Nuove prospettive per la fase luteale.

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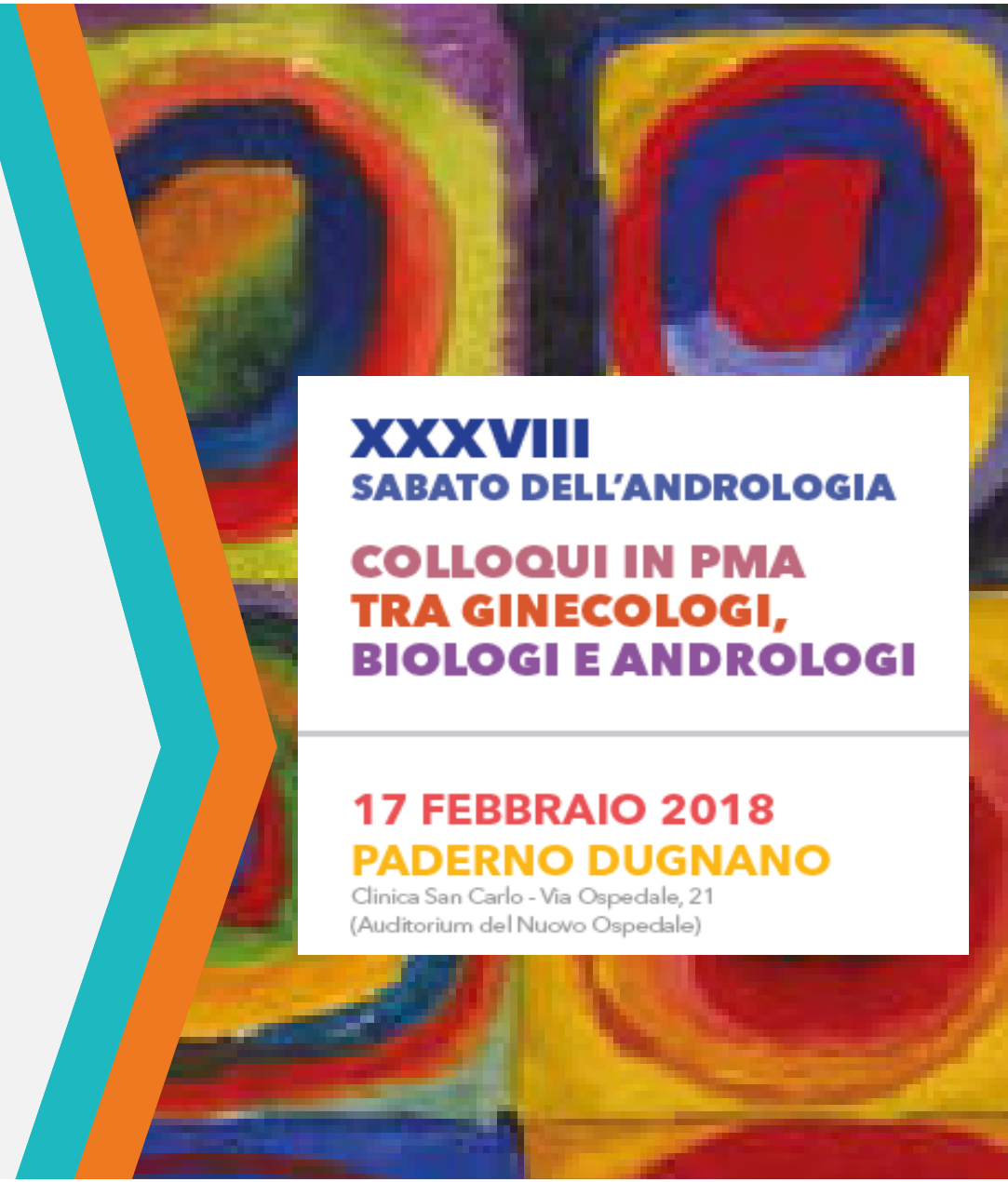
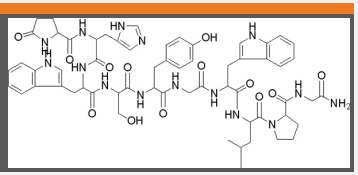
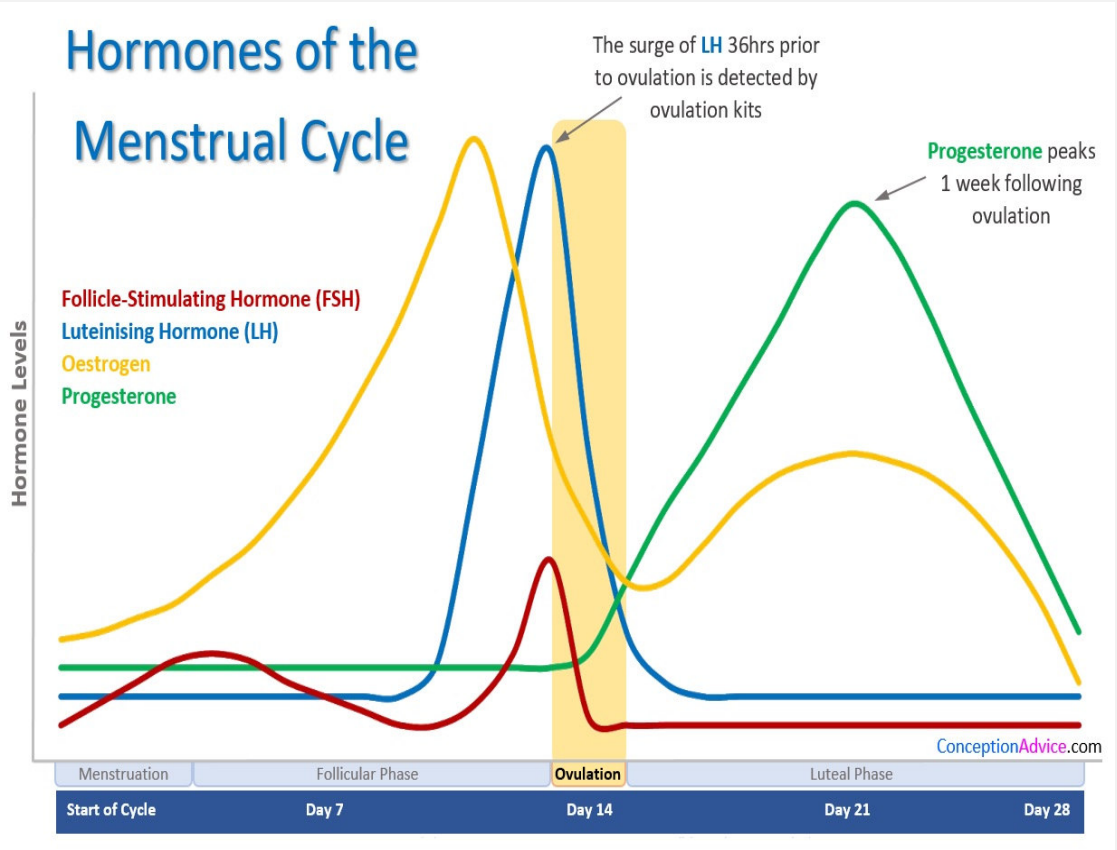


The role of LH and progesterone in the luteal phase

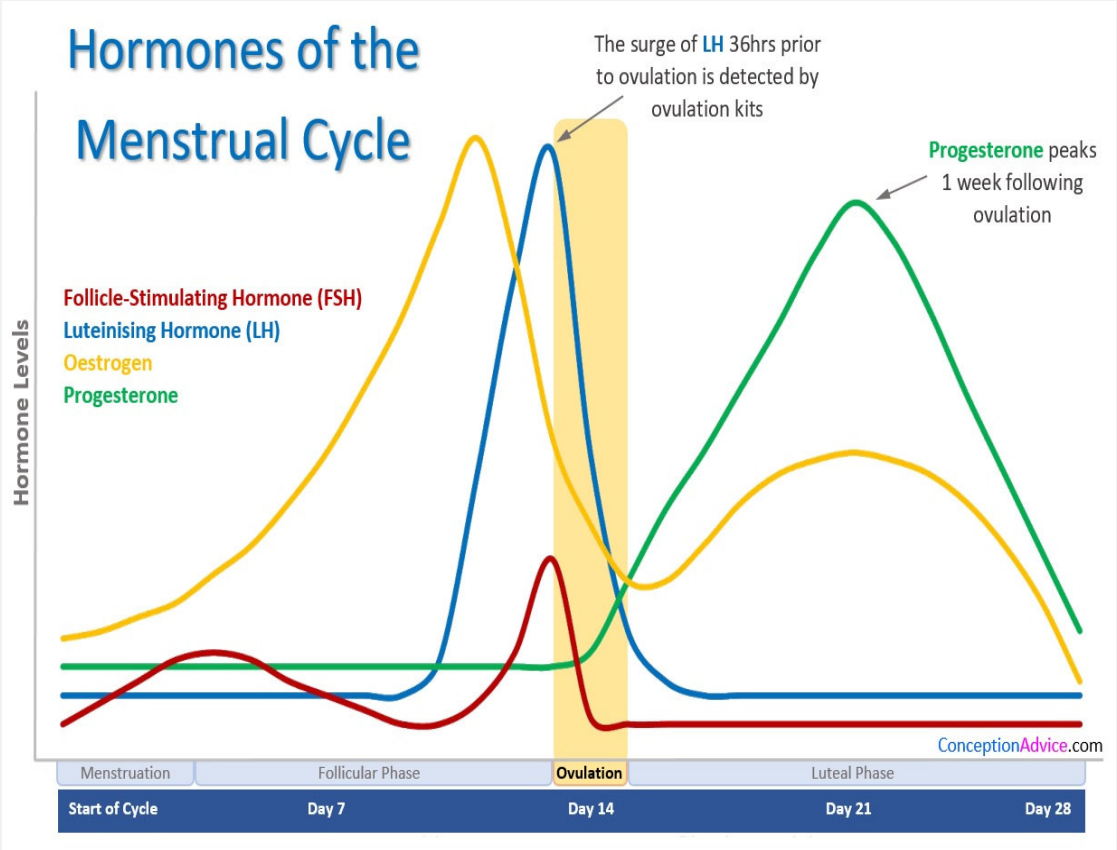
- ✓ Totally responsible for steroidogenic activity of the corpus luteum (Casper and Yen, 1979)
- ✓ Upregulation of growth factors, VEGF-A, FGF2 (Sugino et al., 2004; Wang et al., 2002)
- ✓ Upregulation of cytokines involved in implantation (Licht et al., 2001)
- ✓ Stimulation of LH receptors in endometrium (Rao, 2001; Tesarik et al., 2003)

LH



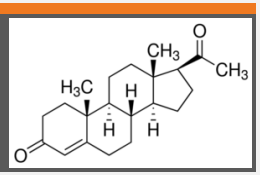


The role of LH and progesterone in the luteal phase



- ✓ Induces secretory transformation of the endometrium in the luteal phase (Bourgain et al., 1990)
- ✓ Progesterone deficiency delays endometrial maturation (Dallenbach-Hellweg, 1984)
- ✓ Removal of CL prior to 7 weeks of gestation leads to pregnancy loss (Csapo, 1972)
- ✓ Normal pregnancy was sustained when progesterone was given after removal of CL (Csapo, 1973)

Progesterone



Abnormal Luteal Phase of Stimulated Cycles

"Ovarian stimulation regimens used in assisted reproduction cycles alter the luteal phase"

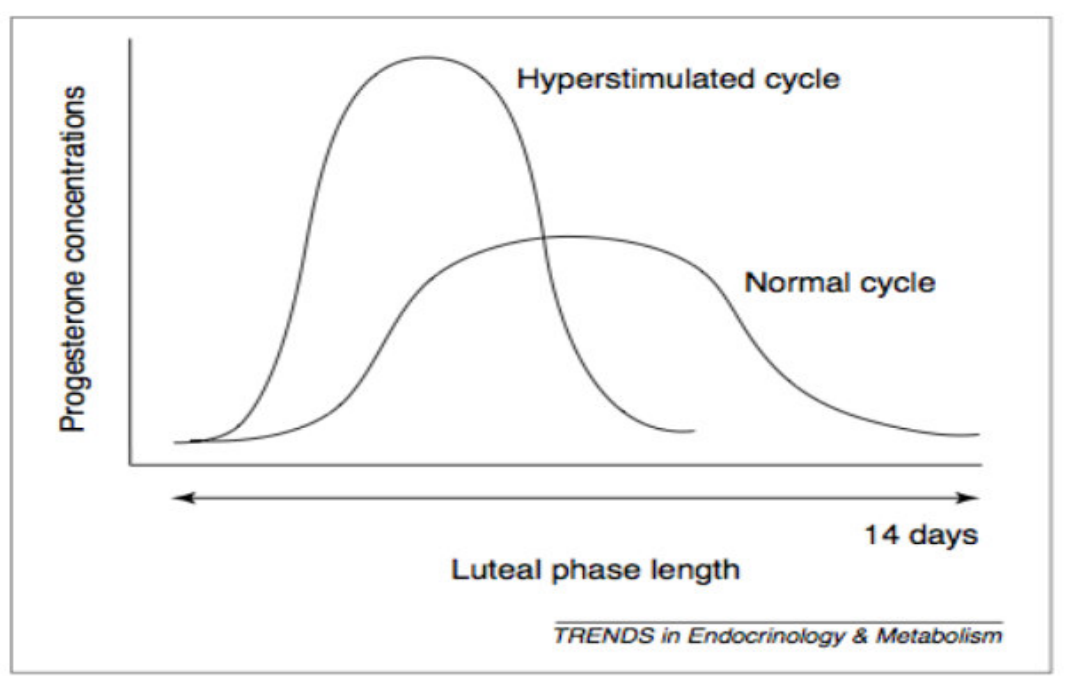
Kolibianakis et al 2003

Ovarian stimulation causes:

