Correspondence address. E-mail: elke.kahler@abbott.com

Submitted on November 7, 2016; resubmitted on January 16, 2017; accepted on January 25, 2017

Study methods

LOTUS 1 STUDY

- ✓ Multicenter, phase III, double-blind, double-crossed study conducted on two objectives at 38 countries from 23/08/2013 to 26/03/2016

- ✓ Comparative study evaluating the efficacy of

  - Oral **Dydrogesterone** 30 mg/day (10 mg/3 times/day – TID)

not inferior to

  - **Micronized Vaginal Progesterone (MVP)** 600 mg/day (200 mg TID)

    - ➢ For luteal phase support in *in vitro* fertilization (IVF) support

- ✓ Efficacy was evaluated based on the occurrence of fetal heart (defined by vaginal ultrasonography at week 2 of pregnancy)

Study methods – population characteristics in the study

LOTUS 1 STUDY

Table I Demographics and baseline characteristics (full analysis sample).

	Oral DYD ($n = 497$)	MVP ($n = 477$)	All ($N = 974$)
Demographics			
Mean age, years (SD)	32.5 (4.5)	32.5 (4.4)	32.5 (4.4)
Age category, *n* (%)			
≤35 years of age	352 (70.8)	348 (73.0)	700 (71.9)
>35 years of age	145 (29.2)	129 (27.0)	274 (28.1)
Race or ethnicity, *n* (%)			
Caucasian	485 (97.6)	453 (95.0)	938 (96.3)
Black or African American	9 (1.8)	14 (2.9)	23 (2.4)
Asian	4 (0.8)	9 (1.9)	13 (1.3)
Other	0 (0.0)	2 (0.4)	2 (0.2)
Mean BMI, kg/m^2 (SD)	23.3 (3.1)[a]	23.2 (3.1)[b]	23.2 (3.1)[c]
Prior treatment, *n* (%)	30 (6.0)	25 (5.2)	55 (5.6)

Note: Percentages are based on the number of subjects in the full analysis sample with data available. Body mass index (BMI) values were calculated from the following populations: [a]$n = 496$; [b]$n = 476$; [c]$n = 972$.

DYD, dydrogesterone; MVP, micronized vaginal progesterone; SD, standard deviation.

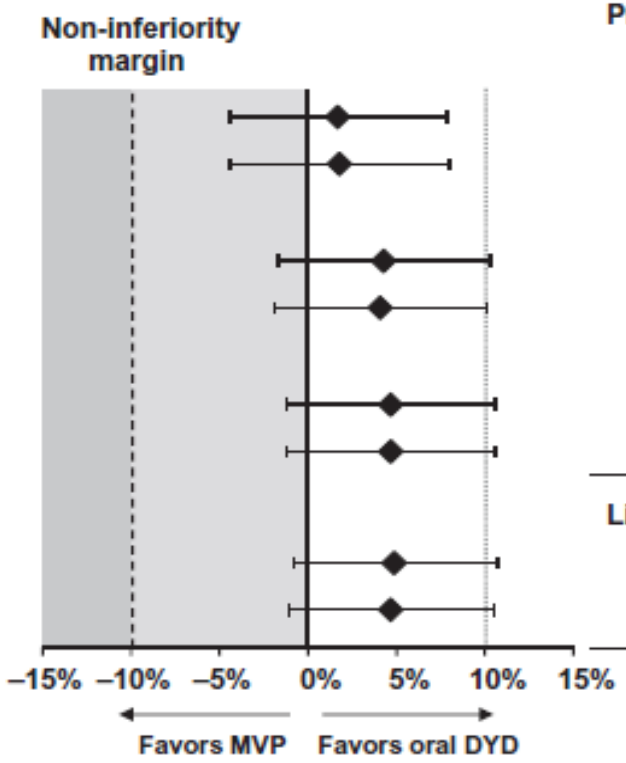
Tournaye et al. Human Reproduction, pp. 1–9, 2017

