LUTEAL PHASE SUPPORT IN MODERN ART: THE "WHYs" AND THE "HOWs"

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Disclosures (past 3 years)

- Merck: Travel support, unrestricted research funding, honoraria, advisory boards
- Merck, Sharp & Dohme: Travel support, unrestricted research funding, honoraria, advisory boards
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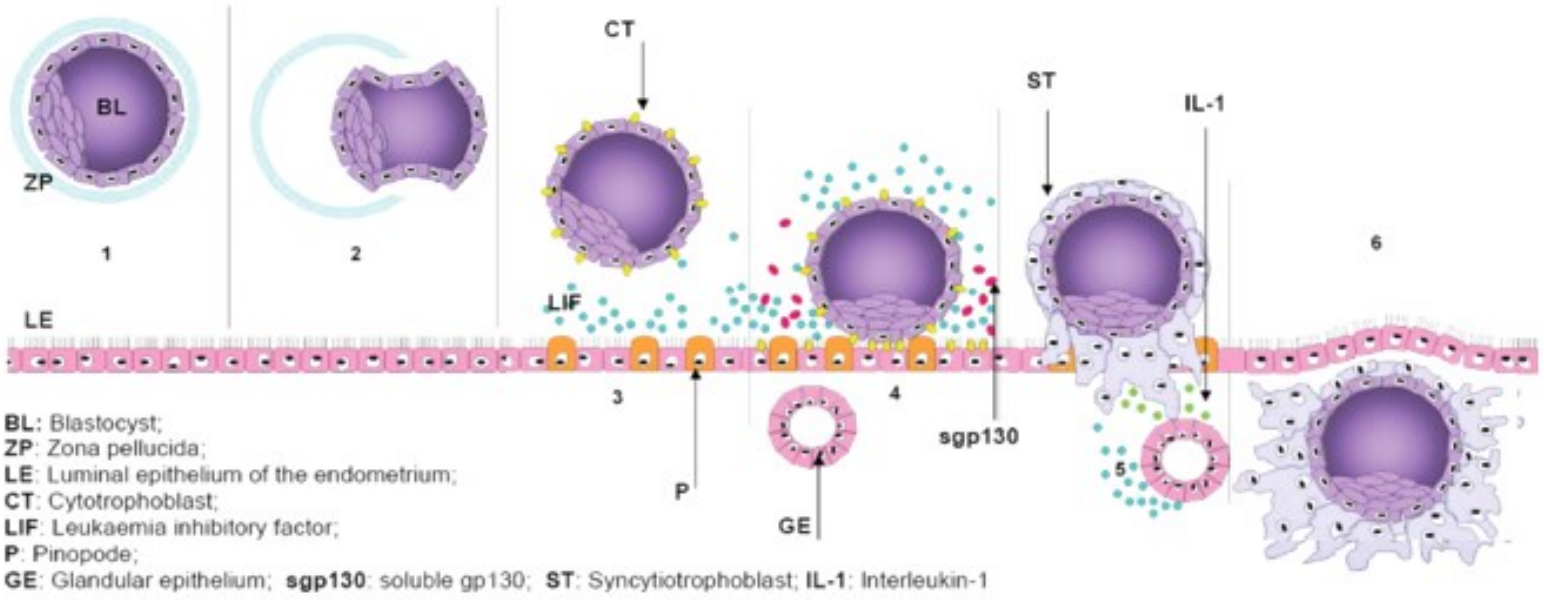
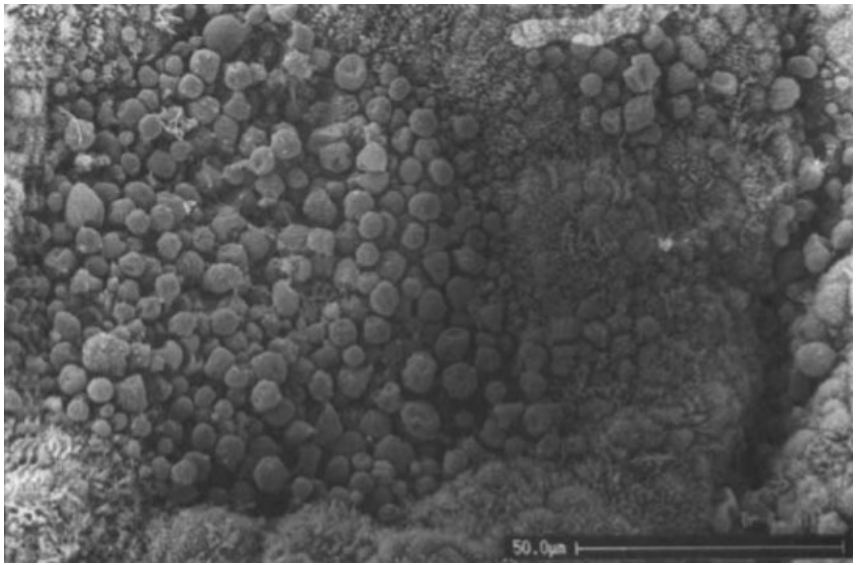
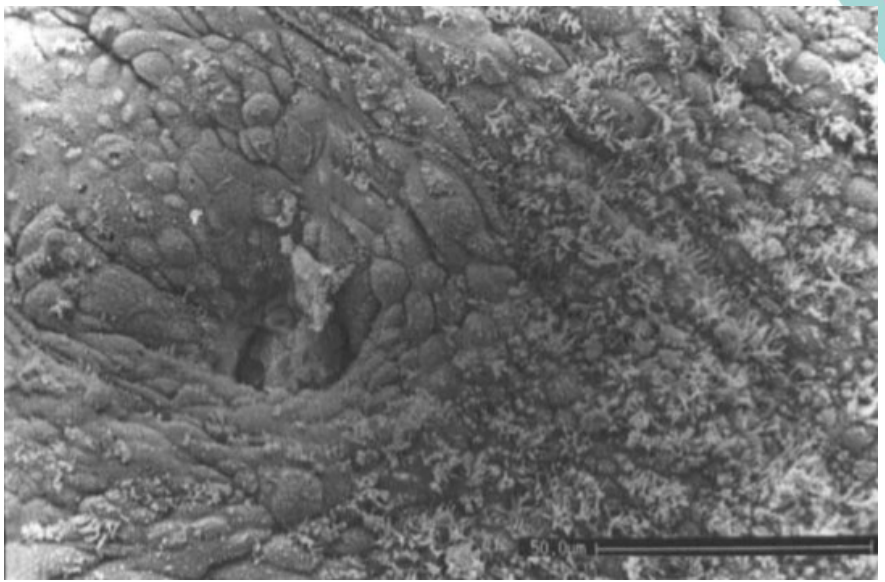
Implantation: The black box



Fitzgerald JS, et al. Hum Reprod Update. 2008;14:335-44.

