E & P Add-Back in ART: Why, When, How Much and What Sources of Steroids- Clinical Outcomes

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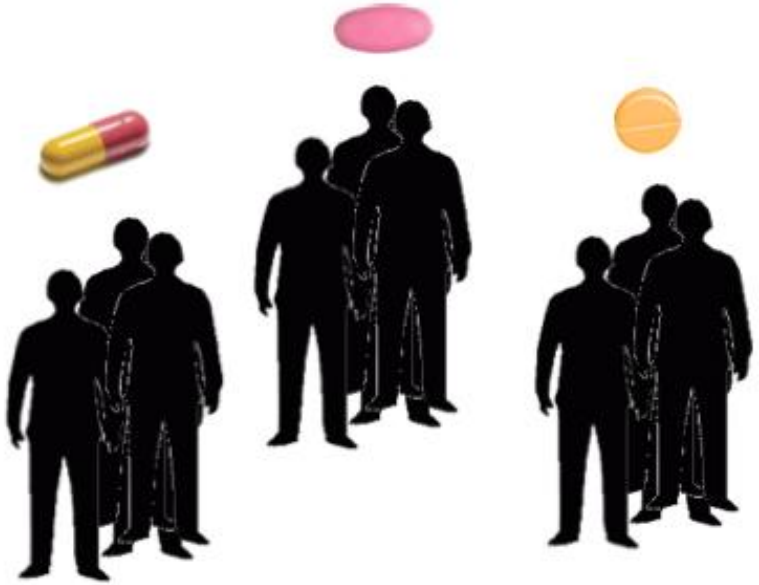
ANATOLIA
TÜP BEBEK VE KADIN SAĞLIĞI MERKEZİ

Defining Personalized Medicine

Current Practice

Trial and error

Personalized Medicine



The right treatment for the right person at the right time

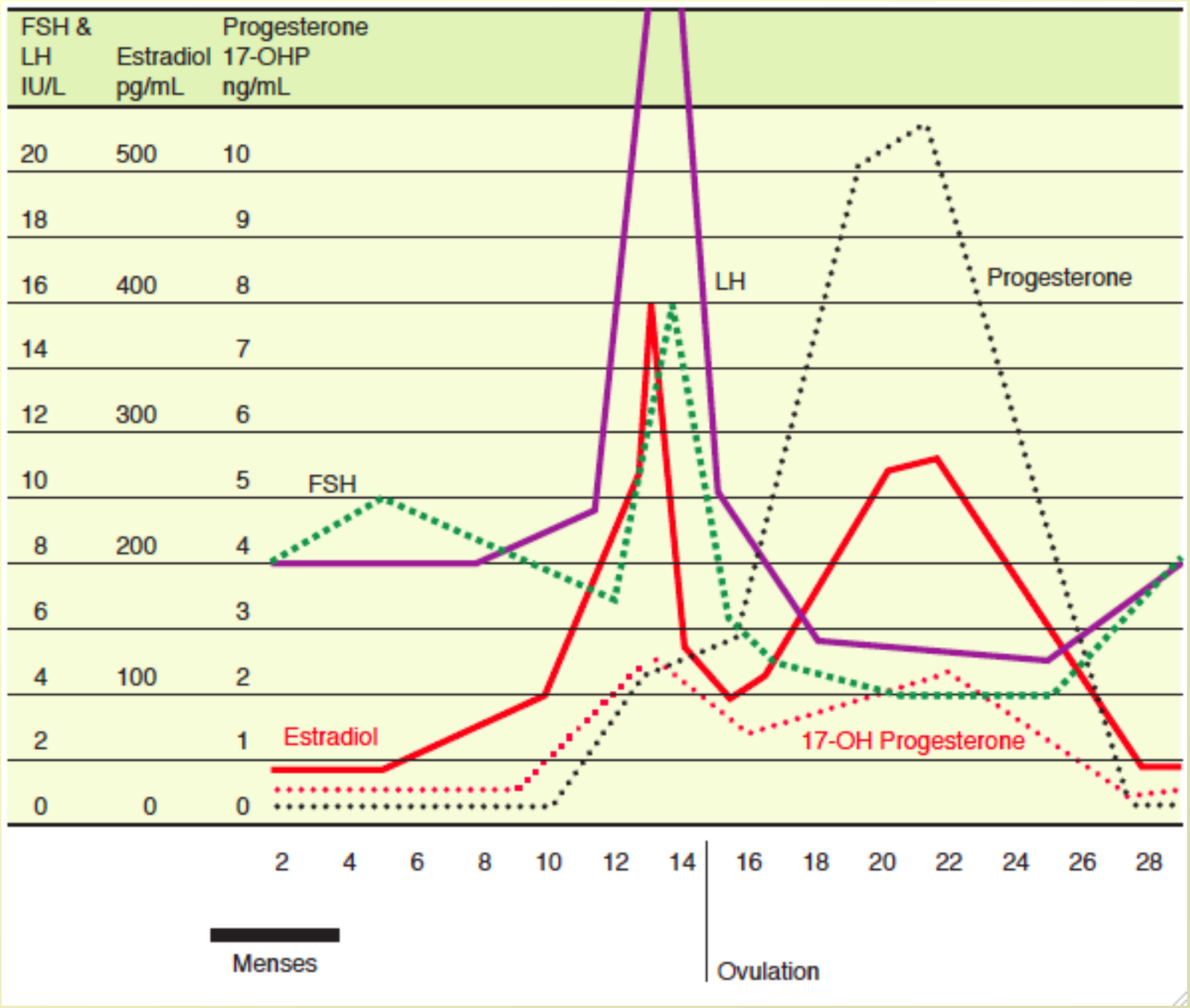
Clinical IVF

Individualization

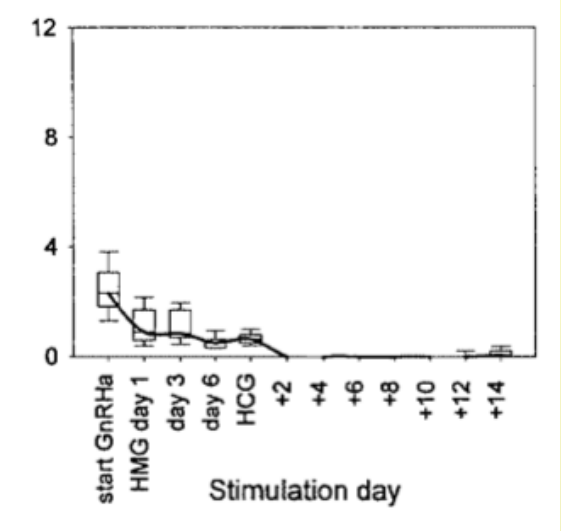
- **Ovarian stimulation**
- **Triggering of final oocyte maturation**
- **Luteal phase**