- ✓ inadequate development of the endometrium
- ✓ asynchrony between the endometrium and the transferred embryo and
- ✓ adverse effects on endometrial receptivity

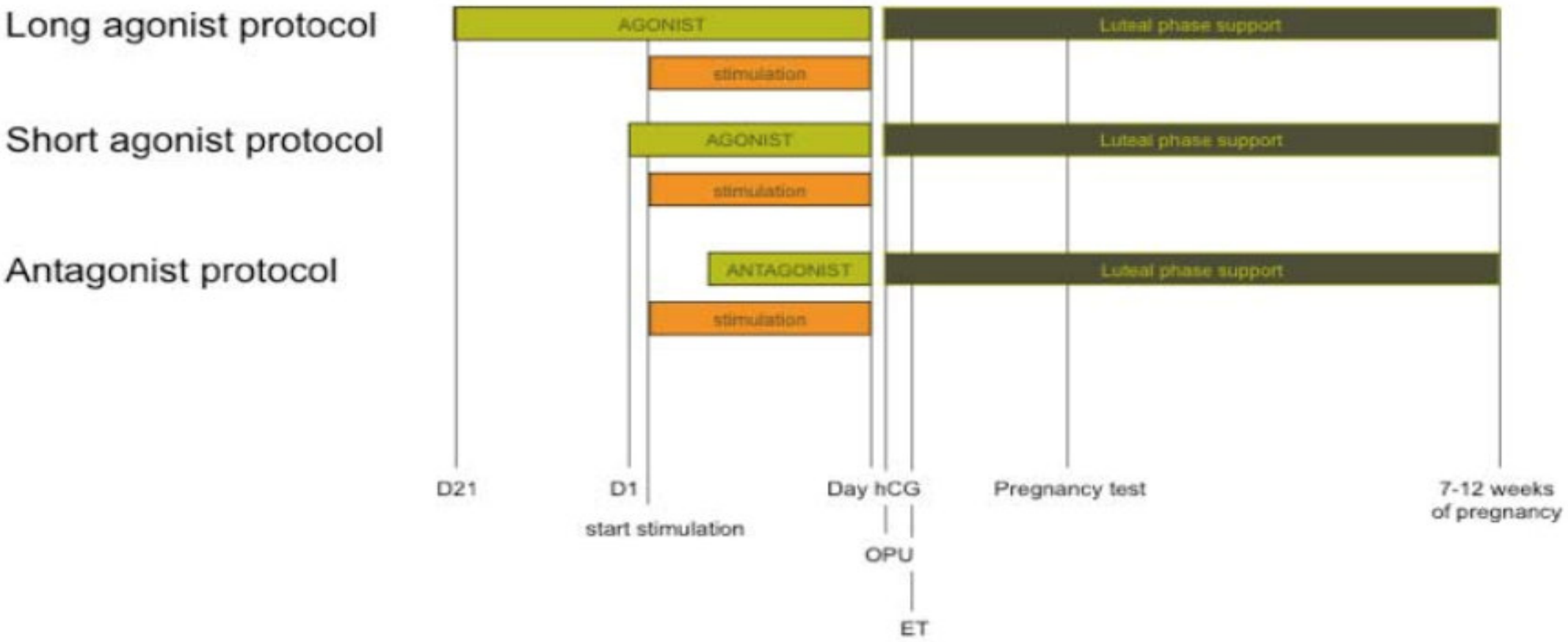
Macklon & Fraser 2000

Devroey et al 2004



The luteal phase defect in IVF is present whether GnRH agonist or antagonist is used.

Friedlers et al 2006

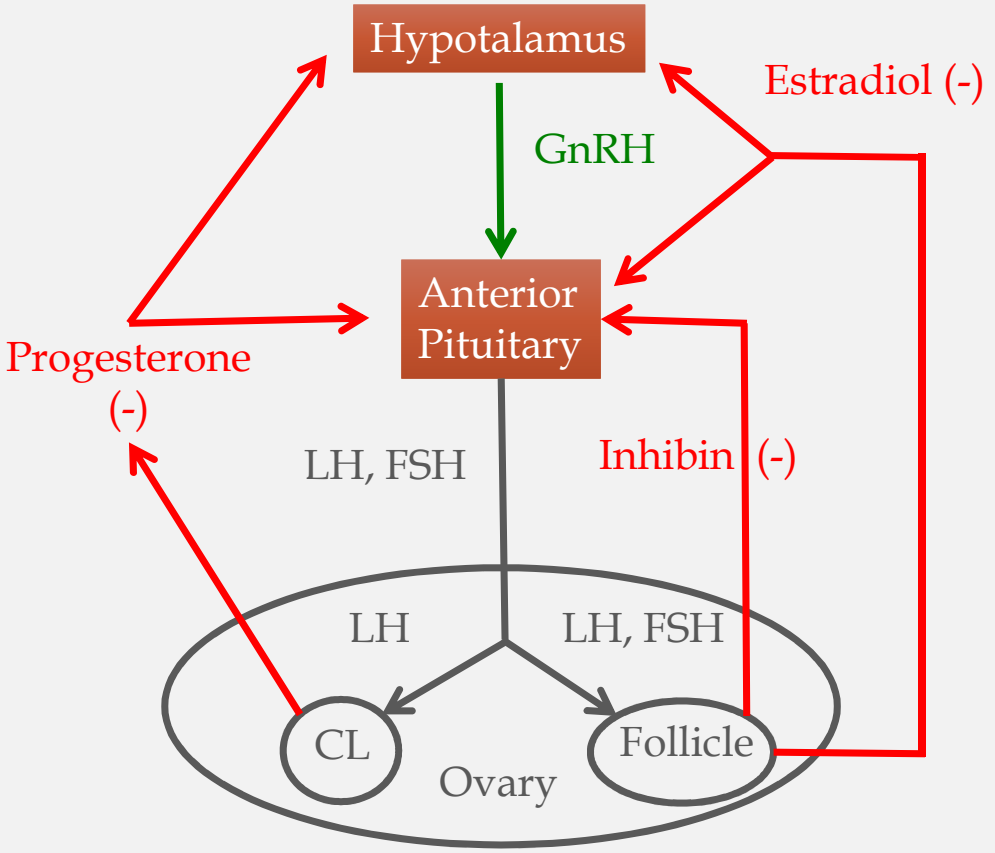


The luteal phase defect in IVF is present whether GnRH agonist or antagonist is used.

Friedlers et al 2006

The possible mechanism responsible may be:

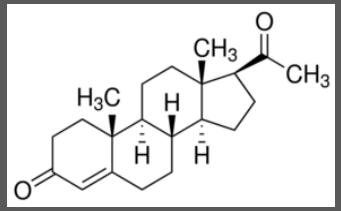
- ✓ Continuation of pituitary down regulation effect
- ✓ Loss of granulosa cells during oocyte retrieval
- ✓ Formation of multiple CL leading to inhibition of pulsatile LH release



Duration of luteal phase is shortened


FAMAS
M4A1
SCAR-H
TAR-21
FAL
M16A4
ACR
F2000
AK-47
MP5k
UMP45
Vector
P90
Mini-Uzi
L86 LSW
RPD
MG4
AUG HBAR
M240
Riot Shield
Intervention
Barrett .50cal
WA2000
M14/M21 EBR

Progesterone



Progesterone alone enough for LPS:

✓ in the presence of estrogen, progesterone trasforms a proliferative into a secretory endometrium, increases the receptivity of the endometrium and acts to maintain the pregnancy.

Micronized	
Oral/vaginal	- 200-600 mg daily
Vaginal Gel (8%)	- 90-180 mg daily
Vaginal Pessary	- 100-400 mg daily
Intramuscular (oil based)	- 100-400 mg daily
Subcutaneous (aqueous preparation)	- 25 mg daily
Synthetic – Dydrogesterone	- 10 mg BD or TDS

Progesterone vs. Placebo or No treatment

✓ Higher live birth / ongoing PR

OR 1.77	95% CI: 1.09-2.86	5 RCTs, 642 women	very low quality evidence

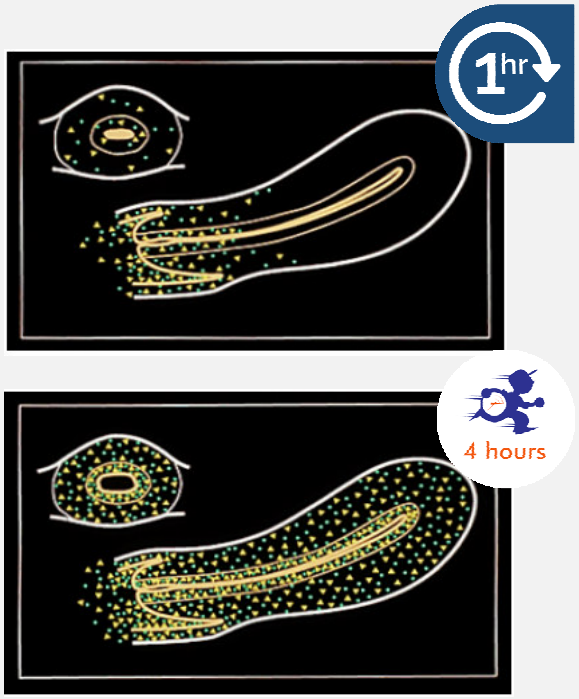
✓ Higher clinical PR

OR 1.89	95% CI: 1.30-2.75	7 RCTs, 841 women	low quality evidence

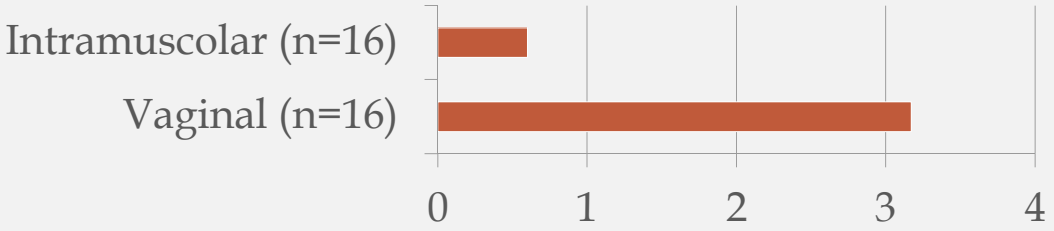
Cochrane Library
Cochrane Database of Systematic Reviews

van der Linden et al, Cochrane Database Sist Rev. 2015 Jul 7;(7):CD009154.

Progressive diffusion of progesterone from the cervix to the fundus of the uterus



Bulletti et al. Hum Reprod. 1997;12:1073-9



Facicioglu et al. Gynecol Endocrinol 2004;18(5):240-3

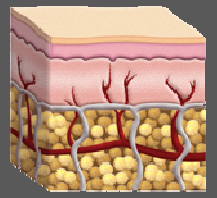
✓Vaginal Progesterone is more patient-friendly.

OR 13.7	95% CI: 8.7-21.5	407 women

Yanushpolsky et al, Fertil Steril. 2010 Dec;94(7):2596-9.


THIS WAY
THAT WAY
ANOTHER WAY

New self-injectable P4 (hydroxypropyl-β-cyclodextrin/progesterone complex)

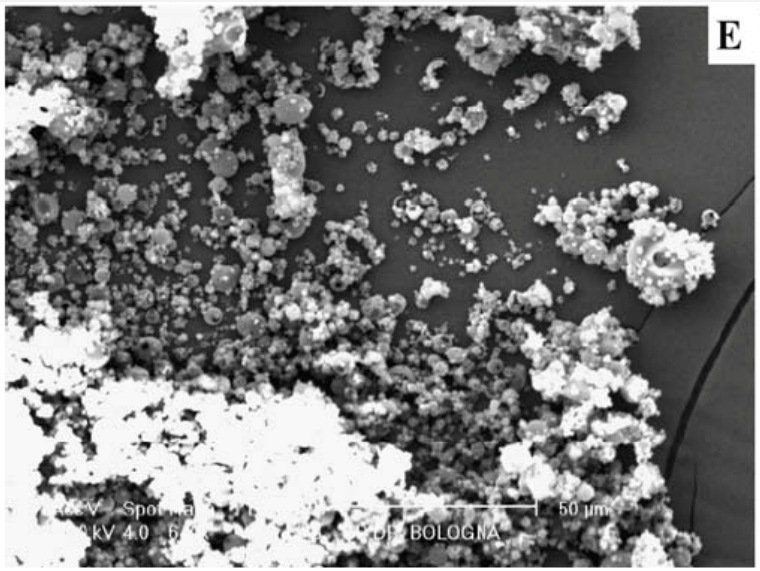


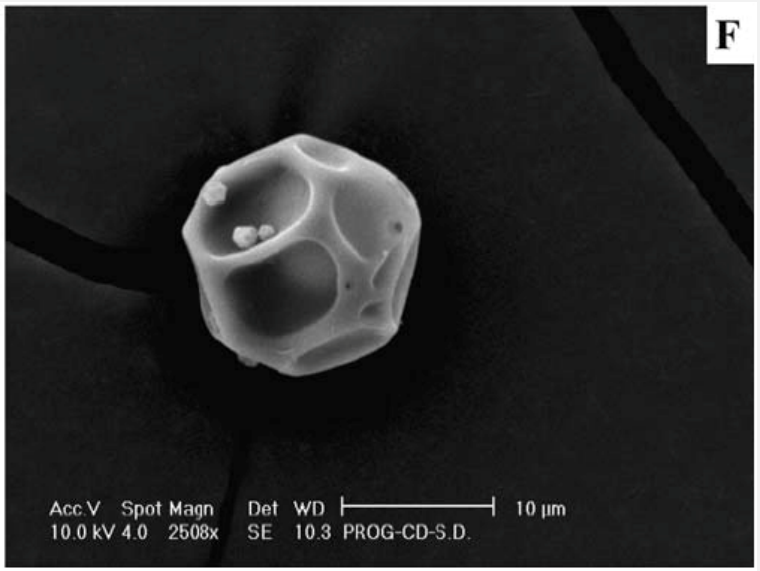
- An inclusion complex between progesterone and HPBCD exists also in the solid state and that included progesterone exists as an amorphous phase inside the complex.