Window of implantation



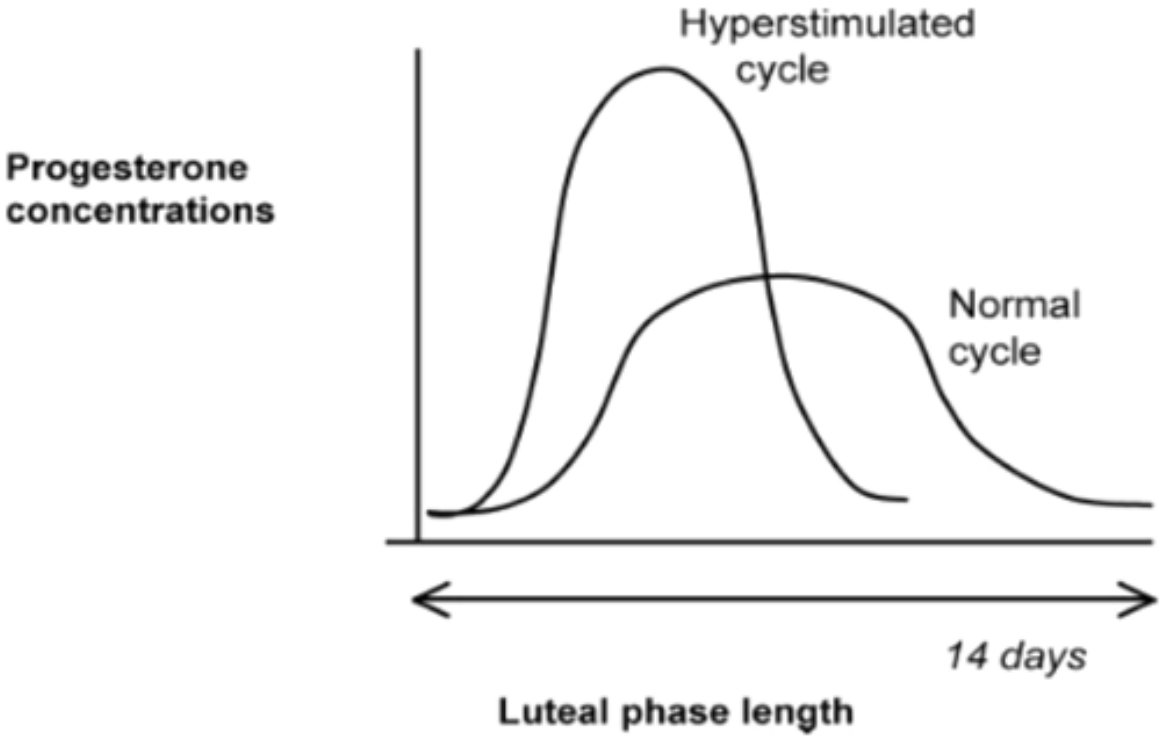


The appearance of pinopodes is dependent on P4

P4, progesterone.

Nikas G, Psychoyos A. Ann N Y Acad Sci. 1997;816:129-42.

Anything different in IVF?



IVF, in vitro fertilization.

Macklon NS, et al. Endocr Rev. 2006;27:170-207.

Inadequate P4 production after IVF

Why?

- Aspiration of the granulosa cells that surround the oocyte

Garcia et al., 1981

- Use of GnRH agonists

Smitz et al., 1988

- hCG administration

Miyake et al., 1979

- High E2 levels present following OPU

Tavaniotou et al., 2001

E2, estradiol; GnRH, gonadotrophin-releasing hormone; hCG, human chorionic gonadotropin; OPU, oocyte pick-up.

Garcia J, et al. Fertil Steril. 1981;36:565-72;
Smitz J, et al. Hum Reprod. 1988;3:585-90;
Miyake A, et al. J Endocrinol. 1979;80:353-6;
Tavaniotou A, et al Hum Reprod. 2001;4:663-7.

Inadequate P4 production after IVF: Why?

Aspiration of granulosa

Aspirating dominant follicle does not alter P4 in the luteal phase as compared to the natural cycle

Kerin et al., 1981

hCG administration can sufficiently support LP

GnRH agonists

Rapid recovery of luteal function with GnRH antagonists

Albano et al., 1996

GnRH antagonist administration also associated with LPD

Beckers et al., 2003

hCG administration

Administration of hCG did not downregulate LH secretion in unstimulated cycles

Tavaniotou et al., 2003

hCG administration can sufficiently support LP

High E2 levels

GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone; LP, luteal phase; LPD, luteal phase duration.

Kerin JF, et al. Br J Obstet Gynaecol. 1981;88:1021–8; Albano C, et al. Hum Reprod. 1996;11:2114-8; Beckers NG, et al. J Clin Endocrinol Metab. 2003; 88:4186–92; Tavaniotou A, Devroey P. Fertil Steril. 2003;80:654-5.

What if?

Helen 32 years old

Tubal factor infertility – for IVF

Stimulated with **125 IU** Gonal F + Cetrorelix, and after 10 days of stimulation she is triggered with 250 mcg Ovidrel

On trigger day her hormone levels are:

1) E2: 1075 pmol/L
2) P4: 2.4 nmol/L
3) LH: 1.4 mIU/L

2 oocytes are collected

Does she need luteal phase support?

Luteal phase support: Why?

Reproductive BioMedicine Online (2016) ■■, ■■–■■

ELSEVIER

www.sciencedirect.com
www.rbmonline.com

ARTICLE

No need for luteal phase support in IVF cycles after mild stimulation: proof-of-concept study

Anna Pia Ferraretti *, Paul Devroey, M Cristina Magli, Luca Gianaroli

Patients (*n*)	15
Age (mean ± SD)	33.5 ± 2.6
FSH IU (mean ± SD)	450 ± 75
Oestradiol at HCG (pg/ml) (mean ± SD)	980 ± 250
Total oocytes collected *n* (mean ± SD)	82 (5.4 ± 2.9)
Inseminated eggs (*n*)	73
2 PN *n* (fertilization rate %)	62 (85)
Embryos on day 2 *n* (cleavage rate %)	61 (98)
Grade 1 embryos on the total number of embryos on days 3–5 (%)	36/55 (65)
Transferred embryos *n* (mean ± SD)	20 (1.2 ± 0.3)
Cryopreserved embryos (*n*)	21 (in 10 cycles)
Clinical pregnancies (*n*)	6
Implantation rate % (*n*)	30% (6/20)
Miscarriages (*n*)	0
Delivery rate % (*n*)	40 (6/15)

Ferrarretti AP, et al. Reprod Biomed Online. 2017;34:162-5.