Study results

- In assessment analysis, embryo transfer was performed in both groups used Dydrogesterone (n = 497) and MVP (n = 477).
- Non-superior results of oral Dydrogesterone use resulted in **pregnancy result** at week 12 of pregnancy was **37.6%** vs. **33.1%** in the MPV group *(difference 4.7%; 95% CI: −1.2–10.6%)*.
- **Live birth rate** reached **34.6%** (172 pregnant women with 213 recent delivery cases) in the dydrogesterone group compared to **29.8%** (142 pregnant women with 158 recent delivery cases) in the MPV group (difference 4.9%, 95% CI: 0.8-10.7%).
- Dydrogesterone resulted in good tolerability and had a safety database being equivalent to MVP

Tournaye et al. Human Reproduction, pp. 1–9, 2017

Study results



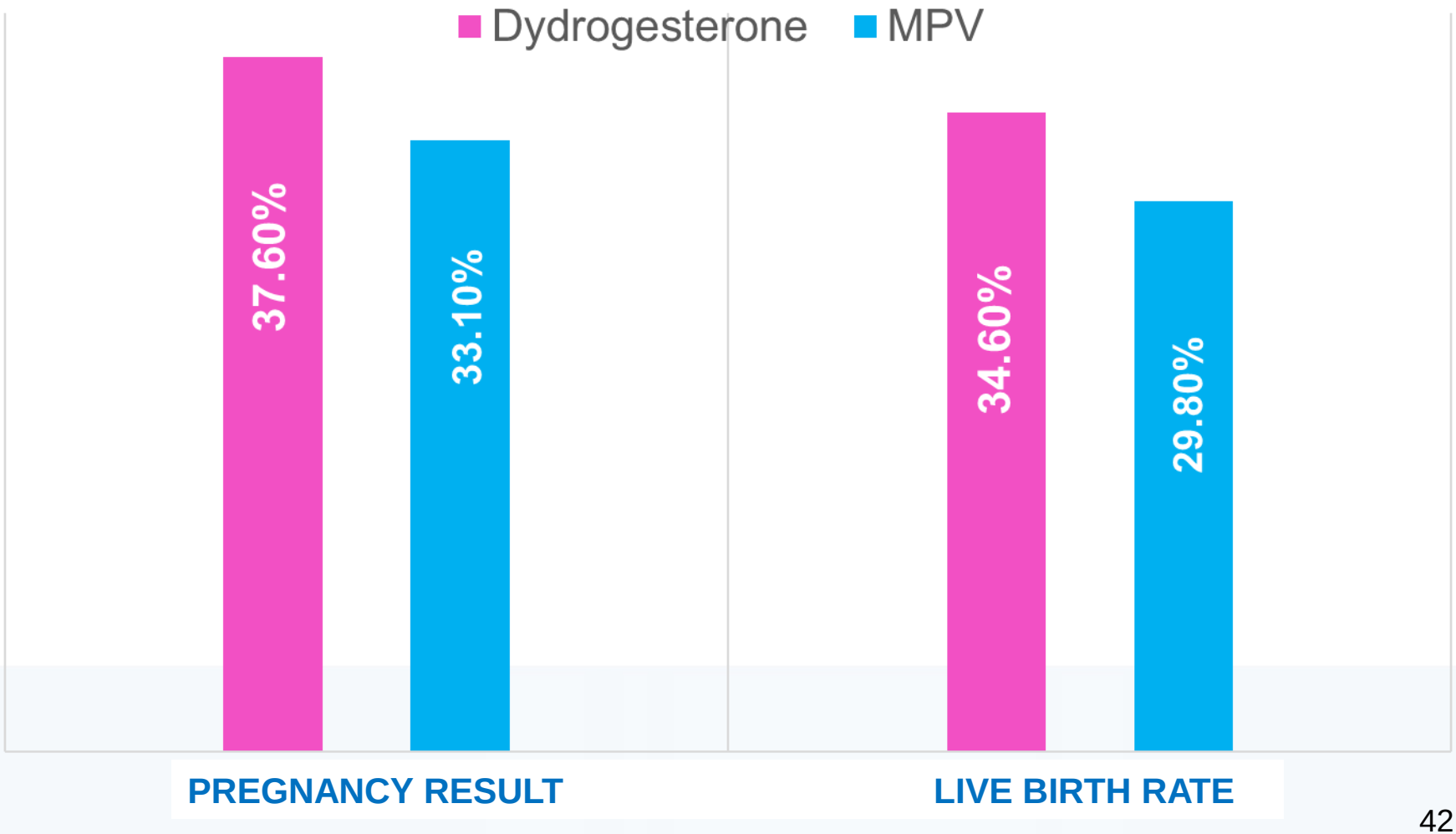
Outcome	% (*n*/*N*)		Difference in pregnancy rate (Oral DYD–MVP)	95% CI
	Oral DYD	MVP		
Pregnancy rate				
4 weeks of gestation				
FAS	47.1 (234/497)	45.5 (217/477)	1.7	–4.4–7.9
PPS	47.2 (232/492)	45.5 (216/475)	1.8	–4.4–8.0
8 weeks of gestation				
FAS	39.6 (197/497)	35.4 (169/477)	4.3	–1.7–10.3
PPS	39.6 (195/492)	35.6 (169/475)	4.1	–1.9–10.1
12 weeks of gestation				
FAS	37.6 (187/497)	33.1 (158/477)	4.7	–1.2–10.6
PPS	37.6 (185/492)	33.1 (157/475)	4.7	–1.2–10.6
Live birth rate				
FAS	34.6 (172/497)	29.8 (142/477)	4.9	–0.8–10.7
PPS	34.6 (170/492)	29.9 (142/475)	4.7	–1.1–10.5