Zoppetti et al, J Pharm Sci 2007;96(7):1729-36.

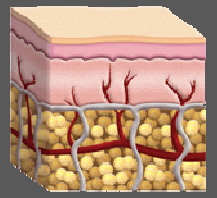
Spray dried HPBCD/P (SD) particles at different magnifications.

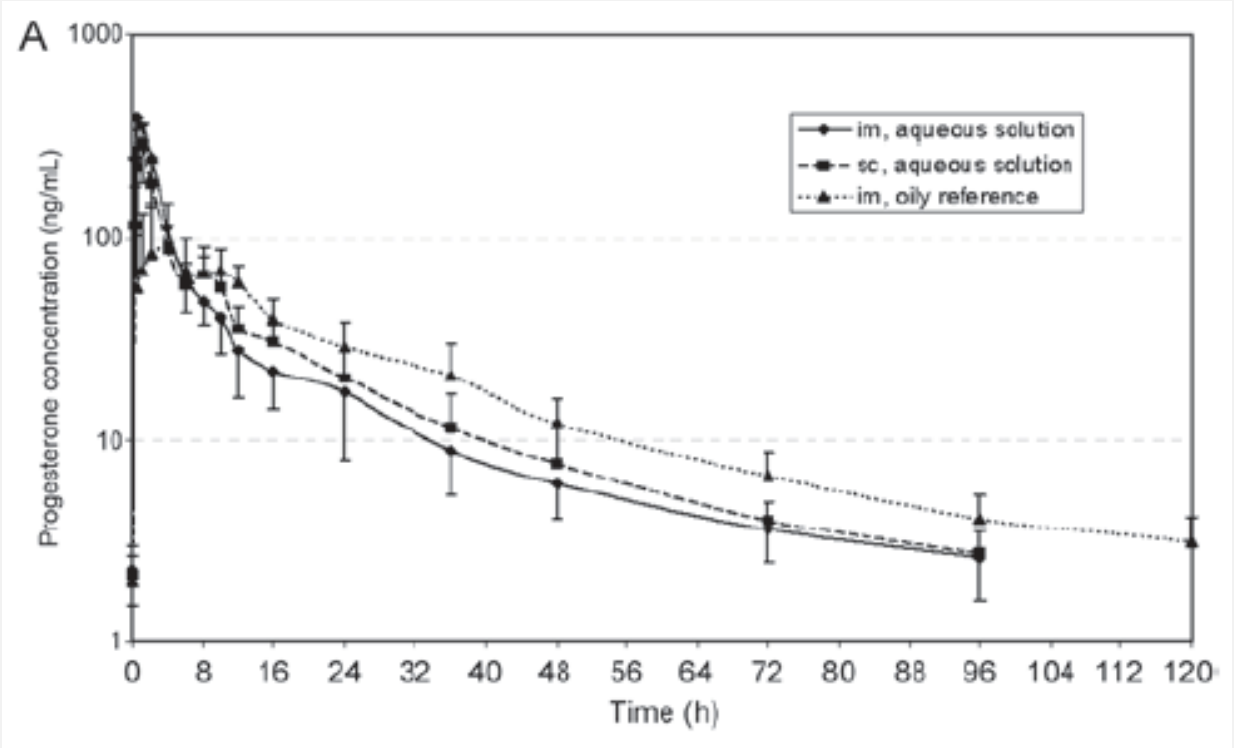
Fini et al, Pharm Res 2008;25(9):2030-40.





New self-injectable P4 (hydroxypropyl-β-cyclodextrin/progesterone complex)

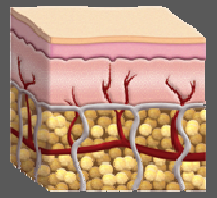




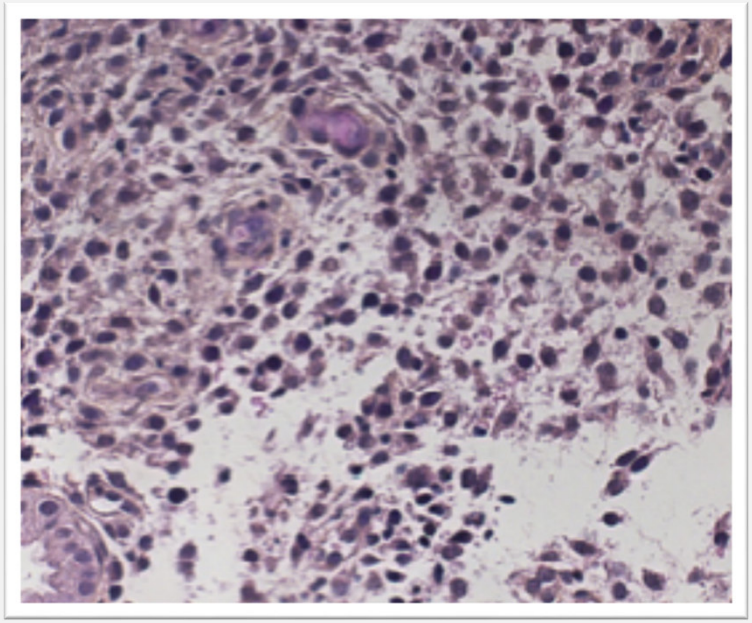
The bioavailability of a water-soluble injectable Progesterone administered SC is equivalent to the IM oil preparation, even though the absorption is definitely more rapid.

Sator et al, Gynecol Endocrinol 2013;29(3):205-8.

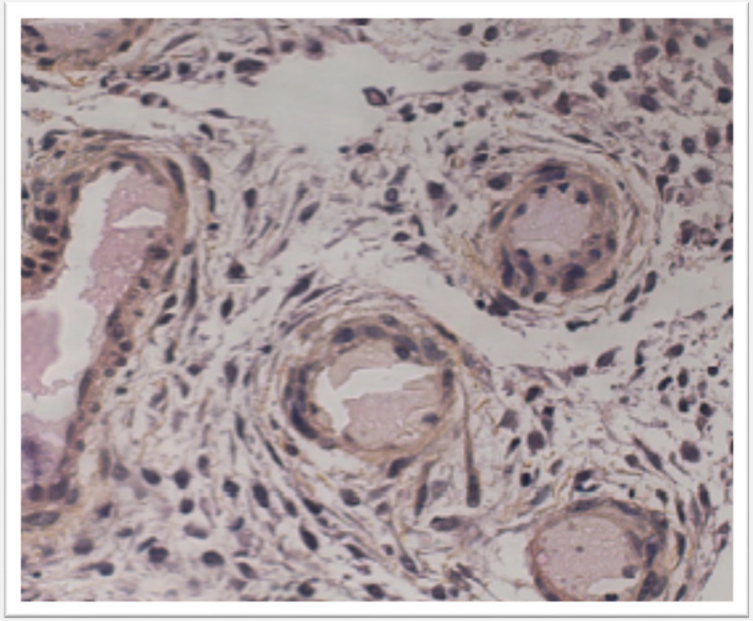
New self-injectable P4 (hydroxypropyl-β-cyclodextrin/progesterone complex)



No difference in the endometrial biopsies having been shown between the two doses tested, we suggest opting for the lowest dose (25 mg/d—the physiologic amount produced by the ovary in the mid luteal phase).



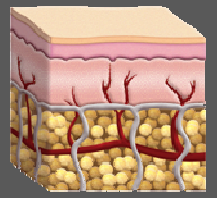
25 mg



50 mg

De Ziegler et al, Fertil Steril 2013;100(3):860-6.

New self-injectable P4 (hydroxypropyl-β-cyclodextrin/progesterone complex)



a noninferiority randomized controlled study

Medication used for cycle synchronization, pituitary desensitization, ovarian stimulation, and hCG trigger (intention-to-treat population), n (%).

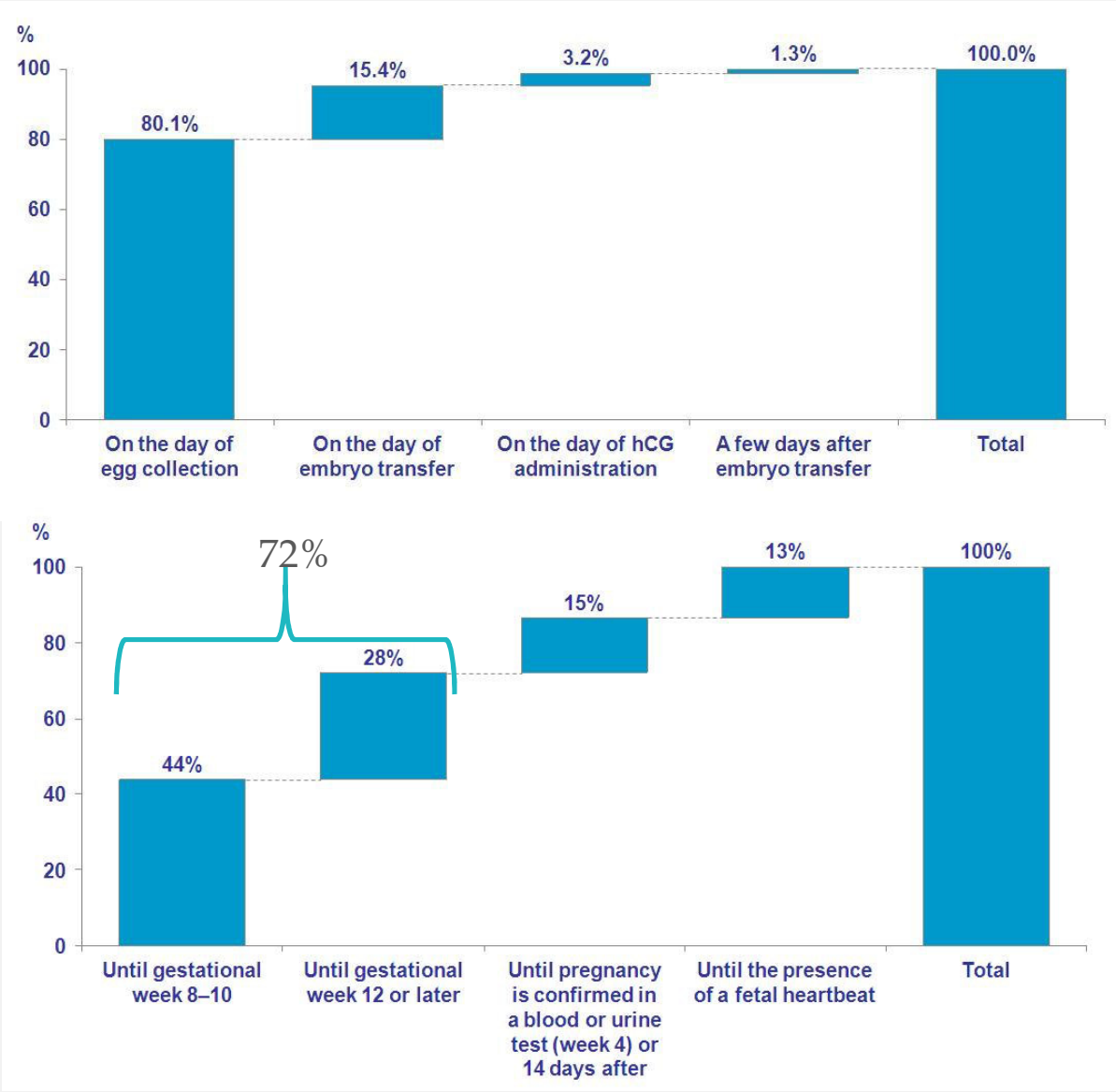
Medication type and drug	Prolutex (n = 339)	Crinone (n = 344)	*P* value[a]
Cycle synchronization			
Oral contraceptive pill	13 (3.83)	13 (3.78)	.969
LH suppression			
GnRH agonist	233 (68.73)	242 (70.35)	.646
GnRH antagonist	106 (31.27)	102 (29.65)	
Ovarian stimulation			
Human FSH	109 (32.15)	122 (35.47)	.777
Recombinant FSH	162 (47.79)	156 (45.35)	
hMG	50 (14.75)	51 (14.83)	
Other	18 (5.31)	15 (4.36)	
hCG triggering			
Human hCG	248 (73.16)	254 (73.84)	.828
Recombinant hCG	91 (26.84)	89 (25.87)	
GnRH agonist	0 (0.00)	1 (0.29)	