Scenario

Helen 32 years old

Tubal factor infertility – for IVF

Stimulated with 200 IU Gonal F + Cetrorelix, and after 12 days of stimulation she is triggered with 250 mcg Ovidrel

On trigger day her hormone levels are:

1) E2: 6296 pmol/L
2) P4: 3.1 nmol/L
3) LH: 1.4 mIU/L

14 oocytes are collected.

Would you give her luteal phase support?

Important or not?

Progesterone is intimately related
to establishment and maintenance of early pregnancy
(Csapo et al., 1972 & 1978)

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OBSTETRICAL AND GYNECOLOGICAL SURVEY

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review

INDISPENSABILITY OF THE HUMAN CORPUS LUTEUM IN THE MAINTENANCE OF EARLY PREGNANCY LUTEECTOMY EVIDENCE

ARPAD I. CSAPO AND MARTTI PULKKINEN

Csapo AI, et al. Am J Obstet Gynecol. 1972;112:1061-7;
Csapo AI, Pulkkinen M. Obstet Gynecol Surv. 1978;33:69-81.

Scenario

Helen 32 years old

Tubal factor infertility – for IVF

What type of LPS would you prescribe?

What dose?

When to start?

If pregnant, when to stop?

LPS, luteal phase support.

The “hows” of luteal phase support in ART cycles

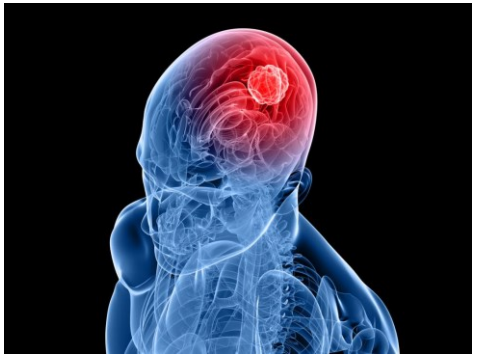
- What is the optimal medication (combination of medications) for luteal phase support?
- What is the optimal time for initiation of luteal phase supplementation?
- What should be the duration of luteal phase support in case of pregnancy?

ART, assisted reproductive technology.

Approaches to luteal phase support

Treating the symptom

Progesterone deficiency



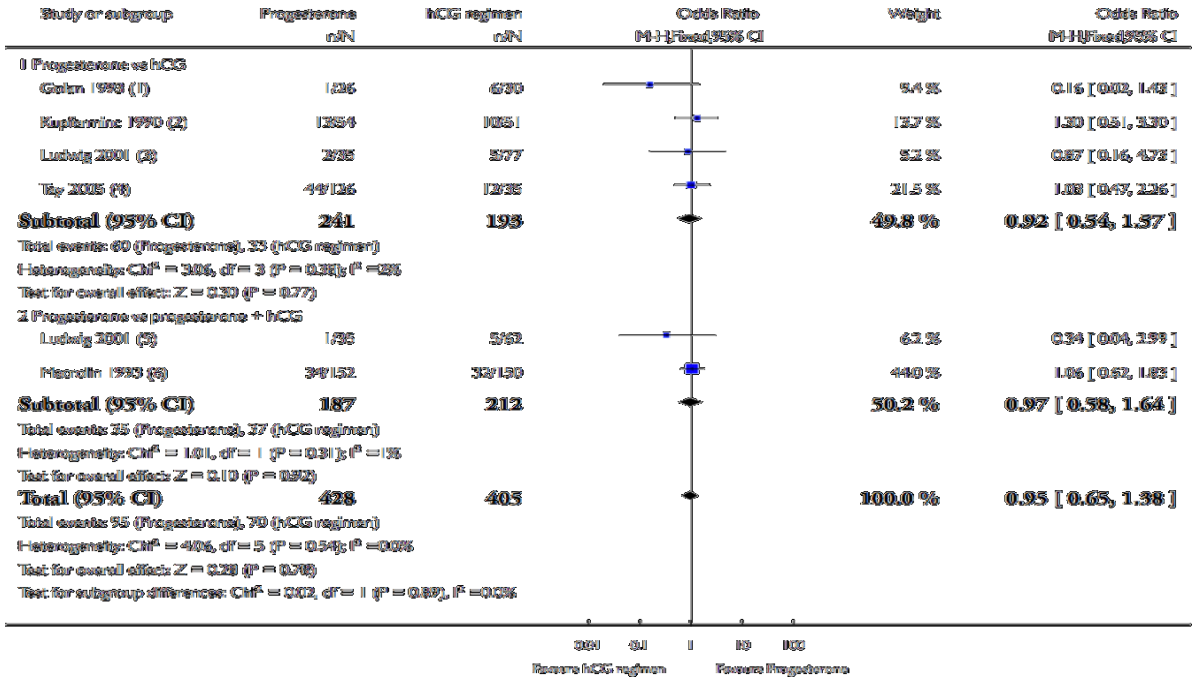
Treating the "disease"

Weak LH stimulation of CL

CL, corpus luteum.

Progesterone vs. hCG LPS

Live birth or ongoing pregnancy



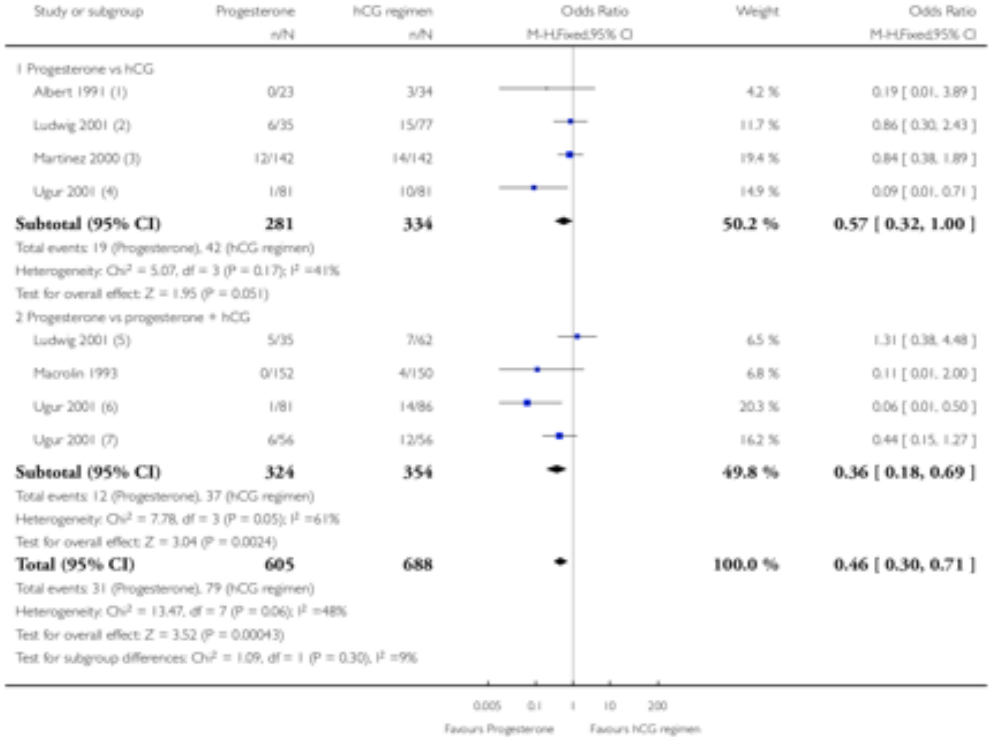
OR: 0.95 (0.65–1.38)

CI, confidence interval; M–H, Mantel–Haenszel.

van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154.

