

Lutheal phase support anno 2015



Human M.Fatemi, MD, PhD

Medical Director
IVI GCC, Abu Dhabi

The Luteal Phase:

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44 pp. 585-595, 2004
November 22, 2005

doi:10.1093/hrt/hpl017

...g luteal phase support in GnRH agonist ...n-regulated IVF/embryo transfer cycles

Monique H.Mochar¹, Madelon Van Wely and Fulco Van der Veen

Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

¹To whom correspondence should be addressed at: Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands. E-mail: m.h.mochar@amc.uva.nl

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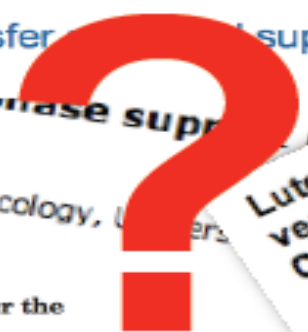
Experience with ne highly suc

Nonsupplemented Luteal Phase Characteristics after the Administration of Recombinant Human Chorionic Gonadotropin, Recombinant Luteinizing Hormone, or Gonadotropin-Releasing Hormone (GnRH) Agonist to Induce Final Oocyte Maturation in *in Vitro* Fertilization Patients after Ovarian Stimulation with Recombinant Follicle-Stimulating Hormone and GnRH Antagonist Cotreatment

NICOLE G. M. BECKERS, NICOLAS S. MACKLON, MARINUS J. ELKREMANNS, MICHAEL LUDWIG, RICARDO E. FELBERBAUM, KLAUS DIEDRICH, SHELLY BUSTON, ERNEST LOUMAYE, AND BART C. J. M. FAUSER

Article

Embryo transfer ... support in natur
cycles

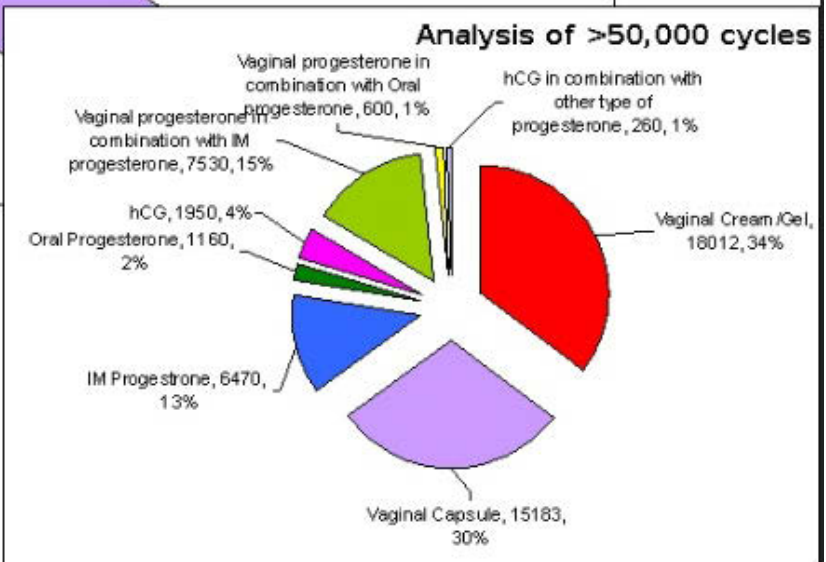
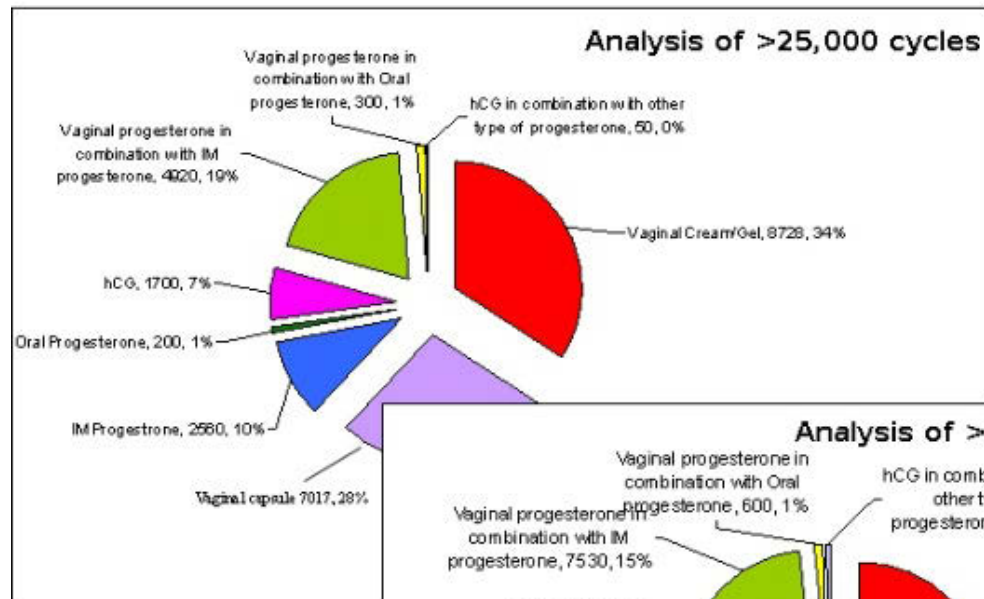