Outline

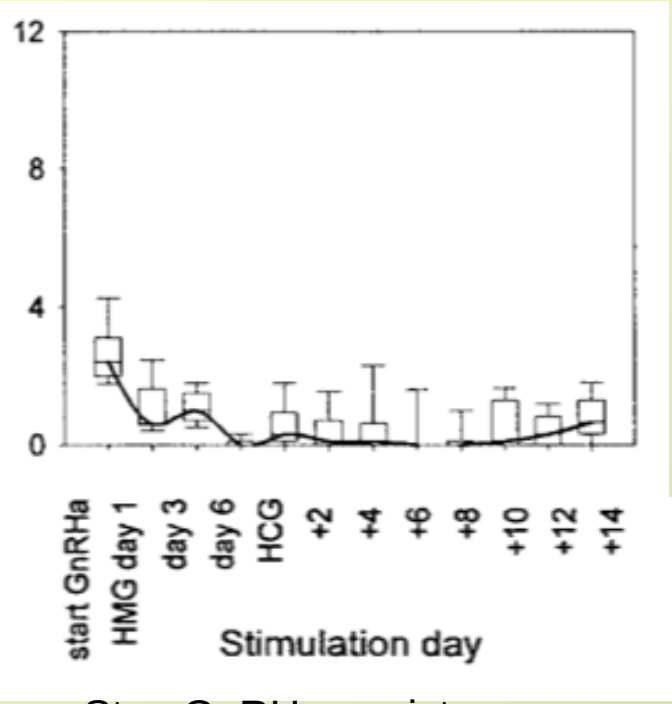
- **Etiology of luteal phase deficiency (LPD) in ART cycles**
- **Agents and routes for luteal phase support (LPS)**
- **When to start and stop LPS?**


FSH & LH IU/L
Estradiol pg/mL
Progesterone 17-OHP ng/mL
20 500 10
18 9
16 400 8
14 7
12 300 6
10 5
8 200 4
6 3
4 100 2
2 1
0 0 0
LH
Progesterone
FSH
Estradiol
17-OH Progesterone
2 4 6 8 10 12 14 16 18 20 22 24 26 28
Menses
Ovulation