Progesterone vs. hCG LPS

OHSS



OR: 0.46 (0.30–0.71)

hCG LPS is associated with higher probability of OHSS

OHSS, ovarian hyperstimulation syndrome; OR, odds ratio.

van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154.

hCG for LPS

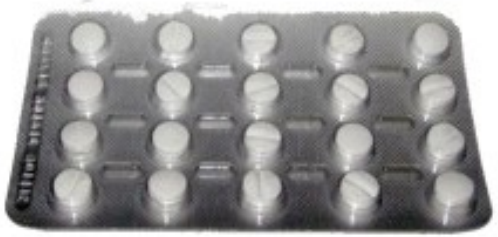
ICU, intensive care unit.

Progesterone vs. hCG LPS

- In ART cycles, progesterone administration seems to be equally efficacious* and safer than hCG for LPS

*In GnRH agonist triggered cycles, progesterone administration might not be adequate LPS

Progesterone regimens



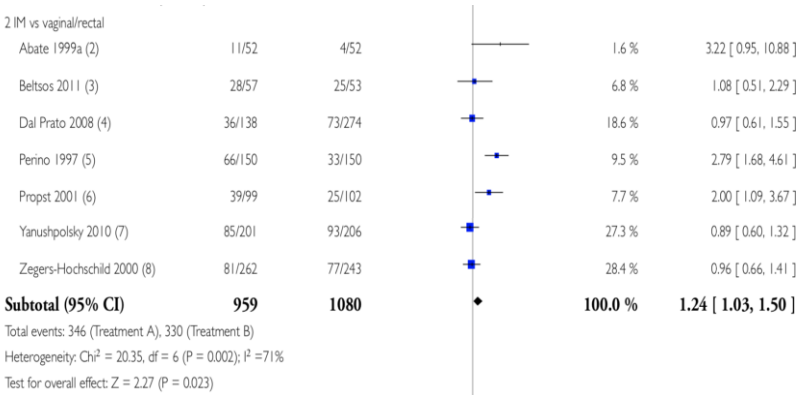
Progesterone for LPS

- Oral ingestion
  - Extensively metabolized; systemic side effects
- Intramuscular injection
  - Effective but inconvenient and sometimes very painful
- Rectal administration
  - Not widely accepted; minimal clinical trials
- Vaginal delivery
  - As effective as intramuscular injection; very low serum levels
  - Standard choice for luteal phase support

Gibbons WE, et al. Fertil Steril. 1998;69:96–101;
Ludwig M, Diedrich K. Acta Obs Gyn Scand. 2001;80:452-66;
Penzias AS. Fert Steril. 2002;77:318-23.

Intramuscular vs. vaginal/rectal

Live birth or ongoing pregnancy



2 IM vs vaginal/rectal				
Abate 1999a (2)	11/52	4/52	1.6 %	3.22 [0.95, 10.88]
Beltsos 2011 (3)	28/57	25/53	6.8 %	1.08 [0.51, 2.29]
Dal Prato 2008 (4)	36/138	73/274	18.6 %	0.97 [0.61, 1.55]
Perino 1997 (5)	66/150	33/150	9.5 %	2.79 [1.68, 4.61]
Propst 2001 (6)	39/99	25/102	7.7 %	2.00 [1.09, 3.67]
Yanushpolsky 2010 (7)	85/201	93/206	27.3 %	0.89 [0.60, 1.32]
Zegers-Hochschild 2000 (8)	81/262	77/243	28.4 %	0.96 [0.66, 1.41]
Subtotal (95% CI)	**959**	**1080**	**100.0 %**	**1.24 [1.03, 1.50]**

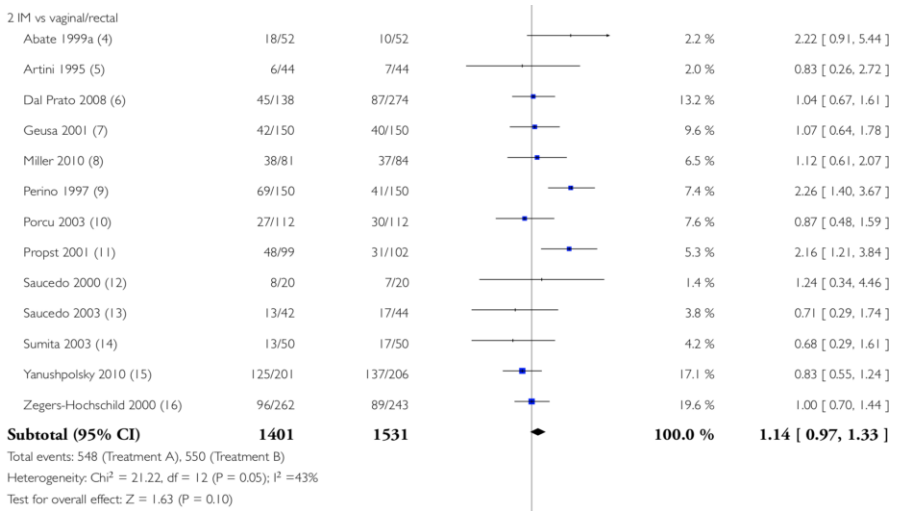
Total events: 346 (Treatment A), 330 (Treatment B)

Heterogeneity: $Chi^2 = 20.35$, $df = 6$ ($P = 0.002$); $I^2 = 71\%$

Test for overall effect: $Z = 2.27$ ($P = 0.023$)

OR: 1.24 (1.03–1.50)