Pregnancy rate and live birth rate by treatment

Variable	Prolutex	Crinone	*P* value[a]
Primary endpoint			
Ongoing pregnancy—ITT, n (%)	93 (27.4)	105 (30.5)	.40
Difference vs. Crinone (95% CI)	−3.09 (−9.91 to 3.73)		
Ongoing pregnancy—PP, n (%)	93 (29.2)	100 (31.2)	.61
Difference vs. Crinone (95% CI)	−2.00 (−9.12 to 5.13)		
Secondary endpoints			
Implantation rate—ITT mean (SD)	22.6 (35.0)	23.1 (33.1)	.85
Difference vs. Crinone (95% CI)	−0.52 (−5.75 to 4.72)		
Implantation rate—PP mean (SD)	22.8 (35.1)	22.7 (32.9)	.97
Difference vs. Crinone (95% CI)	0.12 (−5.16 to 5.39)		
Positive β-hCG test—ITT, n (%)	134 (39.5)	148 (43.0)	.35
Difference vs. Crinone (95% CI)	−3.5 (−10.89 to −3.90)		
Positive β-hCG test—PP, n (%)	134 (42.0)	141 (43.9)	.62
Difference vs. Crinone (95% CI)	−1.9 (−9.60 to 5.77)		
Clinical pregnancy—ITT, n (%)	103 (30.4)	113 (32.9)	.49
Difference vs. Crinone (95% CI)	−2.47 (−9.45 to −4.52)		
Clinical pregnancy—PP, n (%)	103 (32.3)	108 (33.6)	.72
Difference vs. Crinone (95% CI)	−1.36 (−8.65 to 5.94)		
Early spontaneous abortion[b]—ITT, n (%)	14 (4.1)	14 (4.1)	.97
Difference vs. Crinone (95% CI)	0.06 (−2.92 to 3.04)		
Early spontaneous abortion[b]—PP, n (%)	14 (4.4)	14 (4.4)	.99
Difference vs. Crinone (95% CI)	0.03 (−3.15 to 3.20)		
Delivery and live births—ITT, n (%)	91 (26.8)	103 (29.9)	.37
Difference vs. Crinone (95% CI)	−3.10 (−9.87 to 3.68)		
Delivery and live births—PP, n (%)	91 (28.5)	98 (30.5)	.58
Difference vs. Crinone (95% CI)	−2.00 (−9.08 to 5.08)		

Lockwood et al, Fertil Steril 2014;101(1):112-119.

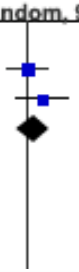
Updated survey on the use of progesterone for luteal phase support in stimulated IVF cycles. July 31, 2012



Study or Subgroup	early P cessation Events	Total	P continuation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 randomization on the day of a clinical pregnancy						
Aboulghar 2008	119	125	126	132	24.3%	1.00 [0.94, 1.05]
Kohls 2012	105	110	101	110	22.8%	1.04 [0.97, 1.11]
Subtotal (95% CI)		**235**		**242**	**47.0%**	**1.01 [0.97, 1.06]**
Total events	224		227			

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

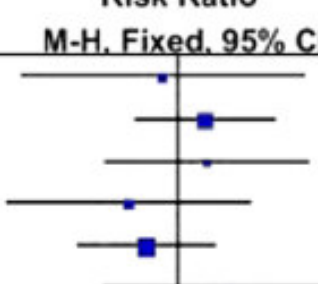
Risk Ratio M-H, Random, 95% CI



REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

Study or Subgroup	early P cessation Events	Total	P continuation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aboulghar 2008	5	125	6	132	8.6%	0.88 [0.28, 2.81]
Andersen 2002	22	150	18	153	26.4%	1.25 [0.70, 2.23]
Goudge 2010	10	35	7	31	11.0%	1.27 [0.55, 2.92]
Kohls 2012	6	110	9	110	13.3%	0.67 [0.25, 1.81]
Kyrou 2011	17	100	22	100	32.6%	0.77 [0.44, 1.37]

Risk Ratio M-H, Fixed, 95% CI



Study or Subgroup	early P cessation Events	Total	P continuation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andersen 2002	118	150	126	153	83.1%	0.96 [0.85, 1.07]
Goudge 2010	25	35	24	31	16.9%	0.92 [0.70, 1.22]
Total (95% CI)		**185**		**184**	**100.0%**	**0.95 [0.86, 1.05]**
Total events	143		150			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

Risk Ratio M-H, Fixed, 95% CI

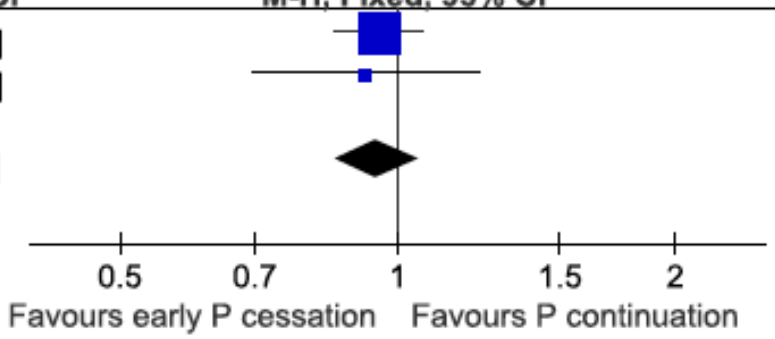
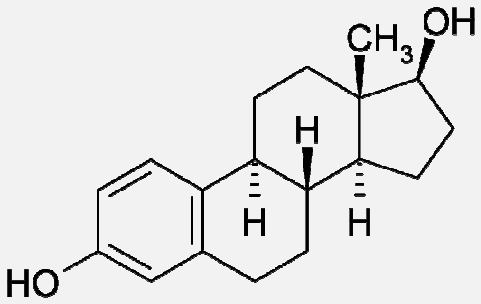


Figure 4 Live birth rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

Liu et al, Reprod Biol Endocrinol 2012;10:107.


FAMAS
M4A1
SCAR-H
TAR-21
FAL
F2000
AK-47
Vector
P90
RPD
MG4
M240
Riot Shield
Intervention
Barrett .50cal
WA2000
M14/M21 EBR
HEY SONNY, YOU LOOK DEPRESSED. HERE, TAKE SOME PROZAC. YOU'RE HYPERACTIVE, YOU NEED RITALIN. TAKE THIS -TAKE THAT, IT'S OK, I'M A DOCTOR.
The Drug Pusher

Estrogen as an adjuvant to LPS



Preparations avalaible

Estradiol valerate
Oral/vaginal - 2-6 mg daily

Micronized estradiol
Oral/vaginal - 2-6 mg daily

Transdermal estradiol
Patches, 2 per week - 0,05-0,1 mg daily

Fertility and Sterility

Midluteal decline of serum E2 has an impact on endometrial receptivity and is deleterious to successful conception?

- ✓ In a group of normal- and high-response patients treated with a similar long protocol and supplemented with vaginal micronized P, neither the significant decline of midluteal E2 nor the absolute serum concentration of E2 correlated with implantation failure and therefore were not detrimental to IVF-ET outcome.

Friedler et al, Fertil Steril 2005;83(1):54-60.

- ✓ E2 level seems to play a critical role in predicting clinical pregnancy: a markedly higher luteal E2 level in pregnant and a declining trend in non pregnant women.

Ganesh et al, Fertil Steril 2009;91(4):1018-22.

P vs P&E - Meta-analyses

The currently available evidence suggests that the addition of estrogen to progesterone for luteal phase support does not increase the probability of pregnancy in IVF.

Kolibianakis et al, Hum Reprod 2008;23(6):1346-54.

Progesterone compared with progesterone + oestrogen for assisted reproduction cycles

Population: subfertile women
Setting: assisted reproduction
Intervention: progesterone
Comparison: progesterone + oestrogen (route of oestrogen: oral, transdermal, vaginal or oral + transdermal)

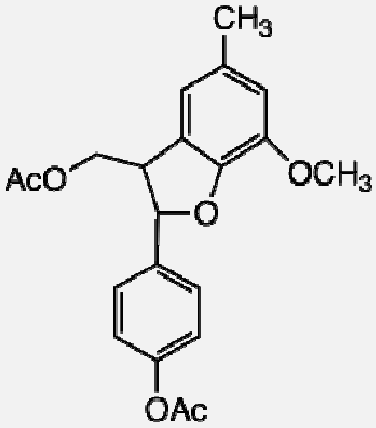
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Progesterone + oestrogen	Progesterone			
Live birth or ongoing pregnancy	367 per 1000	393 per 1000 (345 to 444)	OR 1.12 (0.91 to 1.38)	1651 (9 RCTs)	
Clinical pregnancy	433 per 1000	397 per 1000 (355 to 443)	OR 0.86 (0.72 to 1.04)	2169 (14 RCTs)	
OHSS	51 per 1000	30 per 1000 (11 to 82)	OR 0.58 (0.2 to 1.68)	461 (2 RCTs)	

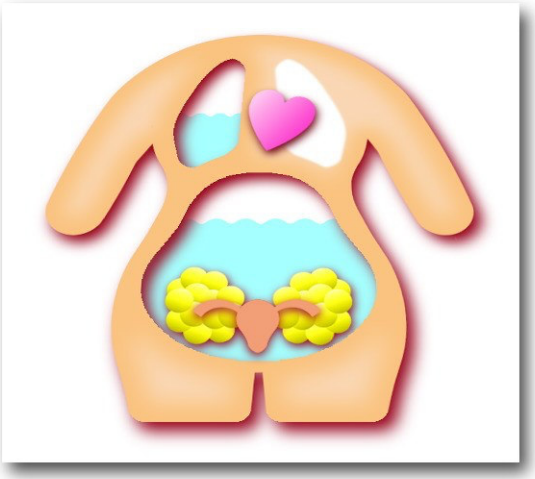
A forest plot demonstrates no benefit of estrogen supplement during luteal phase of IVF cycles using GnRH agonist or antagonist in terms of clinical pregnancy rate (PR) per patient.

Jee et al, Fertil Steril 2010;93(2):428-36.

van der Linden et al, Cochrane Database Sist Rev. 2015 Jul 7;(7):CD009154.

hCG



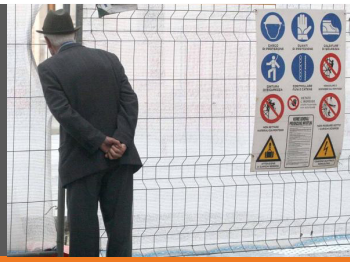


hCG addition to LPS. Background:

- ✓ hCG both bind to and activate the LH/ hCG receptor:
  - ✓ induction of final follicular maturation and maintenance of the CL for early LPS.
- ✓ The half-life of hCG is significantly longer (days) than that of endogenous LH (hours) (Hoff et al., 1983; Weissman et al., 1996) and thus, a bolus of hCG leads to a prolonged luteotropic effect which in combination with the formation of multiple corpora lutea (CL) may lead to the development of ovarian hyperstimulation syndrome (OHSS) (Haning et al., 1985).
- ✓ Modified luteal phase support after GnRHa trigger, using a bolus of hCG to compensate for the LH activity deficiency during the early luteal phase seen after GnRHa trigger and, thus, dissociating the ovulation trigger from the luteal support.

Humaidan et al, Hum Reprod 2013;28(9):2511-21.

hCG: an old innovation?



Hum Reprod. 1990 Apr;5(3):271-3.

A prospective randomized trial of human chorionic gonadotrophin or dydrogesterone support following in-vitro fertilization and embryo transfer.

Kupferminc MJ[1], Lessing JB, Amit A, Yovel I, David MP, Peyser MR.

Obstet Gynecol. 1992 Jun;79(6):983-7.

Luteal phase support with hCG does not improve fecundity rate in human menopausal gonadotropin-stimulated cycles.

Keenan JA[1], Moghissi KS.

Hum Reprod. 1993 Sep;8(9):1372-5.

Human chorionic gonadotrophin is a better luteal support than progesterone in ultrashor gonadotrophin-releasing hormone agonist/menotrophin in-vitro fertilization cycles.

Golan A[1], Herman A, Soffer Y, Bukovsky I, Caspi E, Ron-El R.

J Assist Reprod Genet. 1994 Feb;11(2):74-8.

Prospective randomized comparison of human chorionic gonadotropin versus intramuscular progesterone for luteal-phase support in assisted reproduction.

Araujo E Jr[1], Bernardini L, Frederick JL, Asch RH, Balmaceda JP.

Progesterone vs. Progesterone + hCG
Caligara 2007
Fujimoto 2002
Geber 2007
Ludwig 2001
Macrolin 1993
Ugur 2001
Wong 1990

Progesterone vs. hCG
Albert 1991
Artini 1995
Golan 1993
Humaidan 2006
Kupferminc 1990
Lam 2008
Loh 1996
Ludwig 2001
Martinez
Ugur 2001
Vimpeli 2001

van der Linden et al, Cochrane Database Sist Rev. 2015 Jul 7;(7):CD009154.