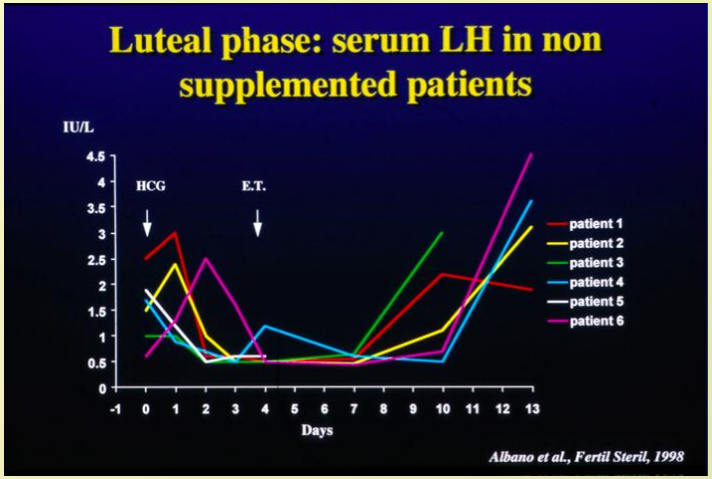
LUTEAL LH LEVELS



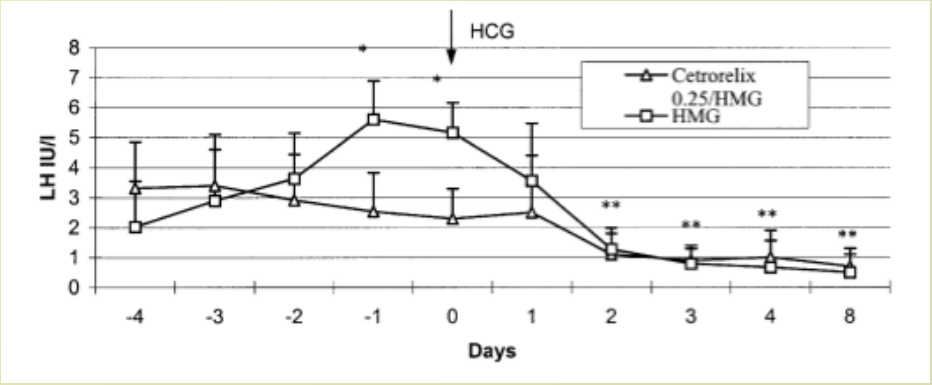
GnRH agonist *(Beckers et al-2000)*



Stop GnRH agonist *(Beckers et al-2000)*

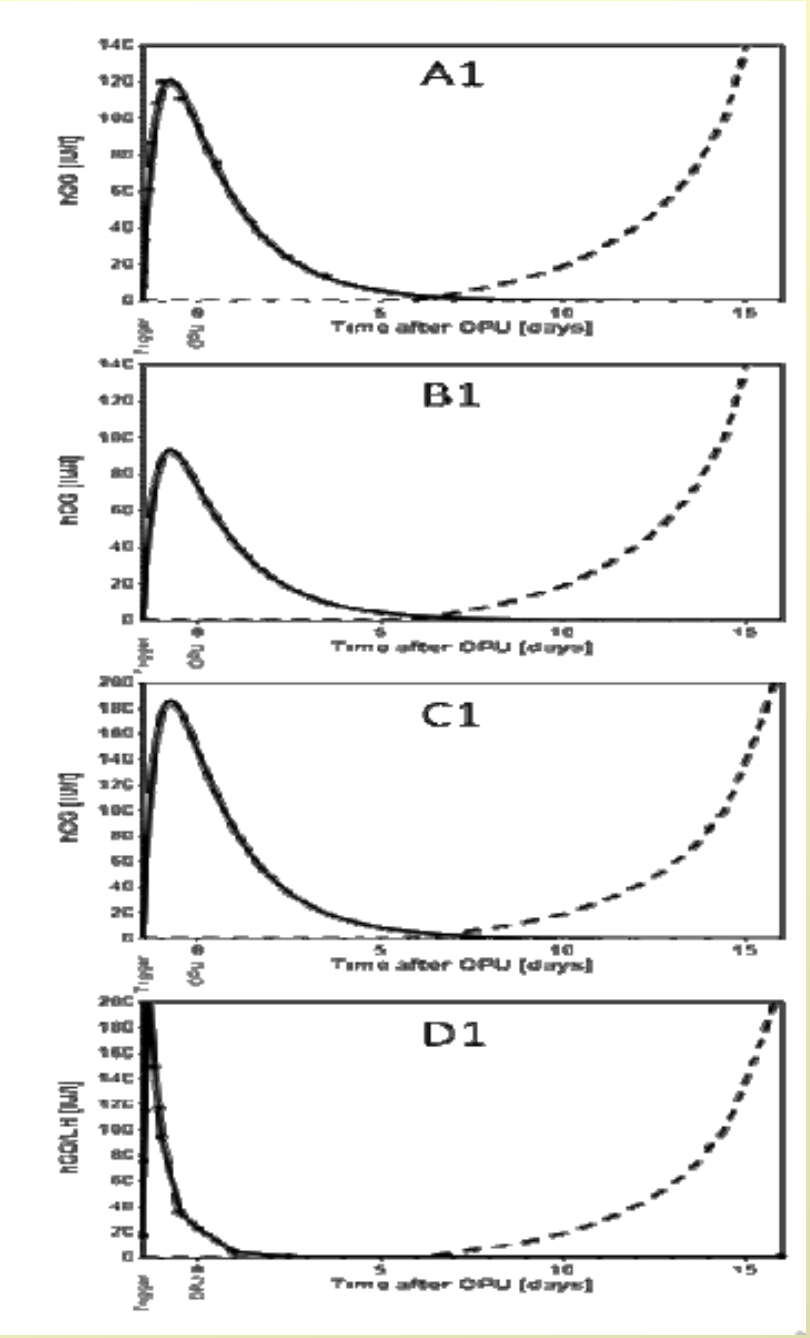


GnRH antagonist *(Albano et al-1998)*



Gonadotropin alone (*Tavaniotou et al. HR 2001)*

hCG Concent.



250 µg rhCG=6500 IU

5000 IU uhCG

10,000 IU uhCG

Endogenous LH following GnRH-a trigger

Trinchard-Lugan et al., 2002
Itskovitz et al., 1991
Sherbahn, 2013

LPD in IVF

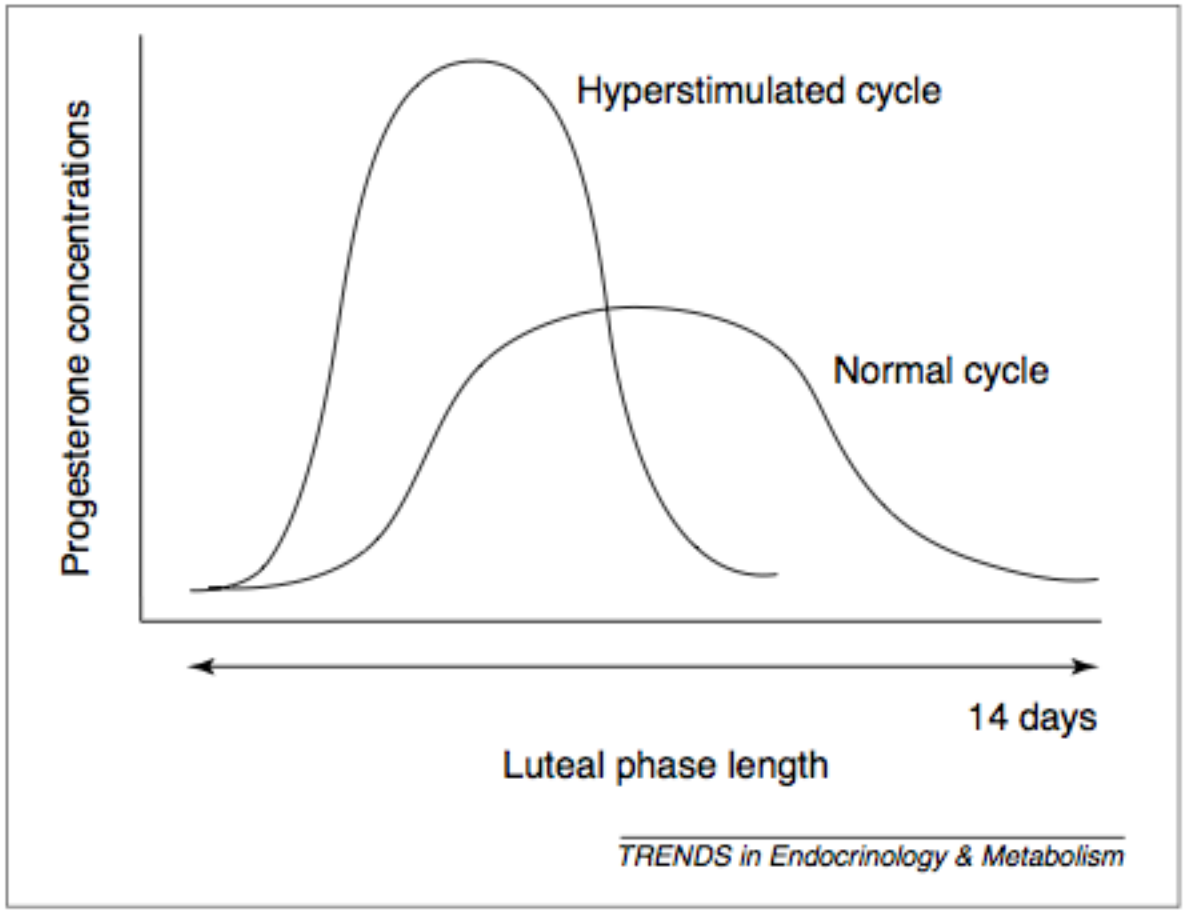


Fig. 2. Abnormal corpus luteum function following ovarian stimulation for *in vitro* fertilization. Abnormally raised progesterone levels during the early luteal phase coincide with premature luteolysis. Adapted, with permission, from [48].