Clinical pregnancy



2 IM vs vaginal/rectal				
Abate 1999a (4)	18/52	10/52	2.2 %	2.22 [0.91, 5.44]
Artini 1995 (5)	6/44	7/44	2.0 %	0.83 [0.26, 2.72]
Dal Prato 2008 (6)	45/138	87/274	13.2 %	1.04 [0.67, 1.61]
Geusa 2001 (7)	42/150	40/150	9.6 %	1.07 [0.64, 1.78]
Miller 2010 (8)	38/81	37/84	6.5 %	1.12 [0.61, 2.07]
Perino 1997 (9)	69/150	41/150	7.4 %	2.26 [1.40, 3.67]
Porcu 2003 (10)	27/112	30/112	7.6 %	0.87 [0.48, 1.59]
Propst 2001 (11)	48/99	31/102	5.3 %	2.16 [1.21, 3.84]
Saucedo 2000 (12)	8/20	7/20	1.4 %	1.24 [0.34, 4.46]
Saucedo 2003 (13)	13/42	17/44	3.8 %	0.71 [0.29, 1.74]
Sumita 2003 (14)	13/50	17/50	4.2 %	0.68 [0.29, 1.61]
Yanushpolsky 2010 (15)	125/201	137/206	17.1 %	0.83 [0.55, 1.24]
Zegers-Hochschild 2000 (16)	96/262	89/243	19.6 %	1.00 [0.70, 1.44]
Subtotal (95% CI)	**1401**	**1531**	**100.0 %**	**1.14 [0.97, 1.33]**

Total events: 548 (Treatment A), 550 (Treatment B)

Heterogeneity: $Chi^2 = 21.22$, $df = 12$ ($P = 0.05$); $I^2 = 43\%$

Test for overall effect: $Z = 1.63$ ($P = 0.10$)

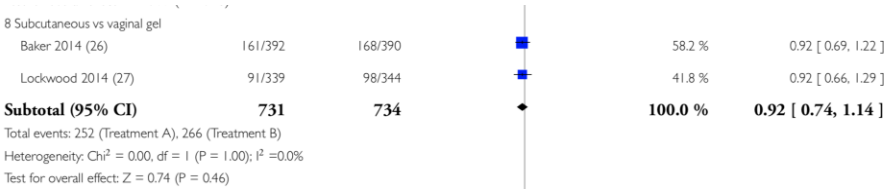
OR: 1.14 (0.97–1.33)

IM, intramuscular.

van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154.

Subcutaneous vs. vaginal

Live birth



OR: 0.92 (0.74–1.14)

Live birth

PLOS ONE

RESEARCH ARTICLE

Subcutaneous Progesterone Is Effective and Safe for Luteal Phase Support in IVF: An Individual Patient Data Meta-Analysis of the Phase III Trials

Jakob Doblinger[1], Barbara Cometti[2], Silvia Trevisan[2], Georg Griesinger[3]*

OR: 0.89(0.71–1.11)

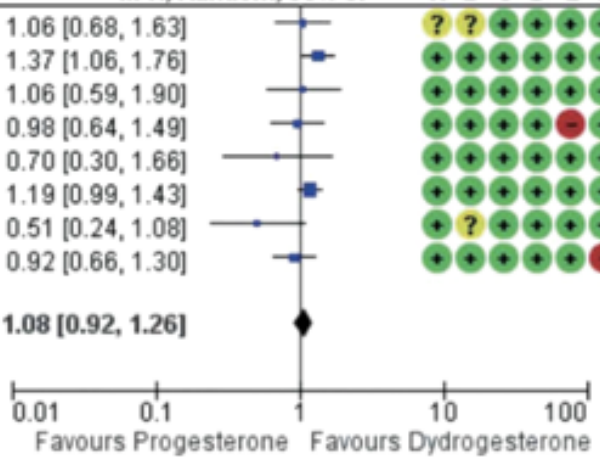
van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154;
Doblinger J, et al. PLOS One 2016;11:e0151388.

Oral (dydrogesterone) vs. vaginal progesterone

Live birth or ongoing pregnancy

Study or Subgroup	Dydrogesterone Events	Total	Progesterone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Chakravarty 2005	19	79	80	351	10.4%	1.06 [0.68, 1.63]	? ? + + + + -
Ganesh 2011	107	422	85	459	21.5%	1.37 [1.06, 1.76]	+ + + + + + +
Rashidi 2016	17	60	16	60	6.5%	1.06 [0.59, 1.90]	+ + + + + + +
Saharkhiz 2016	28	96	34	114	11.0%	0.98 [0.64, 1.49]	+ + + + - + +
Salehpour 2013	7	40	10	40	3.2%	0.70 [0.30, 1.66]	+ + + + + + +
Tournaye 2017	172	520	142	511	28.4%	1.19 [0.99, 1.43]	+ + + + + + +
Zarei 2017	9	110	18	112	4.1%	0.51 [0.24, 1.08]	+ ? + + + + +
Zargar 2016	50	212	51	200	15.0%	0.92 [0.66, 1.30]	+ + + + + - +
Total (95% CI)	409	1539	436	1847	100.0%	**1.08 [0.92, 1.26]**	

Heterogeneity: I^2 = 29%; Test for overall effect: (P = 0.37)



OR: 1.08 (0.92–1.26)

Barbosa MWP, et al. JBRA Assist Reprod, 2018;22:148-56.

Overall conclusion

Luteal phase support for assisted reproduction cycles (Review)

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M

THE COCHRANE COLLABORATION®

AUTHORS' CONCLUSIONS

Implications for practice

Progesterone during the luteal phase is associated with higher rates of live birth or ongoing pregnancy than placebo. The addition of GnRHa to progesterone is associated with an improvement in pregnancy outcomes. OHSS rates are increased with hCG compared to placebo (one study only). The addition of oestrogen does not seem to improve outcomes. The route of progesterone administration is not associated with an improvement in outcomes.

van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154.

What is the right dose?

50–100 mg/d

90–180 mg/d

300–800 mg/d

20–30 mg/d

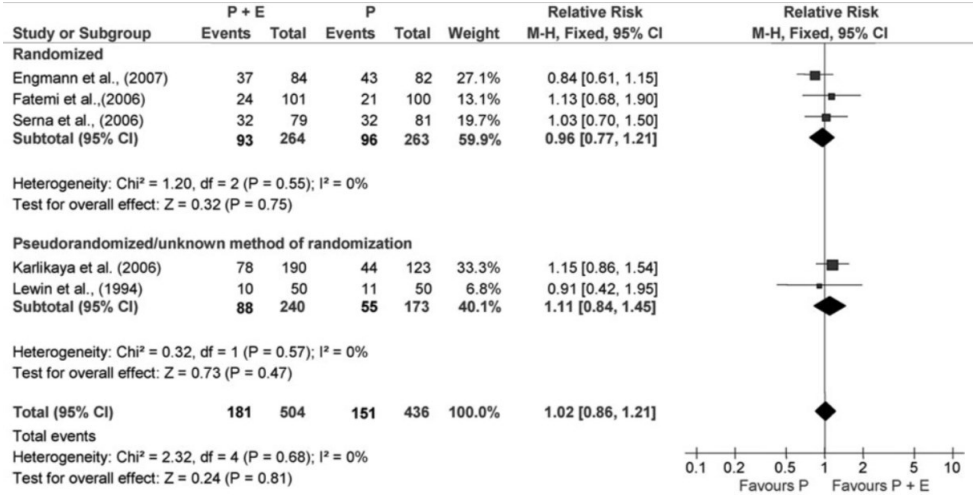
Yanushpolsky EH. Semin Reprod Med. 2015;33:118-27.