Progesterone vs. hCG
Progesterone vs. Progesterone + hCG

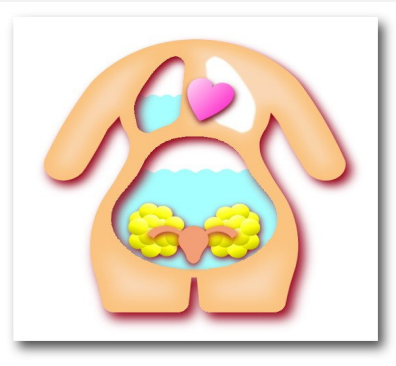
NO DIFFERENCES

- ✓ Live birth / ongoing PR
- ✓ Clinical PR
- ✓ Miscarriage
- ✓ Multiple pregnancy

OHSS:

- ✓ Progesterone was associated with lower rates of OHSS rates than hCG with or without progesterone (OR 0.46, 95% CI 0.30 to 0.71, 5 RCTs, 1293 women).

The use of hCG should therefore be avoided?



van der Linden et al, Cochrane Database Sist Rev. 2015 Jul 7;(7):CD009154.

Progesterone vs. hCG
Progesterone vs. Progesterone + hCG

- ✓ The average levels of hCG range between 40 and 80 IU/l during the entire length of the luteal phase.
- ✓ This is around ten times higher than the LH concentration observed during the natural menstrual cycle (i.e. 4–10 IU/l).

- ✓ It is therefore not surprising that the incidence of OHSS was increased.

Andersen et al, J Assist Reprod Genet 2016;33(10):1311-1318.

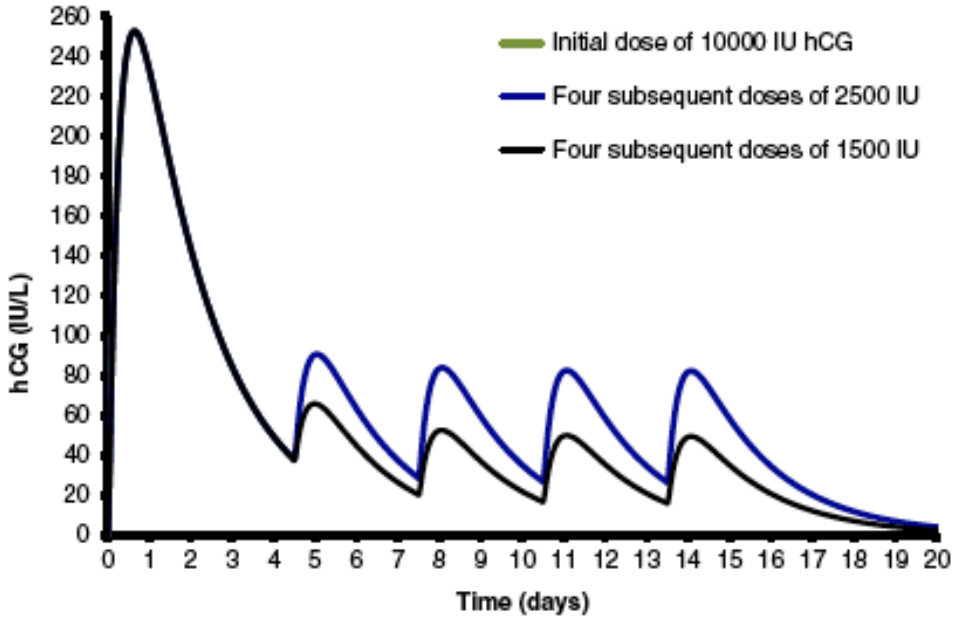
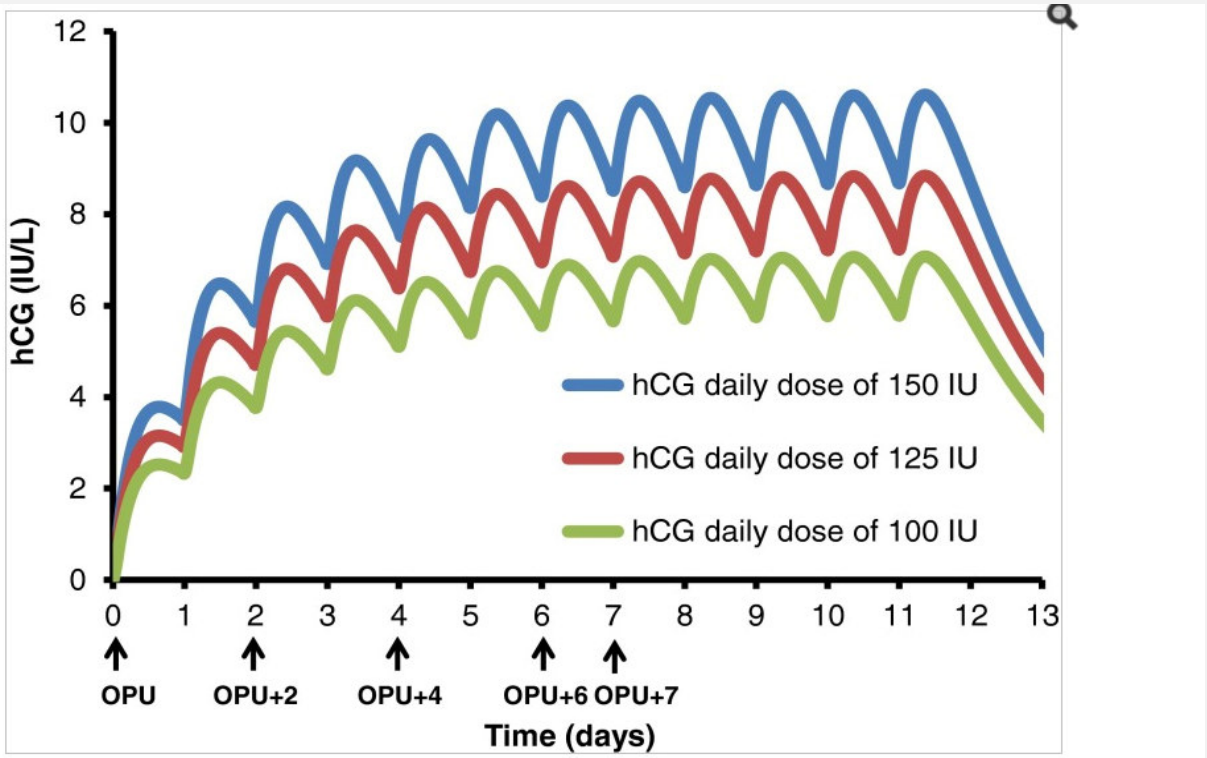


Fig. 1 hCG dose of 1500 IU or 2500 IU four times. The *graph* represents the circulatory concentrations of hCG after exogenous hCG administration of 10,000 IU hCG followed by four administrations of either 1500 or 2500 IU of hCG during the luteal phase. Data are calculated based on the information from exogenous administration of 250-μg recombinant hCG [17], fitted to represent a fit to a pharmacokinetic model with first-order absorption and linear elimination including a lag time

hCG: new ways



hCG doses of 100 IU, 125 IU or 150 IU daily. The *graph* represents the circulatory concentrations of hCG after use of the GnRHa trigger for the final maturation of follicles (devoid of hCG activity) followed by daily administration of either 100, 125 or 150 IU hCG throughout the luteal phase. The calculated concentration of hCG on day OPU + 7 is ≈6 IU/l, ≈8 IU/l, ≈9.5 IU/l. For data calculation, see legend to Fig. 1.
Legend: *OPU* oocyte pick up

The ultimate goal may be to develop a long-acting hCG variant in connection with the GnRHa trigger that can provide a constant low level of hCG in the physiological range throughout the luteal phase, potentially providing a new alternative LPS.

Andersen et al, J Assist Reprod Genet 2016;33(10):1311-1318.

LPS: new ways

'Luteal coasting' after GnRH agonist trigger – individualized, HCG-based, progesterone-free luteal support in 'high responders': a case series

Shahar Kol [a,*], Tatiana Breyzman [a], Linoy Segal [b], Peter Humaidan [c]

GnRHa trigger and luteal coasting: a new approach for the ovarian hyperstimulation syndrome high-risk patient?

Barbara Lawrenz [a,b,], Peter Humaidan [c], Shahar Kol [d], Human M Fatemi [a]*

- ✓ Daily monitoring of serum progesterone concentrations.
- ✓ 1500 HCG rescue bolus once progesterone concentrations drop below 30 nmol/l.

The basic principle of this new concept – 'luteal coasting'– is to closely monitor the individual luteolytic process after GnRHa trigger in terms, and to intervene with an HCG rescue bolus when the process is firmly underway, but well before total and irreversible luteolysis has occurred.

GnRH agonist

GnRH	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-Gly^{6}-Leu^{7}-Arg^{8}-Pro^{9}-Gly^{10}- NH_2
Agonists	
Buserelin	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-D-Ser(tBu) ^{6}-Leu^{7}-Arg^{8}-Pro^{9} - NHEt
Goserelin	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-D-Ser(tBu) ^{6}-Leu^{7}-Arg^{8}-Pro^{9} AzaGly^{10}- NH_2
Leuprolide	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-D-Leu^{6}-Leu^{7}-Arg^{8}-Pro^{9}- NHEt
Triptorelin	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-D-Trp^{6}-Leu^{7}-Arg^{8}-Pro^{9}-Gly^{10}-NH_2

Preparations avalaible

Leuprolide

Triptorelin

Buserelin

Nafarelin

GnRHa addition to LPS. Background:

OVARY

- ✓ GnRHa would restore significant serum LH levels which would be of proven benefit since, beyond maintaining progesterone and E2 levels, this would stimulate other peptides secreted by the corpus luteum, such as relaxin (Loumaye et al., 1984).

ENDOMETRIUM

- ✓ A direct beneficial effect of LH on the endometrium which include stimulation of angiogenic and growth factors, as well as cytokines involved in implantation (Licht et al., 2001; Stewart, 2001; Rao et al., 2002; Tesarik et al., 200).
- ✓ Both GnRH and GnRHR are expressed in vivo by the human endometrium throughout the menstrual cycle, with an increase during the luteal phase (Raga et al., 1998).

Pirard et al, Hum Reprod 2006;21(7):1894-900.
Maggi et al, Hum Reprod Update 2015;22(3).

GnRH agonist

GnRH	pGlu^{1}-His^{2}-Trp^{3}-Ser^{4}-Tyr^{5}-Gly^{6}-Leu^{7}-Arg^{8}-Pro^{9}-Gly^{10}- NH_2
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Preparations avalaible

Leuprolide

Triptorelin

Buserelin

Nafarelin

GnRHa addition to LPS. Background:

ENDOMETRIUM

- ✓ Locally expressed GnRH peptides may regulate the proteolytic degradation of the extracellular matrix of the endometrial stroma and the motility of decidual endometrial stromal cells, which are crucial processes for trophoblast invasion of the maternal endometrium and for embryo implantation (Wu et al., 2009; Yu et al., 2011).

EMBRYO

- ✓ GnRH and GnRHR are expressed at the mRNA level in vitro in cultured mouse embryos during the preimplantation development period (morula to hatching blastocyst stages).
- ✓ Immunoreactive GnRH in the cytotrophoblast of prehatched blastocyst and in the placental cytotrophoblast (Raga et al., 1999).

Pirard et al, Hum Reprod 2006;21(7):1894-900.
Maggi et al, Hum Reprod Update 2015;22(3).

Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles

Table II. Luteal-phase characteristics of patients treated with the long GnRH agonist ovarian stimulation protocol

Characteristics	Patient group[a]	
	Luteal-phase GnRH agonist	Placebo
Serum estradiol (pg ml^{-1})		
Day 7 after ICSI	432 ± 63	418 ± 58
Day 15 after ICSI	480 ± 74[c]	462 ± 71
Serum progesterone (ng ml^{-1})		
Day 7 after ICSI	44 ± 5[c]	39 ± 5
Day 15 after ICSI	47 ± 7[c]	43 ± 6
Serum HCG (IU l^{-1})		
Day 15 after ICSI		
In all conception cycles[b]	66 ± 8[c]	42 ± 7
In singleton pregnancies	53 ± 6[c]	34 ± 5

Values are mean ± SD.
[a]Group of patients having terminated the study ($n = 283$).
[b]Only cycles that resulted in a clinical pregnancy are included.
[c]Significantly different from the placebo group ($P < 0.05$).

Table V. Luteal-phase characteristics of patients treated with the GnRH antagonist ovarian stimulation protocol

Characteristics	Patient group[a]	
	Luteal-phase GnRH agonist	Placebo
Serum estradiol (pg ml^{-1})		
Day 7 after ICSI	405 ± 52[c]	372 ± 48
Day 15 after ICSI	420 ± 56[c]	408 ± 46
Serum progesterone (ng ml^{-1})		
Day 7 after ICSI	42 ± 8[c]	29 ± 7
Day 15 after ICSI	48 ± 9[c]	41 ± 7
Serum HCG (IU l^{-1})		
Day 15 after ICSI		
In all conception cycles[b]	64 ± 9[c]	41 ± 7
In singleton pregnancies	50 ± 6[c]	32 ± 5

Values are mean ± SD.
[a]Group of patients having terminated the study ($n = 289$).
[b]Only cycle that resulted in a clinical pregnancy are included.
[c]Significantly different from the placebo group ($P < 0.05$).

Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian

Table III. Clinical outcomes of patients treated with the long GnRH agonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Intention to treat	150	150
Transfer procedures	141	142
Embryos transferred	325	330
Embryos per transfer[a]	2.3 ± 0.5 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer[a]	2.0 ± 0.4	2.0 ± 0.5 (2.0)
Clinical pregnancy rate		
Per embryo transfer	51.1% (72/141)	41.5% (59/142)
Per intention to treat	48.0% (72/150)	39.3% (59/15
Clinical implantation rate	29.8% (97/325)[b]	18.2% (60/330)
Ongoing pregnancy rate		
Per embryo transfer	46.8% (66/141)	38.0% (54/142)
Per intention t…at	44.0% (66/150)	36.0% (54/150)
Live birth rate	27.4% (89/325)[b]	18.2% (60/330)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

Table VI. Clinical outcomes of patients treated with the GnRH antagonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Transfer procedures	145	144
Embryos transferred	317	328
Embryos per transfer[a]	2.2 ± 0.4 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer	1.9 ± 0.4 (2.0)	2.0 ± 0.4 (2.0)
Clinical pregnancy rate		
Per embryo transfer	47.6% (69/145)	37.5% (54/144)
Per intention to treat	46.0% (69/150)	36.0% (54/150)
Clinical implantation rate	27.1% (86/317)[b]	17.4% (57/328)
Ongoing pregnancy rate		
Per embryo transfer	44.8% (65/145)[b]	31.9% (46/144)
Per intention …eat	43.3% (65/150)[b]	30.7% (46/150)
Live birth rate	25.2% (80/317)[b]	14.6% (48/3328)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

human reproduction update

Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis

NO STOP GnRHa

D. Kyrou[1,*], E.M. Kolibianakis[1], H.M. Fatemi[2], T.B. Tarlatzi[1], P. Devroey[2], and B.C. Tarlatzis[1]

2011

Study or Subgroup	Favours control Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
1.3.1 Agonist							
Fujii	65	161	47	158	15.6%	0.11 [0.00, 0.21]	2001
Tesarik a	72	150	59	150	14.1%	0.09 [-0.03, 0.20]	2006
Isikoglou	44	90	45	91	9.4%	-0.01 [-0.15, 0.14]	2007
Ata	122	285	120	285	21.6%	0.01 [-0.07, 0.09]	2008
Razieh	23	90	9	90	14.6%	0.16 [0.05, 0.26]	2009
Subtotal (95% CI)		**776**		**774**	**75.2%**	**0.07 [0.01, 0.13]**	
Total events	326		280				
Heterogeneity: Tau² = 0.00; Chi² = 6.36, df = 4 (P = 0.17); I² = 37%							
Test for overall effect: Z = 2.28 (P = 0.02)							
1.3.2 Antagonist							
Tesarik b	69	150	54	150	14.3%	0.10 [-0.01, 0.21]	2006
Isik	30	82	16	80	10.4%	0.17 [0.03, 0.30]	2009
Subtotal (95% CI)		**232**		**230**	**24.8%**	**0.13 [0.04, 0.21]**	
Total events	99		70				
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%							
Test for overall effect: Z = 2.88 (P = 0.004)							
Total (95% CI)		**1008**		**1004**	**100.0%**	**0.08 [0.03, 0.13]**	
Total events	425		350				
Heterogeneity: Tau² = 0.00; Chi² = 8.30, df = 6 (P = 0.22); I² = 28%							
Test for overall effect: Z = 3.35 (P = 0.0008)							
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.1%							

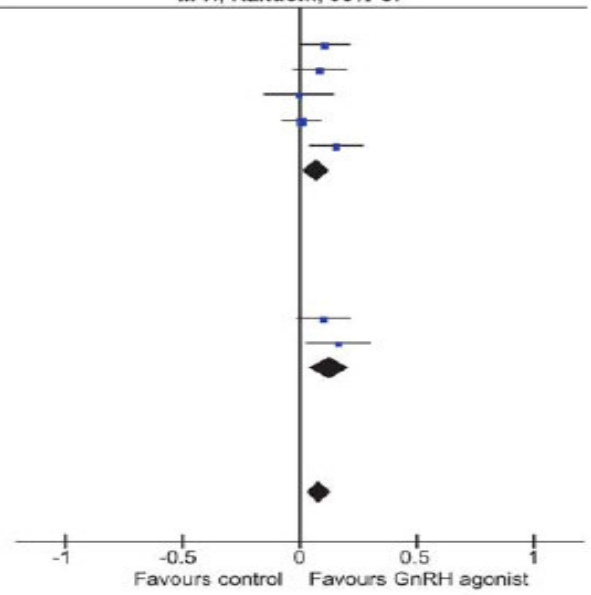


Figure 2 Forest plot clinical pregnancy.

human reproduction update

Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis

NO STOP GnRHa

D. Kyrou[1,*], E.M. Kolibianakis[1], H.M. Fatemi[2], T.B. Tarlatzi[1], P. Devroey[2], and B.C. Tarlatzis[1]

2011

Study or Subgroup	GnRH Agonist Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
1.1.1 Agonist							
Fujii	73	161	44	158	24.2%	0.17 [0.07, 0.28]	2001
Tesarik a	89	150	60	150	21.8%	0.19 [0.08, 0.30]	2006
Isikoglou	34	90	32	91	14.7%	0.03 [-0.11, 0.17]	2007
Subtotal (95% CI)		**401**		**399**	**60.7%**	**0.14 [0.05, 0.23]**	
Total events	196		136				
Heterogeneity: Tau² = 0.00; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%							
Test for overall effect: Z = 2.96 (P = 0.003)							
1.1.2 Antagonist							
Tesarik b	80	150	48	150	22.4%	0.21 [0.10, 0.32]	2006
Isik	26	82	13	80	16.9%	0.15 [0.03, 0.28]	2009
Subtotal (95% CI)		**232**		**230**	**39.3%**	**0.19 [0.11, 0.27]**	
Total events	106		61				
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%							
Test for overall effect: Z = 4.44 (P < 0.00001)							
Total (95% CI)		**633**		**629**	**100.0%**	**0.16 [0.10, 0.22]**	
Total events	302		197				
Heterogeneity: Tau² = 0.00; Chi² = 4.83, df = 4 (P = 0.31); I² = 17%							
Test for overall effect: Z = 5.53 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%							

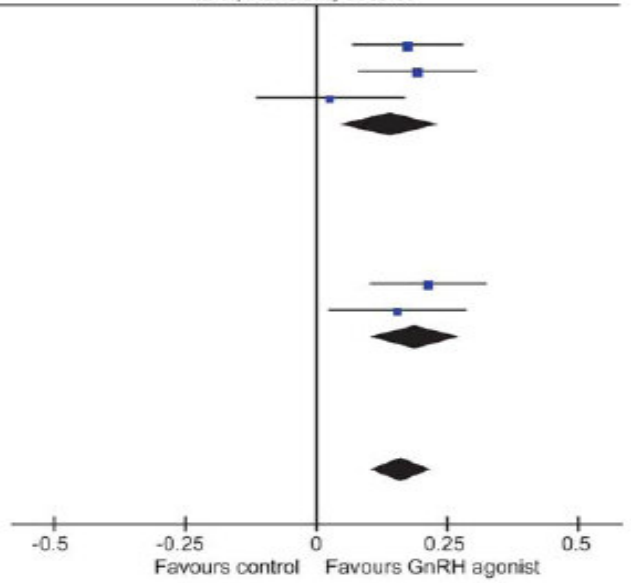


Figure 1 Forest plot live birth.

Table I Characteristics of the RCTs included in the meta-analysis.

Study/ Journal/ Number of centres	Study period	Randomization method/allocation concealment	GnRH analogue/ protocol	Gonadotrophin type/starting dose-adjustment	hCG	Criteria of hCG administration	OR	Fertilization	Embryo transfer day	Embryo transfer policy	LPS	LPS with GnRH agonist in the study group
Fujii *et al.* (2001)/Hum Reprod/ Single centre	February 1997–March 1999	Patient's identification number/not reported	Buserelin/ long agonist	Pure FSH/225–150 IU after 2 days	5000 IU uhCG	Mean follicular diameter 18 mm	34–36 h	IVF/ICSI	Days 2 or 3	<4 embryos	Dydrogesterone 10 mg/day for 14 days starting on the day of embryo transfer and 2500 IU IM hCG on the day of embryo transfer	GnRH agonist during the luteal phase until 14 days after OR
Tesarik *et al.* (2006)/Hum Reprod/ Single centre	September 2003–September 2005	Computer-generated randomization list/ sealed envelopes	Tesarik a Triptorelin/ long agonist Tesarik b Ganirelix or Cetrorelix acetate/ antagonist fixed Day 5	rFSH or HMG/not reported-according to E_2 and LH levels	250 g rhCG	At least three follicles ≥18 mm	Not reported	ICSI	Day 3	1–3 embryos	400 mg progesterone and 4 g E_2 daily from day of OR for 17 days Additionally 250 µg rhCG on the day of embryo transfer	Single dose triptorelin 6 days after ICSI
Isikoglu *et al.* (2007)/ Journal of Reprod Med/ Single centre	Not reported	Computer-generated randomization list/not reported	Leuprolide acetate/long agonist	HMG/ 150–450 IU according to the ovarian reserve	10 000 IU uhCG	At least two follicles >17 mm	35 h	ICSI	Day 2	>4 embryos	Progesterone 50 g/ d IM	GnRH agonist during the luteal phase until 14 days after OR
Ata *et al.* (2008)/Hum Reprod/ Single centre	September 2006–July 2007	Computer-generated randomization list/ sealed envelopes	Triptorelin/ long agonist	rFSH /150–300 IU according to E_2 levels and follicular development	10 000 IU uhCG	Leading follicle 20 mm accompanied by ≥2 follicles >16 mm	36 h	ICSI	Day 3	1–3 embryos	Progesterone	Single dose Triptorelin 6 days after ICSI
Razieh *et al.* (2009)/ Taiwan J Obstet Gynecol/ Single centre	Not reported	Randomization table/ sealed envelopes	Buserelin/ long agonist	rFSH/ 150–225 IU Not reported	10 000 IU uhCG	At least two follicles ≥18 mm	34–36 h	ICSI	Days 2 or 3	2 or 3 embryos	Progesterone 800 mg/day	Single dose Triptorelin 6 days after ICSI
Isik *et al.*(2009)/ RBM online/ Single centre	January 2005–September 2005	Computer-generated random table/not reported	Ganirelix or Cetrorelix acetate/ antagonist flexible	rFSH or HMG/not reported according to the patients response	10 000 IU uhCG or 250 µg rhCG	At least three follicles ≥17 mm	35 h	ICSI	Day 3	1–5 embryos	Progesterone 600 mg/day for 17 days and 2500 IU IM hCG on the day of embryo transfer additionally 1500 IU hCG on Day 8 after ICSI	Single dose 0.5 mg Leuprolide acetate 6 days after ICSI

IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; OR, oocyte retrieval; ET, embryo transfer; hCG, human chorionic gonadotrophin; uhCG, urinary human chorionic gonadotrophin; rhCG, recombinant human chorionic gonadotrophin; GnRH, gonadotrophin-releasing hormone; rFSH, recombinant follicle-stimulating hormone; HMG, human menopausal gonadotrophin; IM, intramuscularly; LPS, luteal phase support.

Extension of GnRH agonist through the luteal phase

Hum Reprod. 2001 Aug;16(8):1671-5.

Continuous administration of gonadotrophin-releasing hormone agonist during the luteal phase in IVF.

Fujii S[1], Sato S, Fukui A, Kimura H, Kasai G, Saito Y.

CONCLUSIONS: Continuation of GnRH agonist administration during the luteal phase might facilitate implantation, and prevent the profound suppression of serum gonadotrophins.

J Reprod Med. 2007 Jul;52(7):639-44.

Extension of GnRH agonist through the luteal phase to improve the outcome of intracytoplasmic sperm injection.

Isikoglu M[1], Ozgur K, Oehninger S.

CONCLUSION: Extending GnRHa treatment through the luteal phase appeared not to have a significant impact on pregnancy or implantation rates in intracytoplasmic sperm injection cycles.

Reprod Biomed Online. 2015 Jan;30(1):52-6. doi: 10.1016/j.rbmo.2014.09.017. Epub 2014 Oct 13.

GnRH agonist plus vaginal progesterone for luteal phase support in ICSI cycles: a randomized study.

Aboulghar MA[1], Marie H[2], Amin YM[3], Aboulghar MM[2], Nasr A[4], Serour GI[3], Mansour RT[3].

Subcutaneous GnRHa during the luteal phase of long GnRHa protocol cycles does not increase clinical or ongoing pregnancy rates after IVF-ICSI.