Adapted from Jones-1996 by Fauser and Devroey-2003

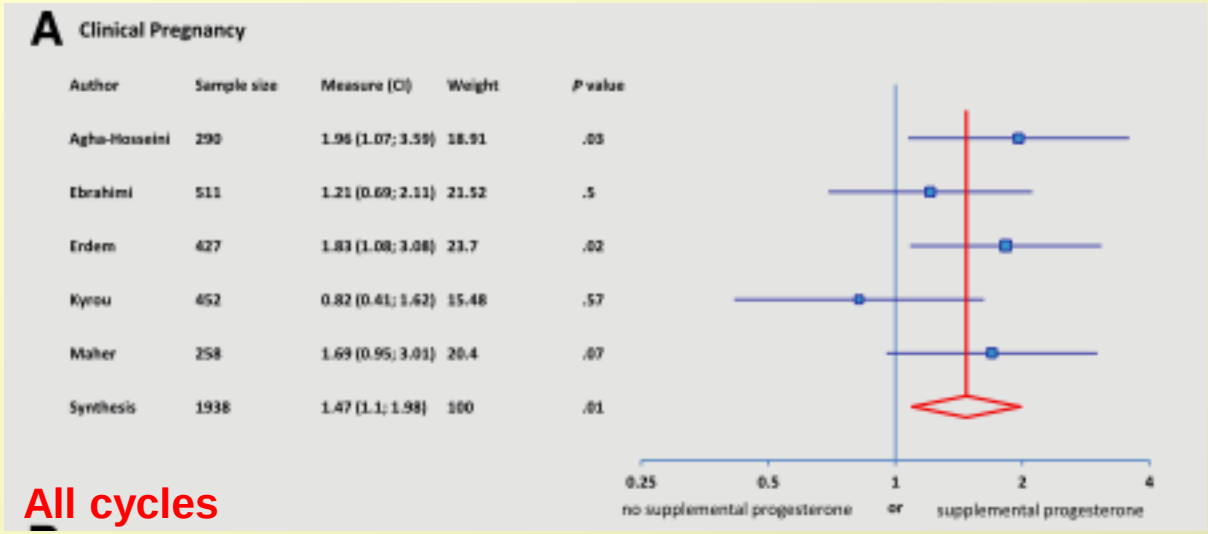
Luteal phase support for assisted reproduction cycles (Review)

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

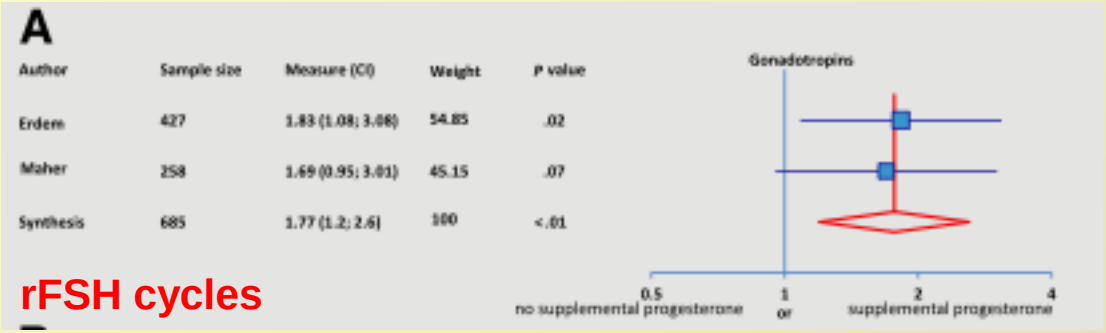
- **hCG vs Placebo/No treatment**
  - **Higher ongoing PRs; OR=1.75 (95% CI: 1.09-2.81)**
- **Progesterone vs Placebo/No treatment**
  - **Higher clinical PRs; OR=1.83 (95% CI: 1.29-2.61)**
  - **Higher ongoing PRs; OR=1.87 (95% CI: 1.19-2.94)**
  - **Higher live birth rates; OR=2.95 (95% CI: 1.02-8.56)**

Cochrane 2011

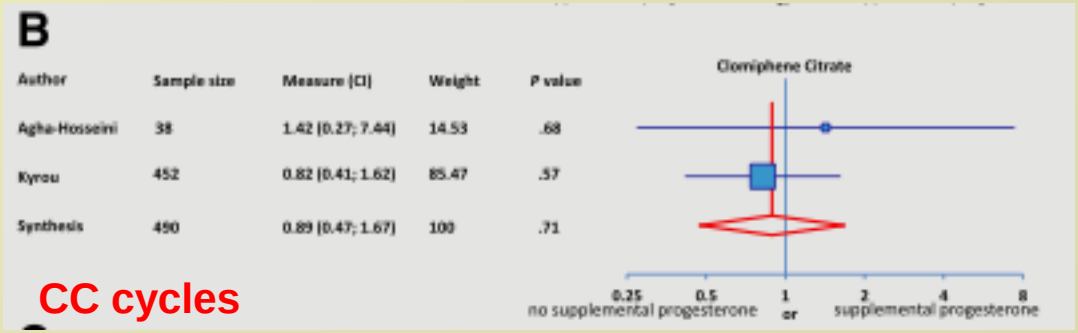
P support after COH&IUI-Meta-analysis *(Hill et al-2013)*



All cycles



rFSH cycles



CC cycles

LPD in IVF-Etiology

Conclusions

- **Inhibition of LH during the luteal phase by supraphysiological steroid levels by multiple corpora lutea**
- **Luteal phase support is mandatory in all stimulated IVF/ICSI cycles**
- **Luteal phase support may be beneficial in rFSH&IUI cycles**

Outline

- Etiology of luteal phase deficiency (LPD) in ART cycles
- **Agents and routes for luteal phase support (LPS)**
- When to start and stop LPS?

Luteal Support

Agents

- **hCG**
- **Progesterone**
- **Progesterone & Estrogen**
- **Progesterone & GnRH agonist**
- **Other**

Progesterone - Routes

Oral Progesterone

- **Simple to use**
- **Drawback**
  - **First pass hepatic metabolism-** ***Maxon 1984***
  - **Low bioavailability of oral micronized progesterone-*****Devroey et al 1989 & Bourgain et al-1990***
  - **Poor results-** ***Buvat et al-1990; Licciardi et al-1999; Friedler et al-1999***
- **Dydrogesterone (DG)**
  - **Similar pregnancy rates-** ***Chakravarty et al-2004; Ganesh et al-2011***
  - **More large RCT's are warranted**

im vs vaginal P

Crinone vs im P: RCT

	im P (n=201)	Crinone 8% (n=206)	p
Implantation (%)	34.7	37.0	NS
Ongoing/delivered (%)	42.2	45.2	NS
Chemical& SAB&Ectopic	32.0	32.1	NS
Miscarriage rate (%)	19.2	14.6	NS
Satisfaction (1-5)	2.8±1.2	4.4±0.9	<0.01

Yanushpolsky et al. Fertil Steril 94: 2596-9, 2010

Patterns of luteal phase bleeding in in vitro fertilization cycles supplemented with Crinone vaginal gel and with intramuscular progesterone—impact of luteal estrogen: prospective, randomized study and post hoc analysis

Elena Yanushpolsky, M.D.,[a] *Shelley Hurwitz, Ph.D.,*[b] *Louise Greenberg, M.Ed.,*[a] *Catherine Racowsky, Ph.D.,*[a] *and Mark Hornstein, M.D.*[a]

Outcome	Crinone (n=190)	im P (n=175)	p
Pregnant (%)	128 (67)	112 (64)	0.51
Ongoing/born (%)	86 (67.2)	79 (70.5)	0.39
LPB (+) (%)	63 (33.2)	45 (25.7)	0.14
LPB (+) among non-pregnant (%)	35/62 (56.5)	24/63 (38.1)	0.05