Do we need to add anything else?

Is progesterone enough?

Do we need to add estrogen?

Live birth

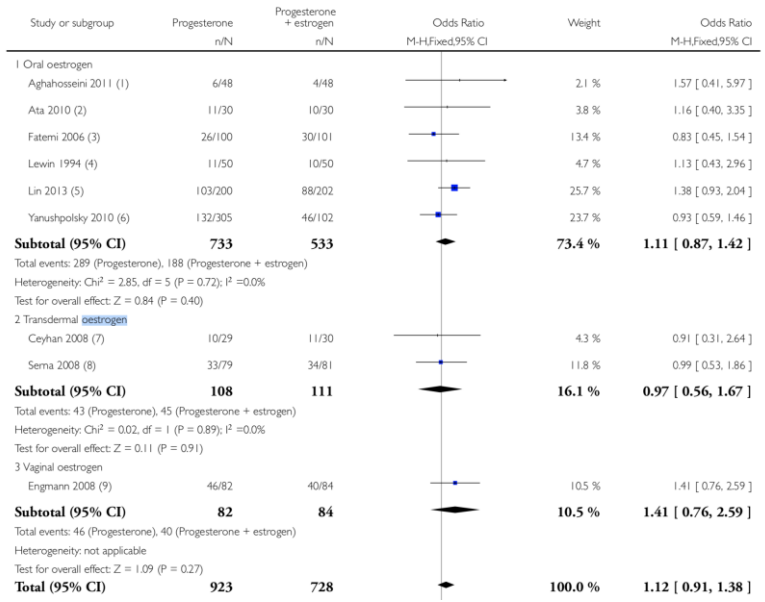


Study or Subgroup	P + E Events	P + E Total	P Events	P Total	Weight	Relative Risk M-H, Fixed, 95% CI
Randomized						
Engmann et al., (2007)	37	84	43	82	27.1%	0.84 [0.61, 1.15]
Fatemi et al.,(2006)	24	101	21	100	13.1%	1.13 [0.68, 1.90]
Serna et al., (2006)	32	79	32	81	19.7%	1.03 [0.70, 1.50]
Subtotal (95% CI)	**93**	**264**	**96**	**263**	**59.9%**	**0.96 [0.77, 1.21]**
Heterogeneity: Chi² = 1.20, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Pseudorandomized/unknown method of randomization						
Karlikaya et al. (2006)	78	190	44	123	33.3%	1.15 [0.86, 1.54]
Lewin et al., (1994)	10	50	11	50	6.8%	0.91 [0.42, 1.95]
Subtotal (95% CI)	**88**	**240**	**55**	**173**	**40.1%**	**1.11 [0.84, 1.45]**
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)	**181**	**504**	**151**	**436**	**100.0%**	**1.02 [0.86, 1.21]**
Total events						
Heterogeneity: Chi² = 2.32, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						

Relative Risk M-H, Fixed, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours P Favours P + E



Study or subgroup	Progesterone n/N	Progesterone + estrogen n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Oral oestrogen					
Aghahosseini 2011 (1)	6/48	4/48		2.1 %	1.57 [0.41, 5.97]
Ata 2010 (2)	11/30	10/30		3.8 %	1.16 [0.40, 3.35]
Fatemi 2006 (3)	26/100	30/101		13.4 %	0.83 [0.45, 1.54]
Lewin 1994 (4)	11/50	10/50		4.7 %	1.13 [0.43, 2.96]
Lin 2013 (5)	103/200	88/202		25.7 %	1.38 [0.93, 2.04]
Yanushpolsky 2010 (6)	132/305	46/102		23.7 %	0.93 [0.59, 1.46]
Subtotal (95% CI)	**733**	**533**		**73.4 %**	**1.11 [0.87, 1.42]**
Total events: 289 (Progesterone), 188 (Progesterone + estrogen)					
Heterogeneity: Chi² = 2.85, df = 5 (P = 0.72); I² =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					
2 Transdermal oestrogen					
Ceyhan 2008 (7)	10/29	11/30		4.3 %	0.91 [0.31, 2.64]
Serna 2008 (8)	33/79	34/81		11.8 %	0.99 [0.53, 1.86]
Subtotal (95% CI)	**108**	**111**		**16.1 %**	**0.97 [0.56, 1.67]**
Total events: 43 (Progesterone), 45 (Progesterone + estrogen)					
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² =0.0%					
Test for overall effect: Z = 0.11 (P = 0.91)					
3 Vaginal oestrogen					
Engmann 2008 (9)	46/82	40/84		10.5 %	1.41 [0.76, 2.59]
Subtotal (95% CI)	**82**	**84**		**10.5 %**	**1.41 [0.76, 2.59]**
Total events: 46 (Progesterone), 40 (Progesterone + estrogen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.27)					
Total (95% CI)	**923**	**728**		**100.0 %**	**1.12 [0.91, 1.38]**

OR: 1.12 (0.91–1.38)

van der Linden M, et al. Cochrane Database Syst Rev. 2015;7:CD009154;
Kolibianakis EM, et al. Hum Reprod. 2008;23:1346-54.

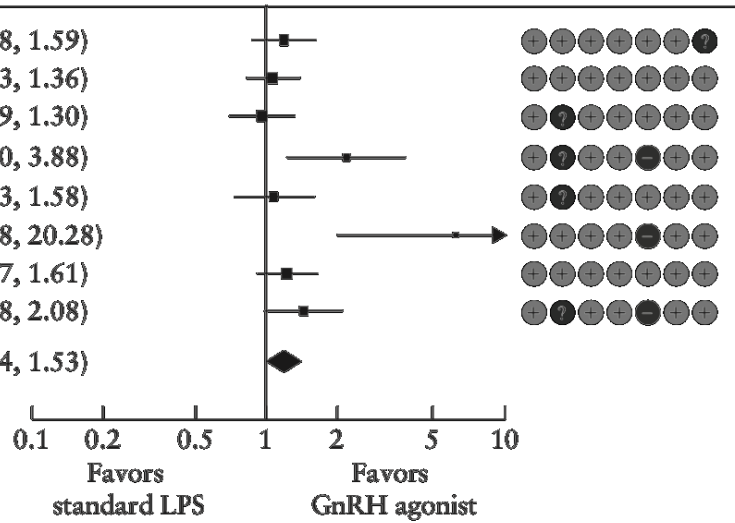
Do we need to add GnRH agonist?