Luteal Phase Support with 17 α -Hydroxyprogesterone versus Unsupported Cycles in *in vitro* Fertilization: A Comparative Randomized Study
A. Abate, A. Biggioni, F.G. Abate, F. Marti, V. Urfier, M. Perrino

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J Smits, P Devroey and A C Van Steirteghem
Centre for Reproductive Medicine, Akademisch Ziekenhuis, Vrije Univ
Brussels, Belgium





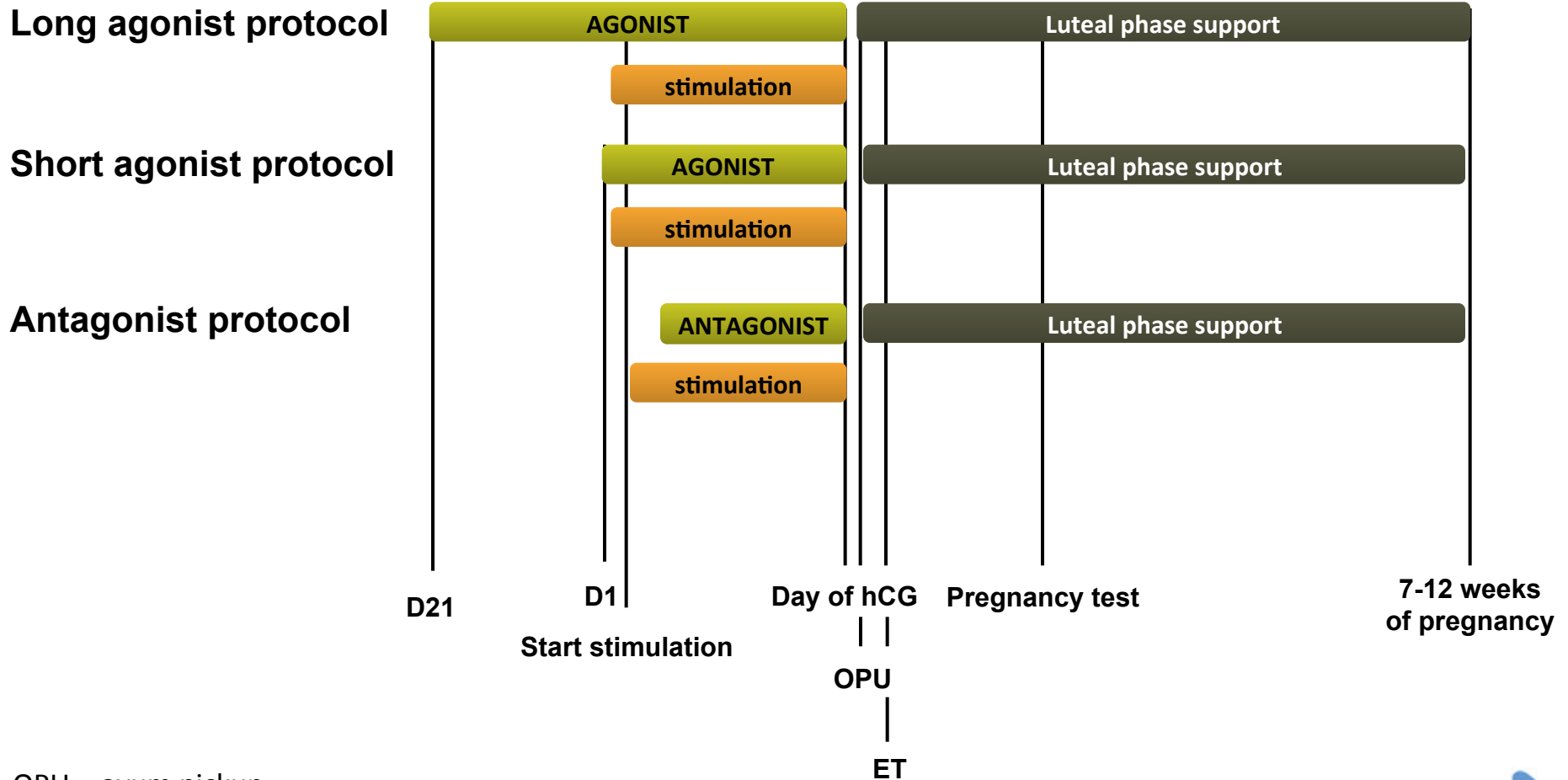
Luteal Phase Defect in Natural Cycle

- 1949: Premature onset of menses
 - luteal phase deficiency of progesterone production, which was shown to be correctable by exogenous progesterone administration (Jones, 1979)