Fertil Steril 2011; 95: 617-20

im vs vaginal P

	No. of studies	No. of participants	OR (95% CI)
Live birth rate	4	1222	0.85 (0.66-1.10) [a]
Clinical pregnancy rate	13	2932	1.14 (0.97-1.33)
Ongoing pregnancy rate	4	1223	1.34 (1.05-1.71) [b]
Miscarriage rate	5	1324	1.18 (0.80-1.72)
Multiple pregnancy rate	1	505	1.03 (0.63-1.67)

a= Heterogeneity; I^2=60%
b= Heterogeneity; I^2=81%

Van der Linden et al-Cochrane 2011

im vs vaginal P

Patient satisfaction

- **Improved patient satisfaction scores with vaginal P**
  - **Easier to use**
  - **Less painful**
  - **Less time consuming**
  - **Associated with fewer discomforts**

Schoolcraft et al-2000; Yanushpolsky et al-2008; Levine-2000

Conclusions

im vs Vaginal P

- **Similar treatment outcomes**
- **Vaginal administration is easier, associated with fewer side effects and higher patient satisfaction scores**

Which Vaginal Progesterone and which dose to use?

Vaginal progesterone gel for luteal phase support in IVF/ICSI cycles: a meta-analysis

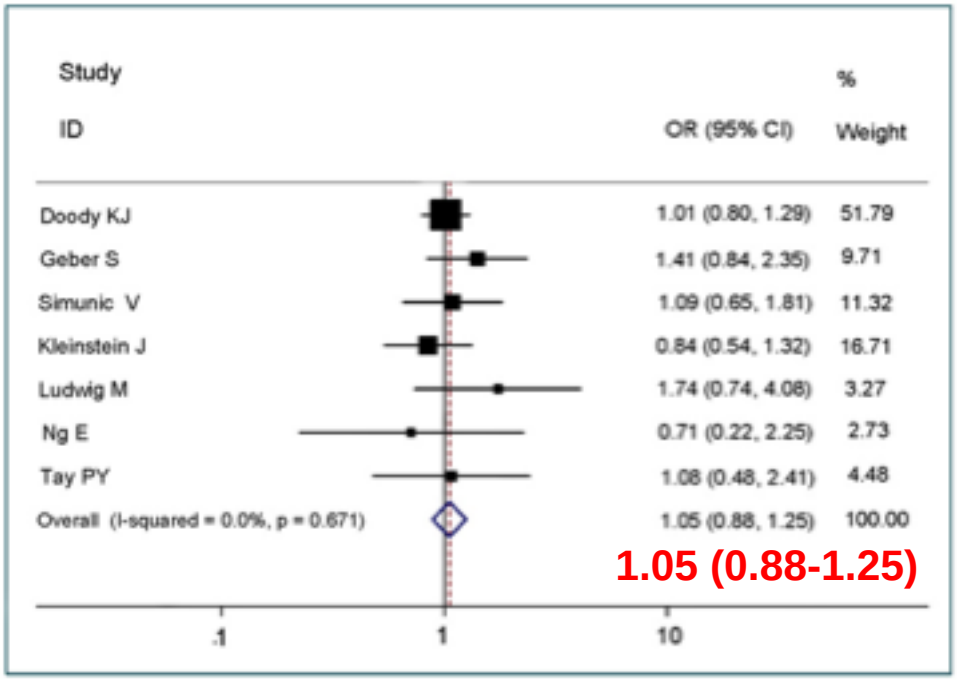
Nikolaos P. Polyzos, M.D.,[a,b] Christina I. Messini, M.D.,[a] Evangelos G. Papanikolaou, M.D., Ph.D.,[c] Davide Mauri, M.D.,[b] Spyridon Tzioras, M.D.,[b] Ahmed Badawy, M.D., Ph.D.,[d] and Ioannis E. Messinis, M.D., Ph.D.[a]

- **7 trials; 2,447 patients**
- **P gel 90 mg once or twice daily vs**
  - **600 mg/d vaginal P capsules (utrogestan, utrogest) (4 trials)**
  - **200, 400, 600 mg utrogestan and 400 mg/d vaginal P pessaries (cyclogest) (1 trial)**
  - **100, 200 mg/d vaginal P inserts (endometrin) (1 trial)**
  - **800 mg/d vaginal P pessaries (cyclogest) (1 trial)**

Fertil Steril 2010; 94: 2083-7

Vaginal progesterone gel for luteal phase support in IVF/ICSI cycles: a meta-analysis

Nikolaos P. Polyzos, M.D.,[a,b] *Christina I. Messini, M.D.,*[a] *Evangelos G. Papanikolaou, M.D., Ph.D.,*[c] *Davide Mauri, M.D.,*[b] *Spyridon Tzioras, M.D.,*[b] *Ahmed Badawy, M.D., Ph.D.,*[d] *and Ioannis E. Messinis, M.D., Ph.D.*[a]



A. Overall clinical pregnancy

Fertil Steril 2010; 94: 2083-7

Progesterone vaginal ring versus vaginal gel for luteal support with in vitro fertilization: a randomized comparative study

Laurel Stadtmauer, M.D., Ph.D.,[a] Kaylen M. Silverberg, M.D.,[b] Elizabeth S. Ginsburg, M.D.,[c] Herman Weiss, M.D.,[d] and Brandon Howard, Ph.D.[e]

TABLE 2

Clinical pregnancy rate per retrieval.

		VR (n = 646)		VG (n = 651)			
	Weeks of pregnancy		n (%)		n (%)	DIFF (VR-VG)	95% CI for DIFF
All ages, 18–42	8	646	310 (48.0)	651	307 (47.2)	0.8%	(−4.6%, 6.3%)
	12		300 (46.4)		294 (45.2)	1.3%	(−4.1%, 6.7%)
Ages, 18–34	8	558	275 (49.3)	560	269 (48.0)	1.2%	(−4.6%, 7.1%)
	12		269 (48.2)		258 (46.1)	2.1%	(−3.7%, 8.0%)
Ages, 35–42[a]	8	88	35 (39.8)	91	38 (41.8)	−2.0%	(−16.4%, 12.4%)
	12		31 (35.2)		36 (39.6)	−4.3%	(−18.5%, 9.8%)

Note: DIFF = between-group difference.

[a] The sample size of this subgroup does not allow statistical inferences regarding noninferiority.

Stadtmauer. P vaginal ring versus gel for IVF. Fertil Steril 2013.