Live birth

Study or subgroup	GnRH agonist Events	GnRH agonist Total	Standard LPS Events	Standard LPS Total	Weight (%)	Risk ratio M-H, random, 95% CI
Aboulghar (2015)[19]	68	224	57	222	15.1	1.18 (0.88, 1.59)
Ata (2008)[16]	89	285	84	285	17.0	1.06 (0.83, 1.36)
Inamdar (2012)[20]	56	213	59	213	14.6	0.95 (0.69, 1.30)
Isik (2009)[21]	26	74	13	80	7.4	2.16 (1.20, 3.88)
Isikoglu (2007)[17]	34	90	32	91	12.2	1.07 (0.73, 1.58)
Qublan (2008)[22]	19	60	3	60	2.4	6.33 (1.98, 20.28)
Tesarik (2006)[24]	131	300	100	300	18.8	1.31 (1.07, 1.61)
Yildiz (2014)[25]	72	184	26	95	12.5	1.43 (0.98, 2.08)
Total (95% CI)		1430		1346	100.0	1.26 (1.04, 1.53)
Total events	495		374			

Heterogeneity: tau^2 = 0.04; chi^2 = 16.79, df = 7 (P = 0.02); I^2 = 58%

Test for overall effect: Z = 2.39 (P = 0.02)



OR: 1.26 (1.04–1.53)

Martins WP, et al. Ultrasound Obstet Gynecol. 2017;495:583-91.

Do we need to add anything else?

No evidence that estrogen addition increases live-birth rates

Very low quality evidence suggests that adding a GnRH agonist during the luteal phase increases live birth rates

The “how” of luteal phase support in ART cycles

- Progesterone administration appears to be the optimal method of luteal phase support for the majority of ART cycles
- It is unlikely that the route of P4 administration is associated with improved outcome
- What is the optimal time for initiation of luteal phase support?

When should we start luteal supplementation?

Timing luteal support in assisted reproductive technology: a systematic review

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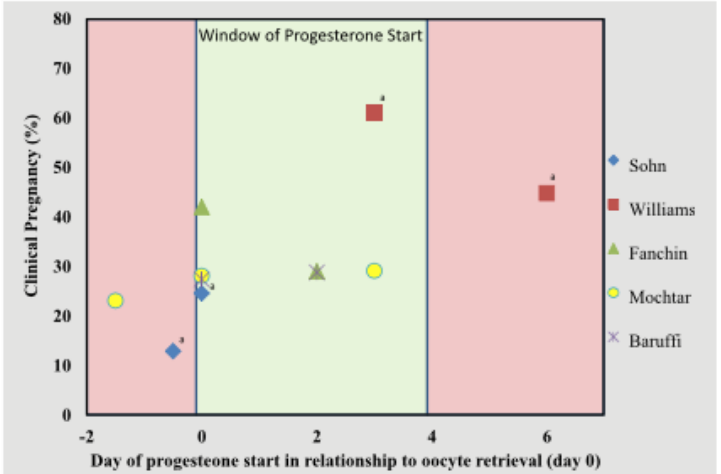
"There appears to be a window of P start time from the evening of oocyte retrieval and day 3 after oocyte retrieval"

FIGURE 1



Window of P initiation. Graphic representation of clinical pregnancy rates (PRs) on the y axis and day of P initiation on the x axis. Markers represent the six different randomized controlled trials results. The *red shaded* area represents time points with potential lowered PRs if P is started. The *green shaded area* represents the window of P start times based on the available randomized controlled data. [a]Results reported as statistically significant in the primary studies.

Connell MT, et al., Fertil Steril. 2015;103:939-46.

When should we stop luteal supplementation?

Liu et al. Reproductive Biology and Endocrinology 2012, 10:107
http://www.rbej.com/content/10/1/107

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

REVIEW Open Access

The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a meta-analysis

Table 1 Characteristics of the studies included in this review

Study Author, year	Timing of randomisation	ART	COH protocols	Total	Initiation of P	Dose & route of administration	No.	Early P cessation group	No.	Continuation group
Kohls, 2012	Clinical pregnancy	IVF/ICSI	GnRH-anta	220	OR	vaginal P 200mg bid	110	week 5	110	week 8
Kyrou, 2011	Positive hCG test	IVF/ICSI	GnRH-anta	200	ET	vaginal P 200mg tid	100	the 16th day post-ET	100	week 7
Goudge, 2010	COH	IVF	GnRH-a/ GnRH-anta	101	ET/OR	IM P50mg qd	53	the 11th day post-ET	48	week 6
Aboulghar, 2008	Clinical pregnancy	ICSI	GnRH-a	257	Unstated	IM or vaginal P	125	week 6-7	132	week 9-10
Andersen, 2002	Positive hCG test	IVF/ICSI	GnRH-a	303	ET	vaginal P 200mg tid	150	the 14th day post-ET	153	week 7
Prietl, 1992	Positive hCG test	IVF	CC/hMG/ GnRH-a	120	Unstated	PC500mg/EV10mg tiw	65	the 12th day post-ET	55	week 12

bid, twice a day; CC, clomiphene citrate; COH, controlled ovarian hyperstimulation; ET, embryo transfer; EV, estradiol valerate; GnRH-a; GnRH agonist; GnRH-antag, GnRH antagonist; hMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; OR, oocyte retrieval; P, progesterone; PC, 17 alpha-hydroxyprogesterone caproate; qd, every day; tid, 3 times a day; tiw, 3 times a week;

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

When should we stop luteal supplementation?