PRODUCT MONOGRAPH

PrDECAPEPTYL®

Triptorelin Acetate Injection

0.1 mg/mL

Luteinizing Hormone-Releasing Hormone (LHRH) Analog

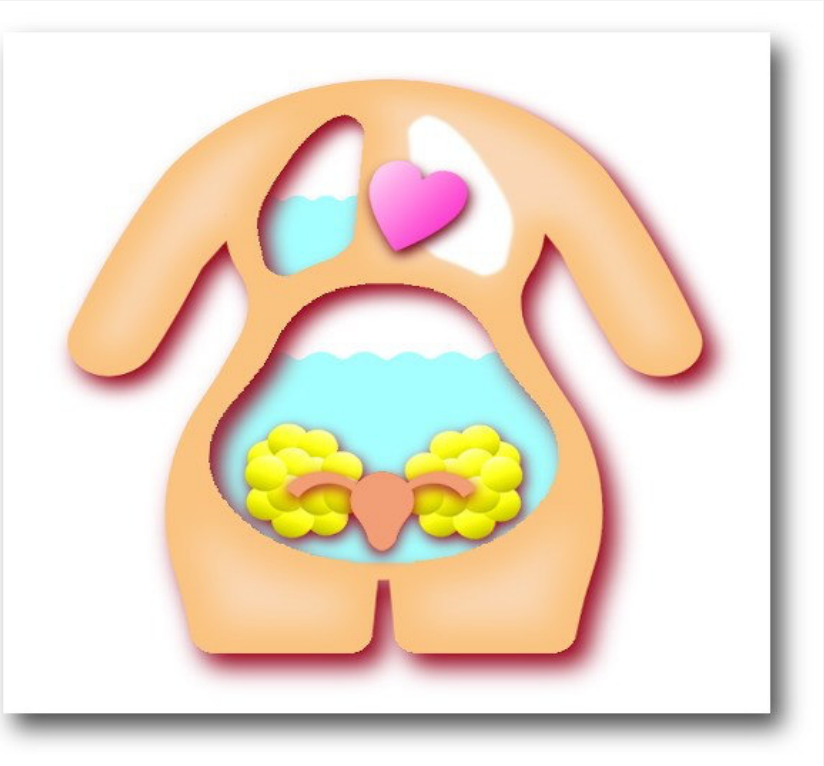
Pharmacodynamics

Continuous administration of triptorelin has a biphasic effect at the pituitary level. After an initial large sudden increase in LH and FSH levels (flare-up), circulating LH and FSH levels decrease due to the pituitary GnRH-receptor desensitization, with a consequent marked reduction in the gonadal production. The exact duration of action of DECAPEPTYL has not been established, but pituitary suppression is maintained for at least 6 days after stopping administration. After discontinuation of DECAPEPTYL, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.

Pharmacokinetics

The pharmacokinetic data suggest that after subcutaneous administration of DECAPEPTYL the systemic bioavailability of triptorelin is close to 100%. The elimination half-life of triptorelin is approximately 3-5 hours, indicating that triptorelin is eliminated within 24 hours and therefore will not be present in circulation at the time of embryo transfer. Metabolism to smaller peptides and amino acids primarily occurs in the liver and kidneys. Triptorelin is predominantly excreted in the urine.

GnRHa Trigger



GnRHa to trigger final oocyte maturation: a time to reconsider

P. Humaidan[1,3], E.G. Papanikolaou[2], and B.C. Tarlatzis[2]

Current evidence seems to support the fact that the luteal phase in IVF/ICSI cycles in which final oocyte maturation was triggered with GnRHa can be rescued

- ✓ by either exogenous LH activity

(Humaidan et al. 2006, 2009)

- ✓ or endogenous LH activity

(Pirard et al., 2006)

resulting in a reproductive outcome comparable to that of hCG triggered final oocyte maturation.

GnRH agonist as sole luteal support

GnRH agonist as novel luteal support: results of a randomized, parallel group, feasibility study using intranasal administration of buserelin*

C.Pirard, J.Donnez[1] and E.Loumaye 2005

GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study

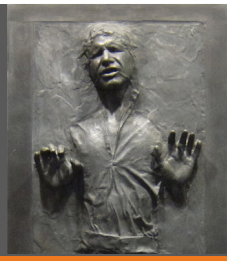
C.Pirard, J.Donnez[1] and E.Loumaye 2006

Contribution to More Patient-Friendly ART Treatment: Efficacy of Continuous Low-Dose GnRH Agonist as the Only Luteal Support—Results of a Prospective, Randomized, Comparative Study

2015 Céline Pirard,[1] Ernest Loumaye,[2] Pascale Laurent,[1] and Christine Wyns[1]

	Group A (buserelin 3x/day) n = 35	Group B (micronized progesterone 3x/day) n = 18	P
IR	11 (22%)	4 (15.4%)	NS
PR/ET	11 (31.4%)	4 (22.2%)	NS
CPR/ET	9 (25.7%)	3 (16.7%)	NS

GnRH agonist as sole luteal support



Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles

Itai Bar Hava, M.D.,[a] Moran Blueshtein, Ph.D.,[b] Hadas Ganer Herman, M.D.,[a] Yeela Omer, M.D.,[a] and Gila Ben David, M.D.[a]

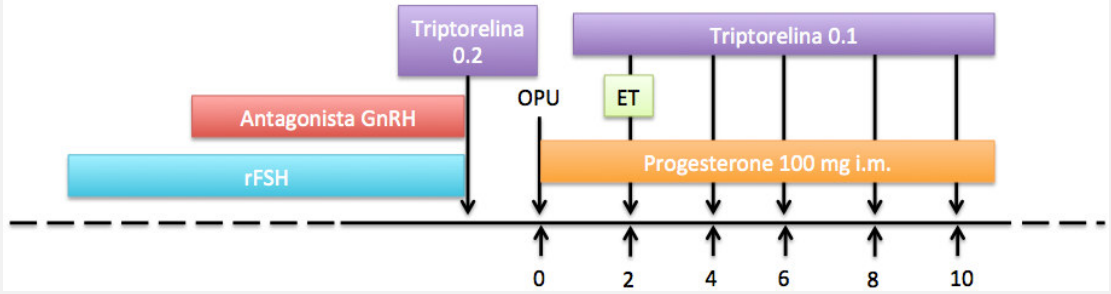
2017

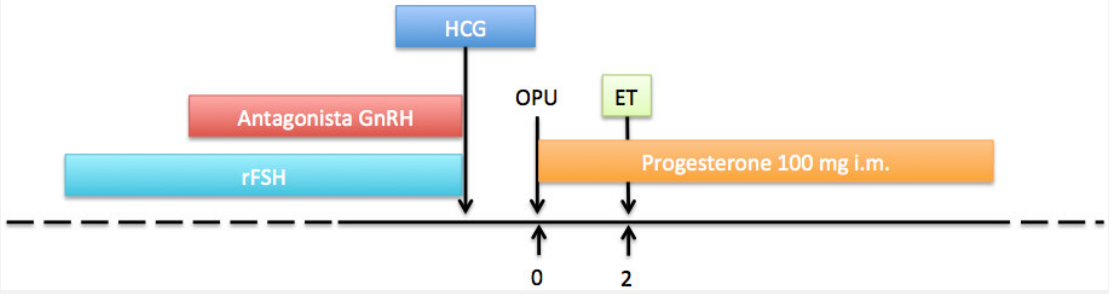
- ✓ Repeated intranasal GnRH-a for luteal phase support is associated with a higher live birth rate compared with standard P supplementations.

Regression results: the effect of GnRH agonist (GnRH-a) on positive β-hCG and live birth.

	Positive β-hCG			Live birth		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
GnRH-a (yes)	1.07	0.86–1.34	.52	1.46	1.10–1.94	.009
Age (y)	0.88	0.86–0.90	<.001	0.85	0.82–0.87	<.001
BMI (kg/m^2)	0.99	0.97–1.02	.94	0.97	0.94–1.001	.06
IVF cycle (n)	0.89	0.81–0.98	.02	0.88	0.78–0.99	.03
Children (n)	1.75	1.52–2.03	<.001	2.40	1.98–2.91	<.001
Previous pregnancies (n)	1.02	0.94–1.11	.49	0.95	0.84–1.07	.45
Oocytes retrieved (n)	1.02	1.007–1.04	.004	1.002	0.98–1.01	.80
Embryos transferred (n)	1.11	1.009–1.22	.03	1.10	0.97–1.25	.11


EXPERIENCE
30%
70%
BUSINESS PLAN
time
money
quality
USER
CLOUD
cost
quality
price
EXPENSES
INCOME





423

	Overall	<35 aa	35-39 aa	>39 aa
IR	14.2% vs 11.9%	19.4% vs 16.3%	13.2% vs 11.7%	5.2% vs 4.0%
CPR	30.1% vs 28.5%	38.4% vs 36.1%	30.4% vs 28.1%	10.5% vs 9.3%
OPR	26.9% vs 24.4%	34.8% vs 30.5%	26.1% vs 25.0%	10.5% vs 9.3%

BIOGENESI

	age	AH	AHT	ATT	
Retrieved oocytes (Mean + SD)	< 35	8.7+4.5	9.2+5.3	9.3+4.2	NS
	> 35	7.8+4.1	7.6+4.3	7.3+2.9	NS
Inseminated oocytes (Mean + SD)	< 35	5.2+2.1	5.3+2.4	4.2+1.4	NS
	> 35	5.7+2.9	5.9+2.6	6.1+2.4	NS
Embryos obtained (Mean + SD)	< 35	3.9+1.8	3.9+1.6	3.1+0.9	NS
	> 35	4.1+2.2	4.0+2.0	4.2+2.1	NS
Transferred embryos (Mean + SD)	< 35	1.7+0.6	1.7+0.6	1.5+0.7	NS
	> 35	2.2+0.6	2.2+0.7	2.3+0.7	NS

No significant differences between groups

Laboratoy data

- ✓ AH = Antagonist cycles with HCG as a trigger
- ✓ AHT= Antagonist cycles with HCG as a trigger and luteal triptorelin
- ✓ ATT= Antagonist cycles with triptorelin as a trigger and luteal triptorelin

Unpublished data

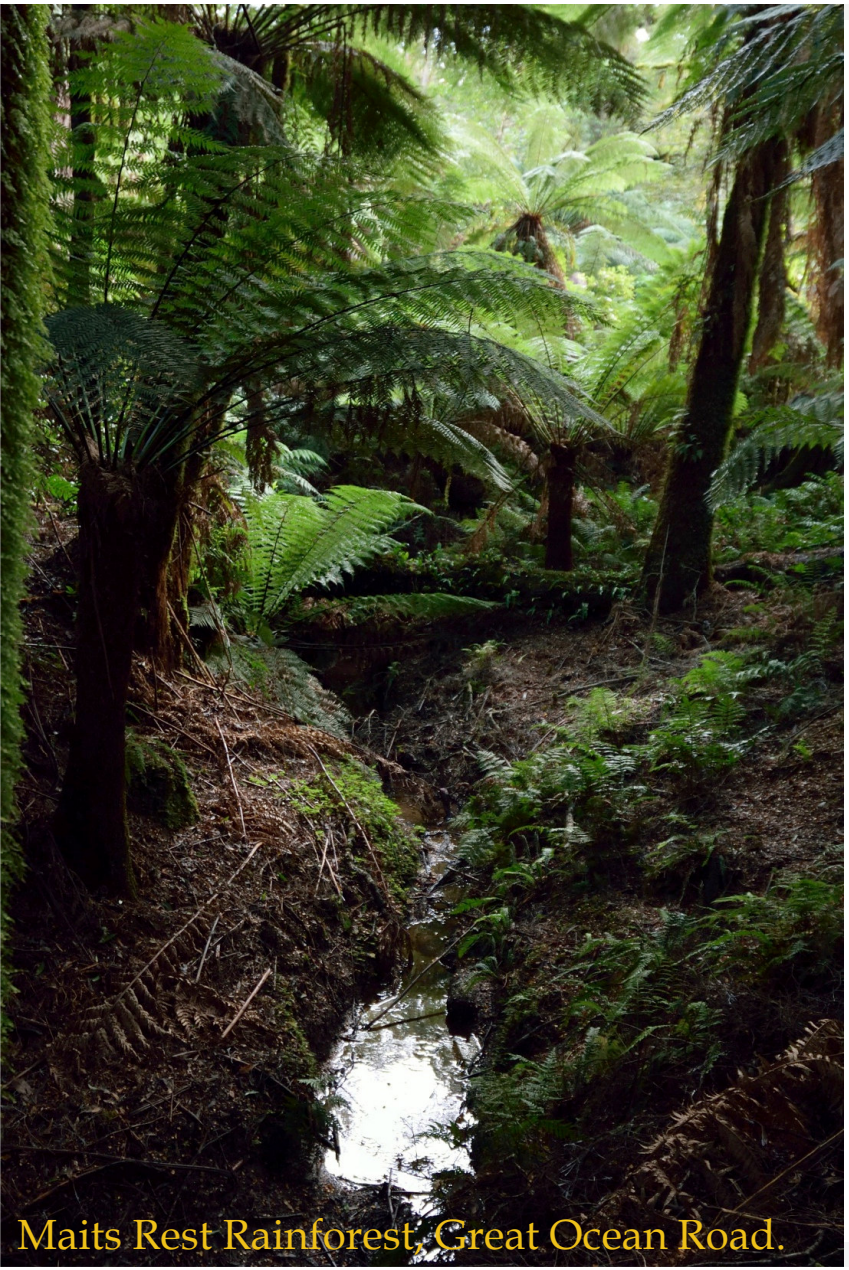
CMR BIOGENESI

Cumulative data		BP	PR	DR	IR	AR
No Triptorelin	< 35	87/279 (31,2%)	72/279 (25,8%)	66/279 (23,6%)	17,52%	24,1%
Triptorelin	< 35	168/507 (33,1%)	153/507 (30,1%)*	143/507 (28,2%)*	23,45%*	14,8%
No Triptorelin	> 35	71/241 (29,4%)	61/241 (25,3%)	54/241 (22,4%)	14,12%	23,9%
Triptorelin	> 35	104/317 (32,8%)	93/317 (29,3%)*	87/317 (27,4%)*	19,78%*	16,3%
No Triptorelin	Total patients	158/520 (30,3%)	133/520 (25,6%)	120/520 (23,1%)	15,6%	24,05%
Triptorelin	Total patients	272/824 (33%)	246/824 (29,8%)**	230/824 (27,9%)**	22,15%**	15,4%