Stadtmauer et al. FS 2013

sc P (Prolutex) vs vaginal P (Crinone)-IVF: A non-inferiority RCT

	Prolutex	Crinone	p
Ongoing pregnancy-ITT	27.4%	30.5%	0.40
Ongoing pregnancy-PP	29.2%	31.2%	0.61
Implantation rate-ITT	35.0	33.1	0.85
Implantation rate-PP	35.1	32.9	0.97
Delivery-live birth-ITT	26.8	29.9	0.37
Delivery-live birth-PP	28.5	30.5	0.58

Lockwood et al. FS 2013

Low-dose (≤100 mg) vs high-dose (>100 mg) vaginal P

Outcome	No. of studies	No. of participants	OR (95% CI)
Live birth	2	1485	1.01 (0.81-1.26)
Clinical preg. rate	12	4973	1.04 (0.92-1.17)
Ongoing preg. rate	5	3034	0.99 (0.85-1.15)
Miscarriage rate	8	2350	1.27 (0.85-1.89)
Multiple preg. rate	4	905	0.95 (0.57-1.58)

Van der Linden et al-Cochrane 2011

Conclusions

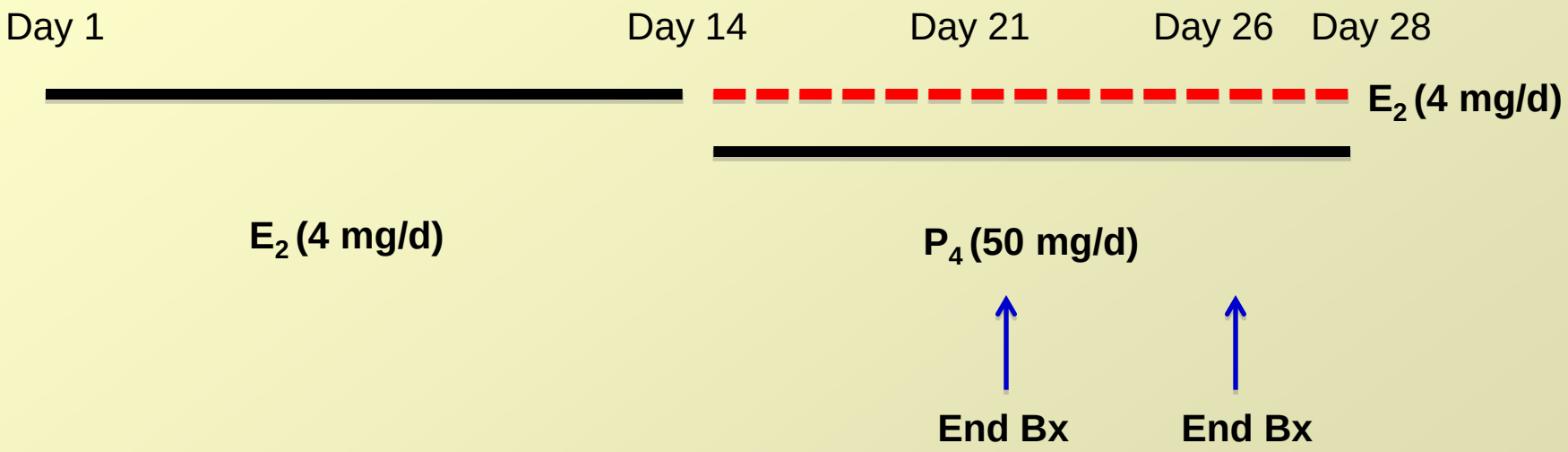
Which vaginal P and which dose to use?

- **Similar treatment outcomes with vaginal gel and all other vaginal preperations**
- **Vaginal gel may be more convenient and is associated with better patient satisfaction scores**
- **Similar outcome with low-dose (≤100 mg) vs high-dose (>100 mg) vaginal P**

P vs P+Estrogen

Is Luteal E_2 mandatory?

14 patients with POF



Similar endometrial dating (glandular and stromal)

Younis et al. Fertil Steril 1994; 62: 103-7

Estrogen supplementation for LPS

Midluteal E_2 or E_2 decline-Relevance for pregnancy

- **Not relevant**
  - Ng et al-2000
  - Friedler -2005
- **Relevant**
  - Sharara et al-1999
  - Akman et al-2002
  - Ganesh et al-2008
  - Elginy et al-2010
  - Var et al-2011

P vs P&E - *Meta-analyses*

- **Similar pregnancy outcome**
  - **Kolibianakis et al. Human Reprod 25: 1346-54, 2008**
  - **Jee et al. Fertil Steril 2010; 93: 428-36**
  - **Van der Linden et al-Cochrane 2011**

Conclusion

E supplementation

- **Routine use is *not* justified**
- **Further studies in different populations are warranted on the type/route/dose of E and timing of E administration**

P vs P+GnRH agonist

GnRHa addition for LPS

Background

- **OVARY**
  - **Induces LH secretion**
- **ENDOMETRIUM**
  - **May stimulate endometrial GnRH receptors** *(Pirard et al-2006)*
- **EMBRYO**
  - **Direct effect on the embryo?**
    - **mRNA of both GnRH and its receptor are expressed in cultured mouse embryos** *(Raga et al-1999)*
    - **Increased β-hCG seceretion** *(Tesarik et al-2004)*

Human Reproduction Update, Vol.17, No.6 pp. 734–740, 2011
Advanced Access publication on July 6, 2011 doi:10.1093/humupd/dmr029