Live birth rate

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)

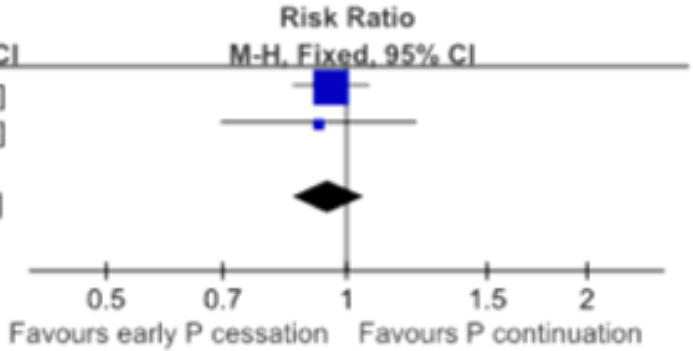


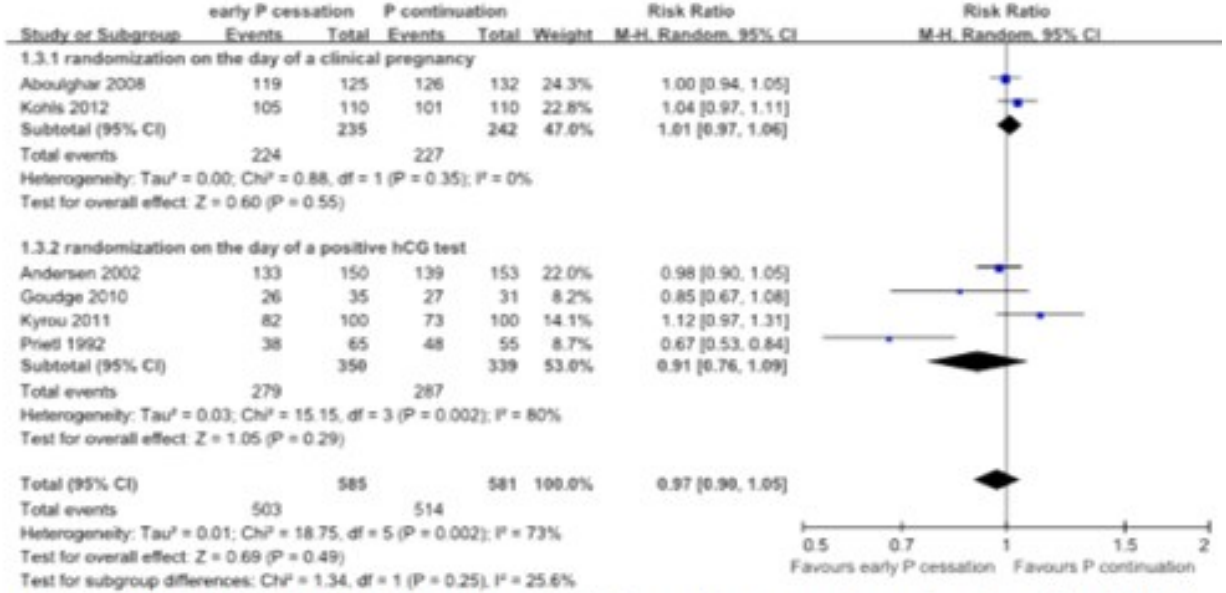
Figure 4 Live birth rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

OR: 0.95 (0.86–1.05)

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

When should we stop luteal supplementation?

Ongoing pregnancy rate



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)						
1.3.2 randomization on the day of a positive hCG test						
Andersen 2002	133	150	139	153	22.0%	0.98 [0.90, 1.05]
Goudge 2010	26	35	27	31	8.2%	0.85 [0.67, 1.08]
Kyrou 2011	82	100	73	100	14.1%	1.12 [0.97, 1.31]
Priedl 1992	38	65	48	55	8.7%	0.67 [0.53, 0.84]
Subtotal (95% CI)		350		339	53.0%	0.91 [0.76, 1.09]
Total events	279		287			
Heterogeneity: Tau² = 0.03; Chi² = 15.15, df = 3 (P = 0.002); I² = 80%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		585		581	100.0%	0.97 [0.90, 1.05]
Total events	503		514			
Heterogeneity: Tau² = 0.01; Chi² = 18.75, df = 5 (P = 0.002); I² = 73%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.6%						

Figure 6 Ongoing pregnancy rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

OR: 0.97 (0.90–1.05)

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When should we stop luteal supplementation?

Miscarriage rate

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]
Prietl 1992	9	65	5	55	8.0%	1.52 [0.54, 4.28]
Total (95% CI)		**585**		**581**	**100.0%**	**1.01 [0.74, 1.38]**
Total events	69		67			

Heterogeneity: $Chi^2 = 2.96$, $df = 5$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 0.05$ ($P = 0.96$)

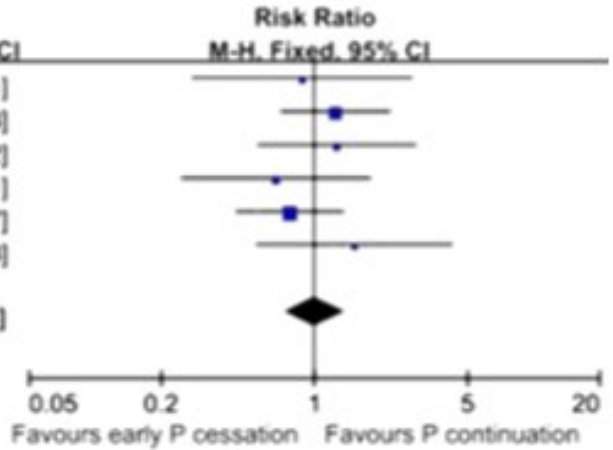

Figure 5 Miscarriage rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

OR: 1.01 (0.74–1.38)

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When should we start and stop luteal support?

In hCG triggered cycles...

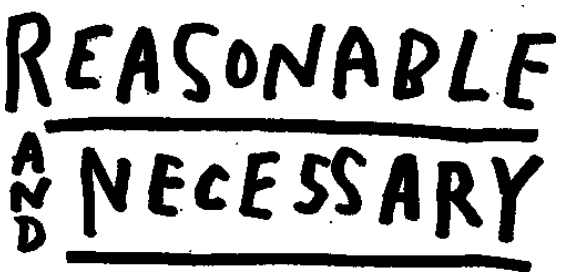
It appears that starting progesterone supplementation
between day 0 and day 3
does not compromise pregnancy rates

Available evidence
does not support a negative effect
of discontinuing luteal phase support
in fresh ART cycles
before 5 weeks of pregnancy

Conclusions

- Luteal phase support is required after ovarian stimulation with multifollicular growth

- A significantly higher probability of OPR and LBR is present when progesterone is used for luteal phase support as compared with no treatment or placebo



Conclusions

- There appears to be no difference in the probability of pregnancy between patients receiving progesterone as compared with those receiving hCG; however, the latter is associated with a significantly increased occurrence of moderate/severe OHSS

Conclusions

- There appears to be no difference between different forms of progesterone used for luteal phase support regarding CPR, OPR, and LBR
- Adding estrogen during the luteal phase does not seem to increase ongoing live birth rates
- The potential benefit of adding a GnRH-a remains highly controversial

Conclusions

- Currently it appears that progesterone supplementation can start after OPU until day 3 post OPU without a decrease in the probability of pregnancy

- Available data on the optimal duration of luteal phase supplementation are not against its discontinuation with a positive pregnancy test

Conclusions

- Rescuing the luteal phase after GnRH-a triggering can be achieved through some form of LH activity
  - This, however, leads to an increase in the risk of OHSS

Thank you!