Figure 2 Pregnancy status post-treatment. Positive pregnancy rates at 4, 8 and 12 weeks of gestation, and the live birth rates are shown for both the FAS and PPS. A non-inferiority margin of 10% was used, whereby the test drug is non-inferior if the lower bound of the 95% CI excludes a difference greater than 10% in favor of the comparator.

CI, confidence interval; DYD, dydrogesterone; FAS, full analysis sample; MVP, micronized vaginal progesterone; PPS, per protocol sample.

Tournaye et al. Human Reproduction, pp. 1–9, 2017

Efficacy of Dydrogesterone compared to Micronized progesterone



Tournaye et al. Human Reproduction, pp. 1–9, 2017

Maternal and fetal adverse events:
equivalent between the two groups

	Oral DYD (30 mg) (n = 518)	MVP (600 mg) (n = 511)	All (n = 1029)
Maternal population, n (%)[a]			
All TEAEs	290 (56.0)	276 (54.0)	566 (55.0)
At least one serious TEAE	56 (10.8)	68 (13.3)	124 (12.1)
At least one severe TEAE	37 (7.1)	54 (10.6)	91 (8.8)
TEAEs leading to study discontinuation	64 (12.4)	82 (16.0)	146 (14.2)
Deaths (maternal)	0 (0.0)	0 (0.0)	0 (0.0)
Liver enzyme analysis	1 (0.2)	2 (0.4)	3 (0.3)
Alanine aminotransferase increased	1 (0.2)	1 (0.2)	2 (0.2)
Hepatic enzyme increased	0 (0.0)	1 (0.2)	1 (0.1)
Vascular disorders	18 (3.5)	18 (3.5)	36 (3.5)
Peripheral embolism and thrombosis	1 (0.2)	1 (0.2)	2 (0.2)
Reproductive system and breast disorders	113 (21.8)	94 (18.4)	207 (20.1)
Vaginal hemorrhage	60 (11.6)	47 (9.2)	107 (10.4)
Gastrointestinal disorders	99 (19.1)	88 (17.2)	187 (18.2)
Nervous system disorders	40 (7.7)	42 (8.2)	82 (8.0)
Fetal/neonatal population, n (%)[b]			