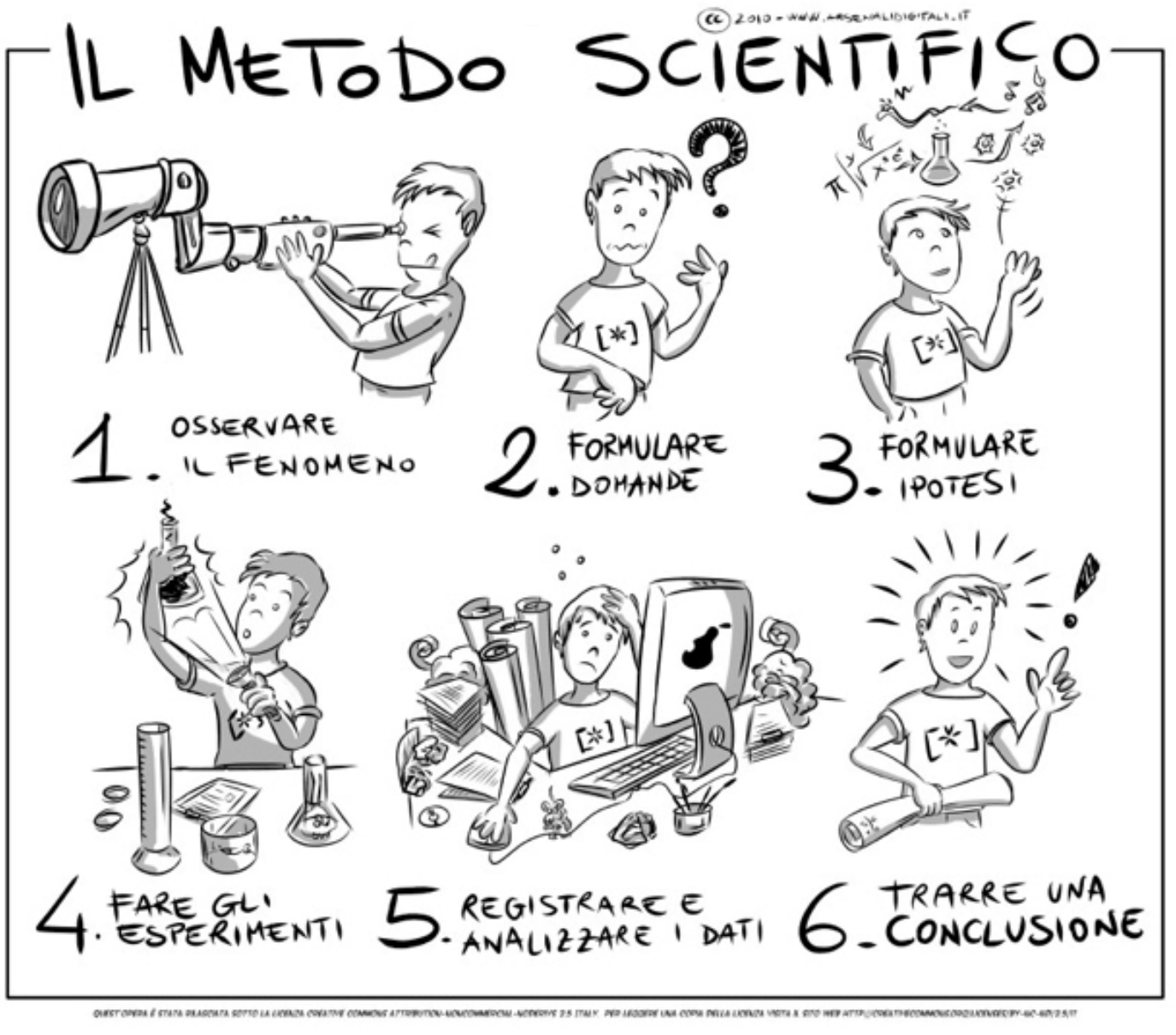
* P< 0,05 compared to the corresponding group with no luteal triptorelin

** p < 0,01 compared to the corresponding group with no luteal triptorelin

Unpublished data



Maits Rest Rainforest, Great Ocean Road.



ence based medicine

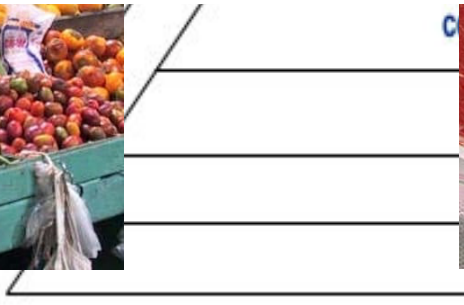
(Meta)analyze this: Systematic reviews might lose credibility

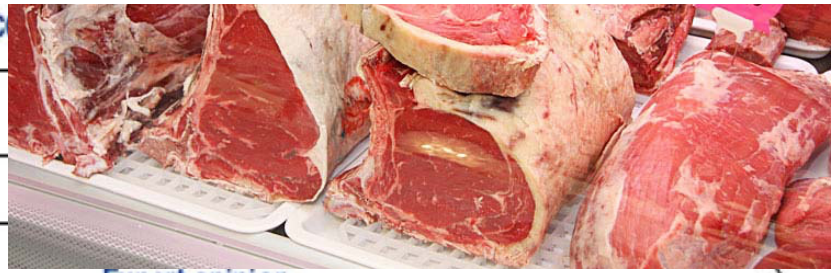
Peter Humaidan & Nikolaos P Polyzos

Peter Humaidan/Nikolaos P Polyzos

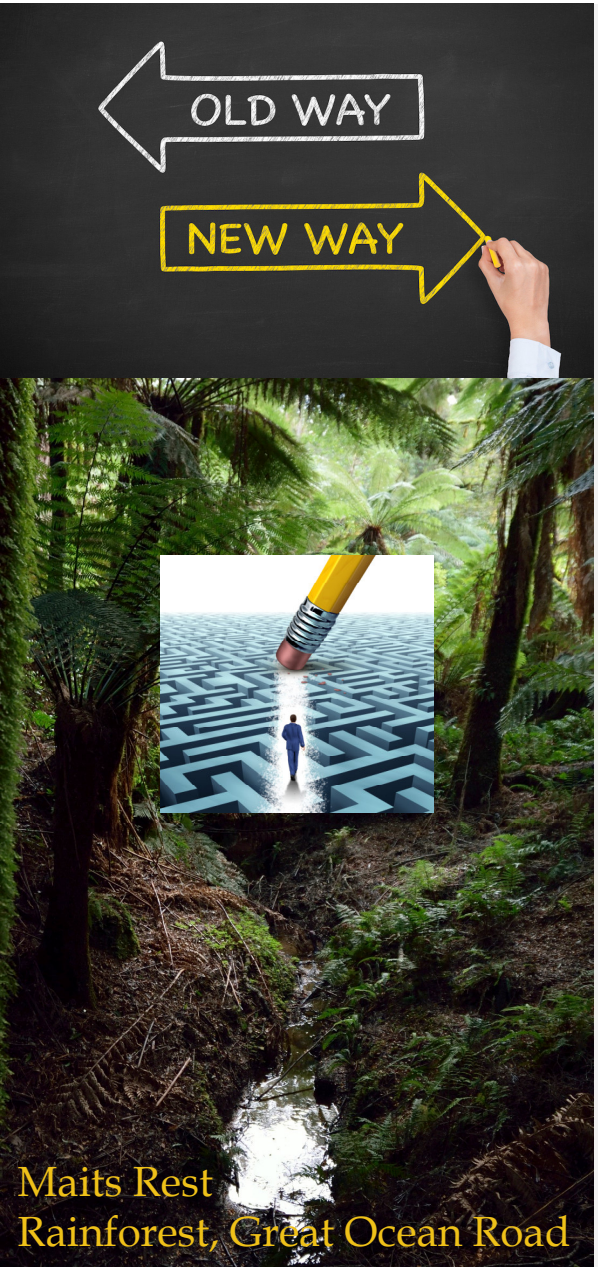
Doctors and regulatory agencies rely on meta-analyses when setting clinical guidelines and making decisions about drugs. However, as the number of these analyses increases, it's clear that many of them lack robust evidence from randomized trials, which may lead to the adoption of treatment modalities of ambiguous value. Without a more disciplined approach requiring a reasonable minimum amount of data, meta-analyses could lose credibility.

Maits Rest Rainforest, Great Ocean Road.

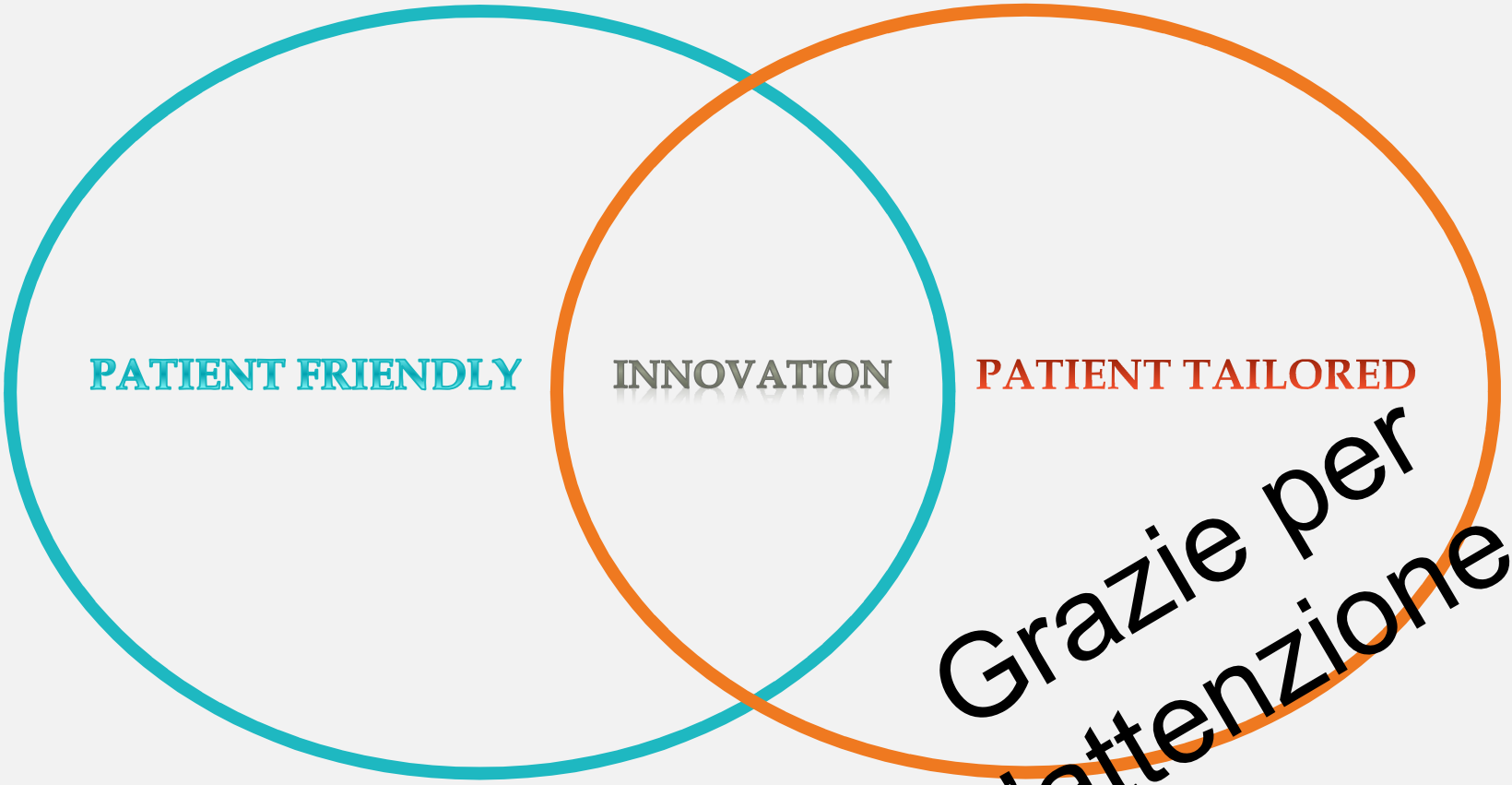




Expert opinion



INNOVATION IS TAKING A RISK ON A NEW APPROACH FOR AN OLD CHALLENGE



Grazie per l'attenzione