human reproduction update

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

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

Live birth

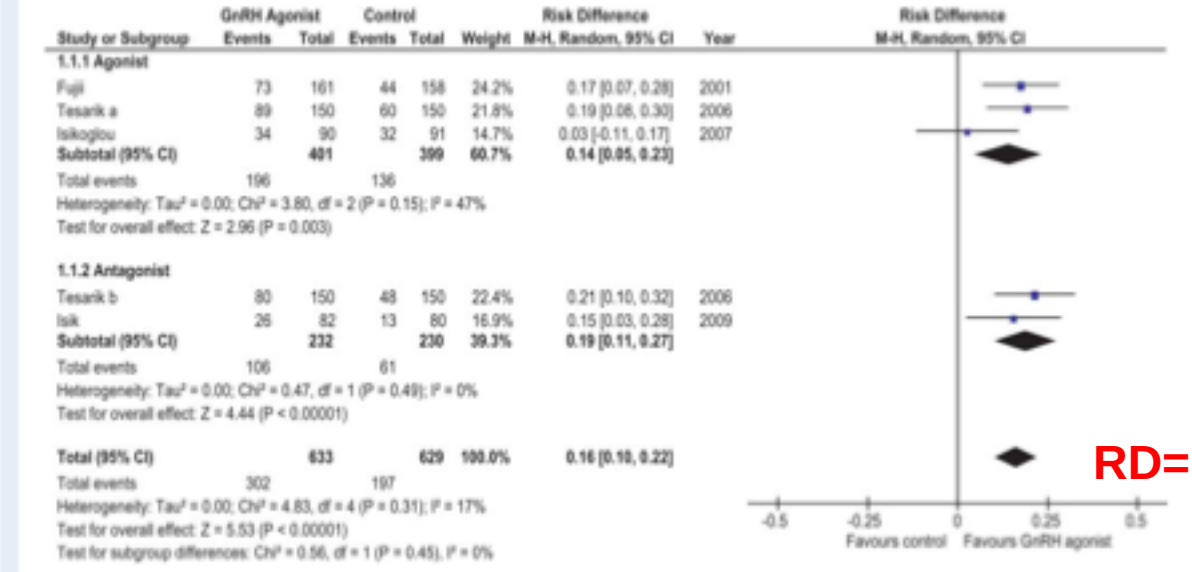


Figure 1 Forest plot live birth.

RD= 0.16 (0.10-0.22)

Luteal Support

Other Agents

- **Progesterone with ascorbic acid**
  - ***Griesinger 2002-<u>No</u> effect***
- **Progesterone with prednisolone**
  - ***Boomsma et al-Cochrane 2010-<u>No</u> effect***
- **Progesterone with aspirin**
  - ***Siristatidis et al-HRU May 2012-<u>No</u> effect***

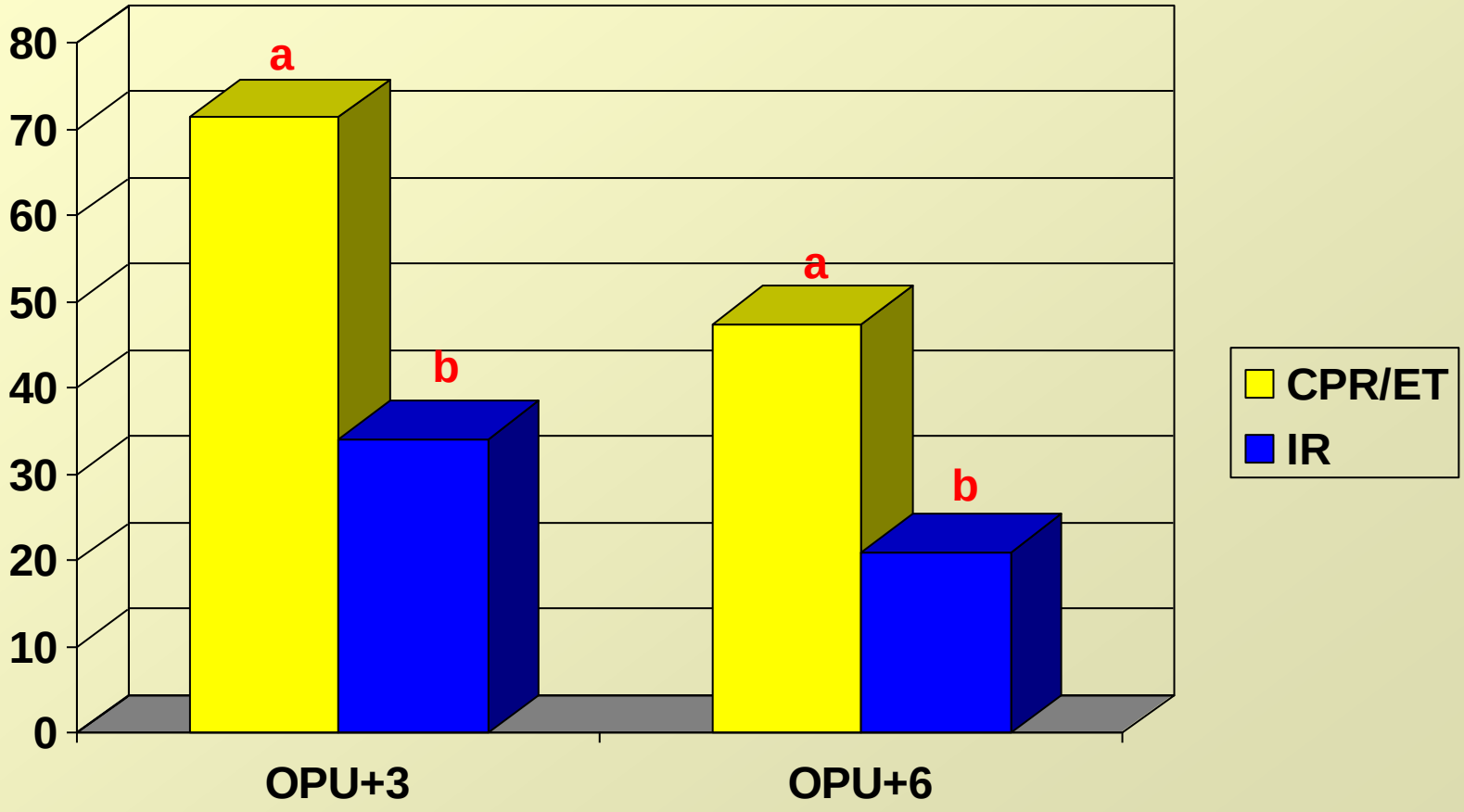
Outline

- Etiology of luteal phase deficiency (LPD) in ART cycles
- Agents and routes for luteal phase support (LPS)
- **When to start and stop LPS?**

When to start Luteal Support?

- hCG day
- OPU day
- OPU + 1 day
- ET day
- Other

When to start Luteal Support? - *RCT*



a= p=0.03; b= P=0.02

Williams et al-2001

Human Reproduction Vol.21, No.4 pp. 905–908, 2006
Advance Access publication December 22, 2005.