- The prevalence of a luteal phase defect in natural cycles in normo-ovulatory patients with primary or secondary infertility was demonstrated to be about **8.1%** (Rosenberg et al, 1980)

How to Define a Luteal Phase Defect

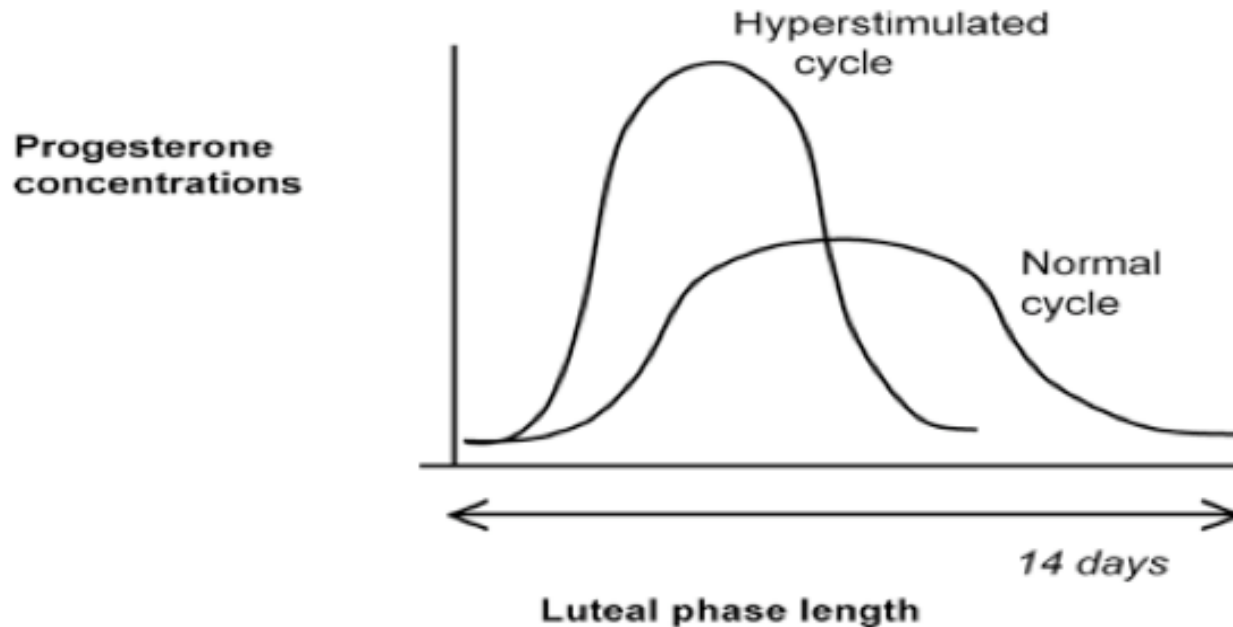
- Defective luteal phase in natural cycle was defined as serum mid-luteal progesterone levels less than 10 ng/mL (Jordan et al, 1994)
- Mid-luteal P levels do not always reflect endometrial maturation (Batista et al, 1994)
- The most reasonable consensus on a defective luteal phase is a lag of more than 2 days in endometrial histological development compared with the expected day of the cycle (Jones, 1991; Dawood, 1994)

Ovarian stimulation for IVF



OPU = ovum pickup.