Rate of side effects:
equivalent between the two treatment groups

	Oral DYD (30 mg) (n = 518)	MVP (600 mg) (n = 511)	All (n = 1029)
TEAEs of special interest relating to congenital, familial and genetic disorders, n (%)[c]			
Congenital, familial and genetic disorders	5 (1.0)	6 (1.2)	11 (1.1)
Congenital hand malformation	0 (0.0)	1 (0.2)	1 (0.1)
Congenital hydrocephalus	0 (0.0)	1 (0.2)	1 (0.1)
Congenital tricuspid valve atresia	0 (0.0)	1 (0.2)	1 (0.1)
Interruption of aortic arch	1 (0.2)	0 (0.0)	1 (0.1)
Kidney malformation	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary artery atresia	0 (0.0)	1 (0.2)	1 (0.1)
Spina bifida	0 (0.0)	1 (0.2)	1 (0.1)
Talipes	1 (0.2)	0 (0.0)	1 (0.1)
Tracheo-esophageal fistula	1 (0.5)	0 (0.0)	1 (0.1)
Univentricular heart	0 (0.0)	1 (0.2)	1 (0.1)
Ventricular septal defect	2 (0.4)	0 (0.0)	2 (0.2)
Trisomy 21	1 (0.2)	2 (0.4)	3 (0.3)
Trisomy 13	0 (0.0)	1 (0.2)	1 (0.1)
Turner's syndrome	1 (0.2)	0 (0.0)	1 (0.1)

[a]Percentages are calculated based on the Safety Sample.
[b]Percentages are calculated based on the infant population (i.e. *N* = 212 for the oral DYD group and *N* = 159 for the MVP group).
[c]Percentages are calculated based on the Safety Sample. Detection and reporting of the congenital, familial, and genetic disorders occurred during with the pre- or post-natal period; some fetuses/neonates had more than one disorder.
AE, adverse event; DYD, dydrogesterone; MVP, micronized vaginal progesterone; TEAE, treatment-emergent adverse event.

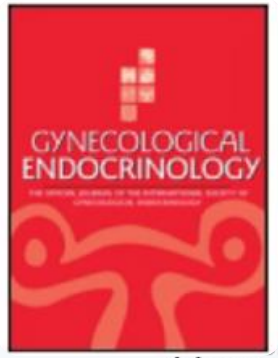
Characteristics of new born children: equivalent between the two groups

	Oral DYD (30 mg)	MVP (600 mg)
	(n = 497)	(n = 477)
Gender, n (%)[a]		
Male	120 (56.3)	88 (55.7)
Female	93 (43.7)	70 (44.3)
Abnormal findings of physical examination, n (%)[a]		
Yes	14 (6.6)	12 (7.6)
No	199 (93.4)	146 (92.4)
Height, cm (mean SD)	48.8 3.9	49.4 2.8
Weight, kg (mean SD)	2.9 0.7	3.0 0.6
Head circumference, cm (mean SD)	33.4 2.4	33.8 1.9
APGAR score (mean SD)		
1 min postpartal	8.1 1.5	8.2 1.5
5 min postpartal	9.0 1.3	9.2 1.1

[a]Percentages are calculated based on the full analysis sample.
APGAR, appearance, pulse, grimace, activity, respiration; DYD, dydrogesterone; MVP, micronized vaginal progesterone; SD, standard deviation.

Dydrogesterone – Safety data

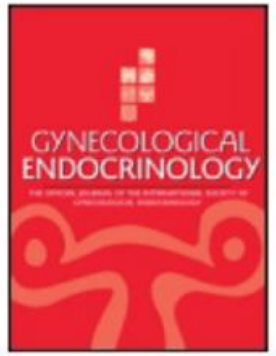
- Dydrogesterone has been marketed and used worldwide since the 1960s for the treatment of some conditions associated with progesterone deficiency
- Consideration of congenital defects from 1977-2005 did not show any supportive evidence for the association between congenital malformations and dydrogesterone
- More than 10 million fetus were exposed to dydrogesterone *in utero* during the study period.



Queisser-Luft A, Early Hum Dev. 2009; 85: 375-7

Dydrogesterone – Safety data

- Based on dydrogesterone sales data, the estimated cumulative number of patients used dydrogesterone in all indications from April 1960 to April 2014 was more than 94 million patients.
- Of these, estimating that more than 20 million fetuses were exposed to dydrogesterone *in utero* without apparent increase in adverse outcomes for pregnancy.



Mirza FG và cộng sự, Gynecol Endocrinol. 2016; 32(2):97-106

Conclusions

- Ovary stimulation in IVF leads to corpus luteum failure. It is needed to support corpus luteum when fresh embryo transfer.
- Progestogen is an important hormone used in assisted reproduction regimens.
- The use of Dydrogestogen in assisted reproduction resulted in equivalent efficacy and safety to the use of MVP → may provide an additional option to support corpus luteum in IVF in the future.

SINCERELY THANKS