Timing luteal phase support in GnRH agonist down-regulated IVF/embryo transfer cycles

Monique H.Mochtar[1], Madelon Van Wely and Fulco Van der Veen

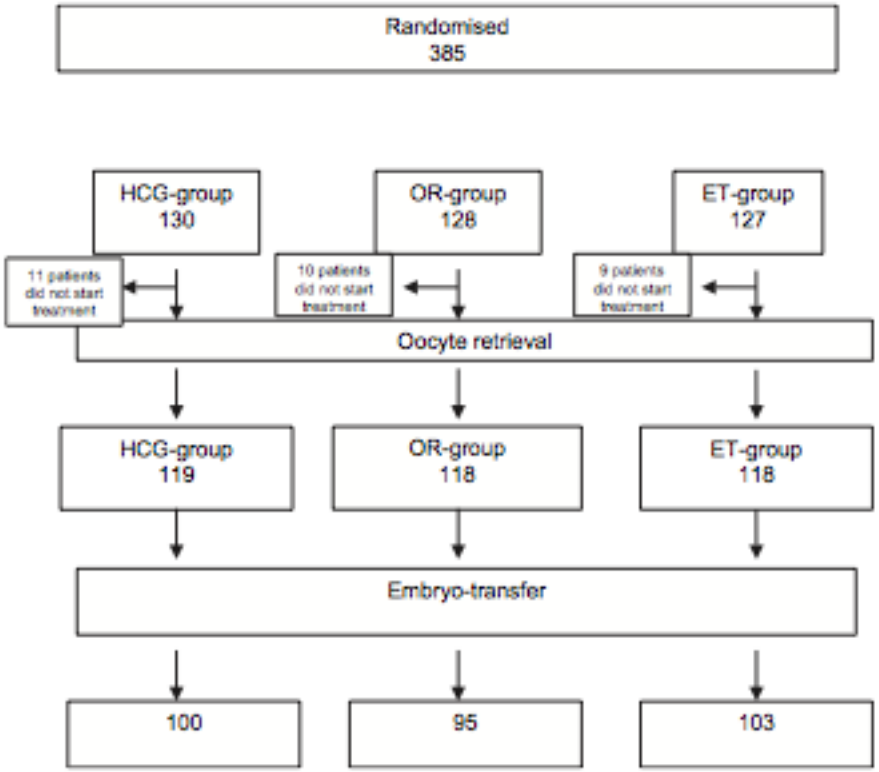


Figure 1. Flow chart of inclusion, randomization, discontinuation and treatment.

RCT; ITT-analysis; GnRH-agonist cycles (n=385)

Human Reproduction Vol.21, No.4 pp. 905–908, 2006
Advance Access publication December 22, 2005.

Timing luteal phase support in GnRH agonist down-regulated IVF/embryo transfer cycles

Monique H.Mochtar[1], Madelon Van Wely and Fulco Van der Veen

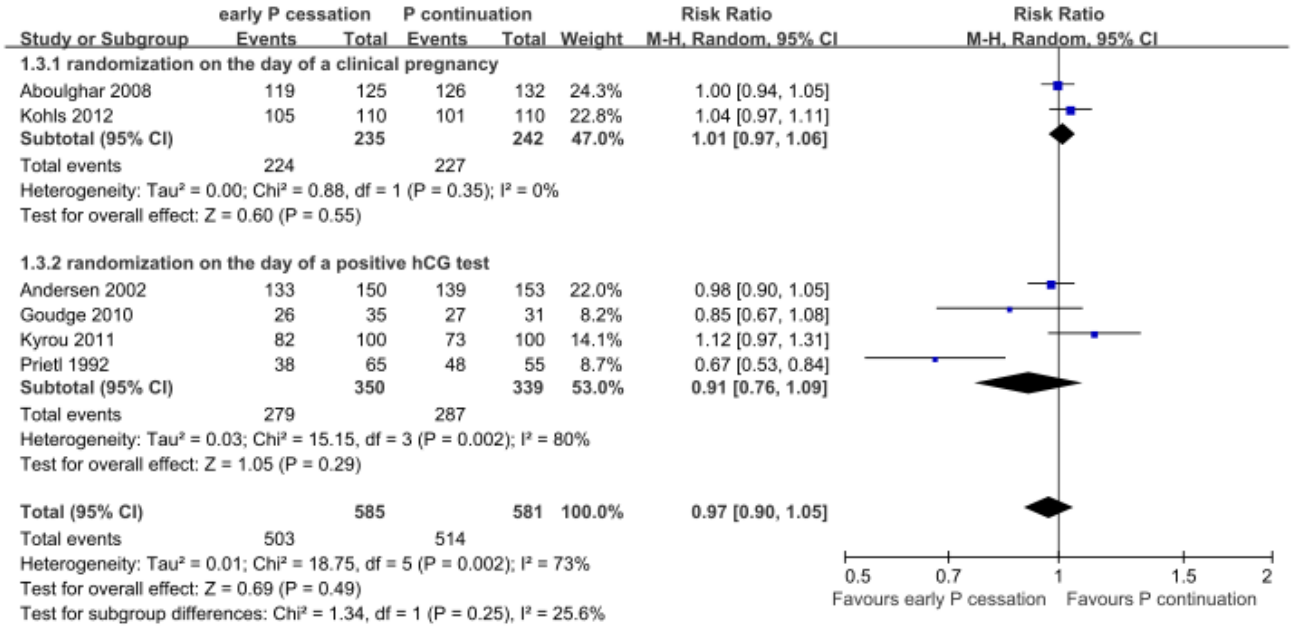
Outcome	N (%)	RR (95% CI)
Clinical		
OR group	36 (28.1)	
hCG group	30 (23.1)	0.82 (0.54-1.24)
ET group	37 (29.1)	1.04 (0.70-1.53)
Ongoing		
OR group	29 (22.7)	
hCG group	27 (20.8)	0.92 (0.58-1.45)
ET group	30 (23.6)	1.04 (0.66-1.62)
Live birth		
OR group	27 (21.1)	
hCG group	26 (20.0)	0.94 (0.58-1.52)
ET group	26 (20.5)	0.97 (0.60-1.56)

RCT; ITT-analysis; GnRH-agonist cycles (n=385)

When to stop Luteal Support?

- **Day of pregnancy test**
  - *Nyboe Andersen et al.-2002; Goudge et al-2010; Kyrou et al-2011*
- **First TV-USG (5^{th}-7^{nd} weeks)**
  - *Aboulghar et al.-2008; Kohls et al.-2012*

When to stop Luteal Support?



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]
Prietl 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.

Liu et al. RBE 2012

Conclusion

When to start and stop LPS?

- **Luteal support should be started latest 3 days after oocyte retrieval**
- **Available evidence justifies stopping on the day of pregnancy test**

Real-life practices reported worldwide by an updated website-based survey

Table 2 Comparison of the initial survey in 2009 with the current survey.

	Current survey (June 2012)	*Previous survey (September 2009)*
Cycles per year	284,600	51,155
Vaginal progesterone only	77	64
i.m. progesterone only	5	13
Oral progesterone only	0.5	2
Combined drugs	17	16
HCG only	0	5
Duration of LPS beyond 8 weeks of gestation	72[a]	67[b]

Values are *n* or%.
HCG = human chorionic gonadotrophin; LPS = luteal-phase supplementation.
[a]Until 8–10 weeks of gestation (44%) or up to 12 weeks or more (28%).
[b]Until 10–12 weeks of gestation.

Vaisbuch et al. RBM 28: 330-5, 2014

Future?

Individualization..

(Progesterone, Estrogen, rLH,r hCG …)