Luteal Phase Defect in Stimulated Cycles



Schematic representation of changes in luteal phase length and progesterone profile induced by ovarian hyperstimulation for IVF (Macklon et al, 2006)

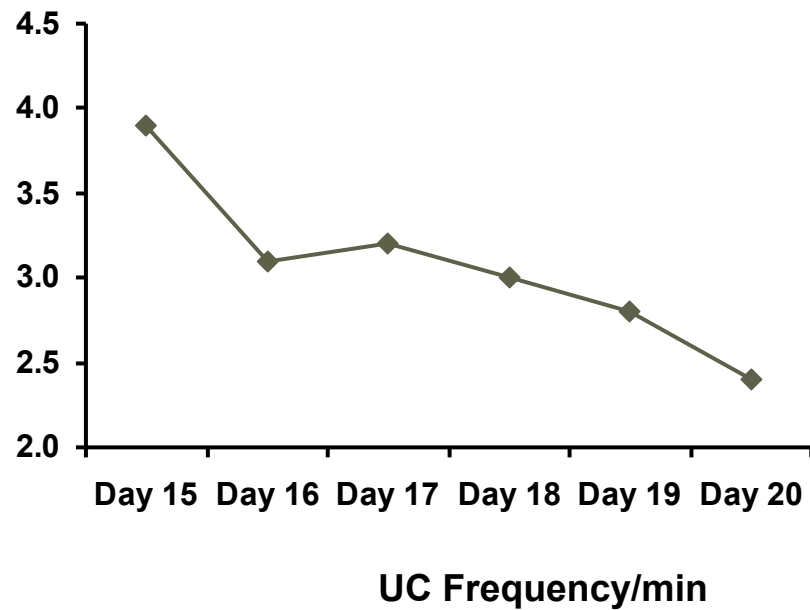
Role of Progesterone

- 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 et al, 1972)
- Normal pregnancy was sustained when progesterone was given after removal of CL (Csapo et al, 1973)

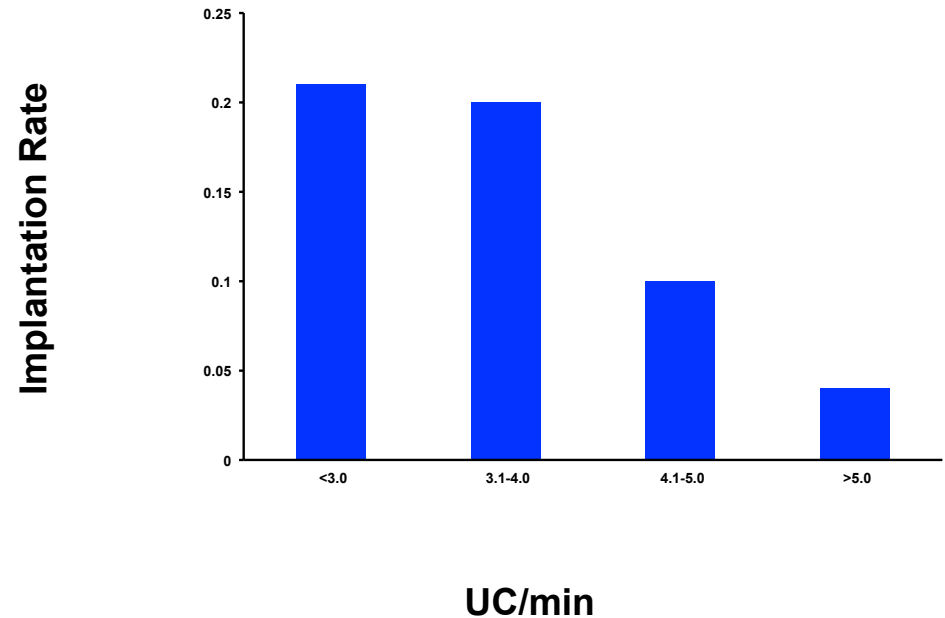
CL = corpus luteum.

Role of Progesterone

(De Ziegler et al, 1996)

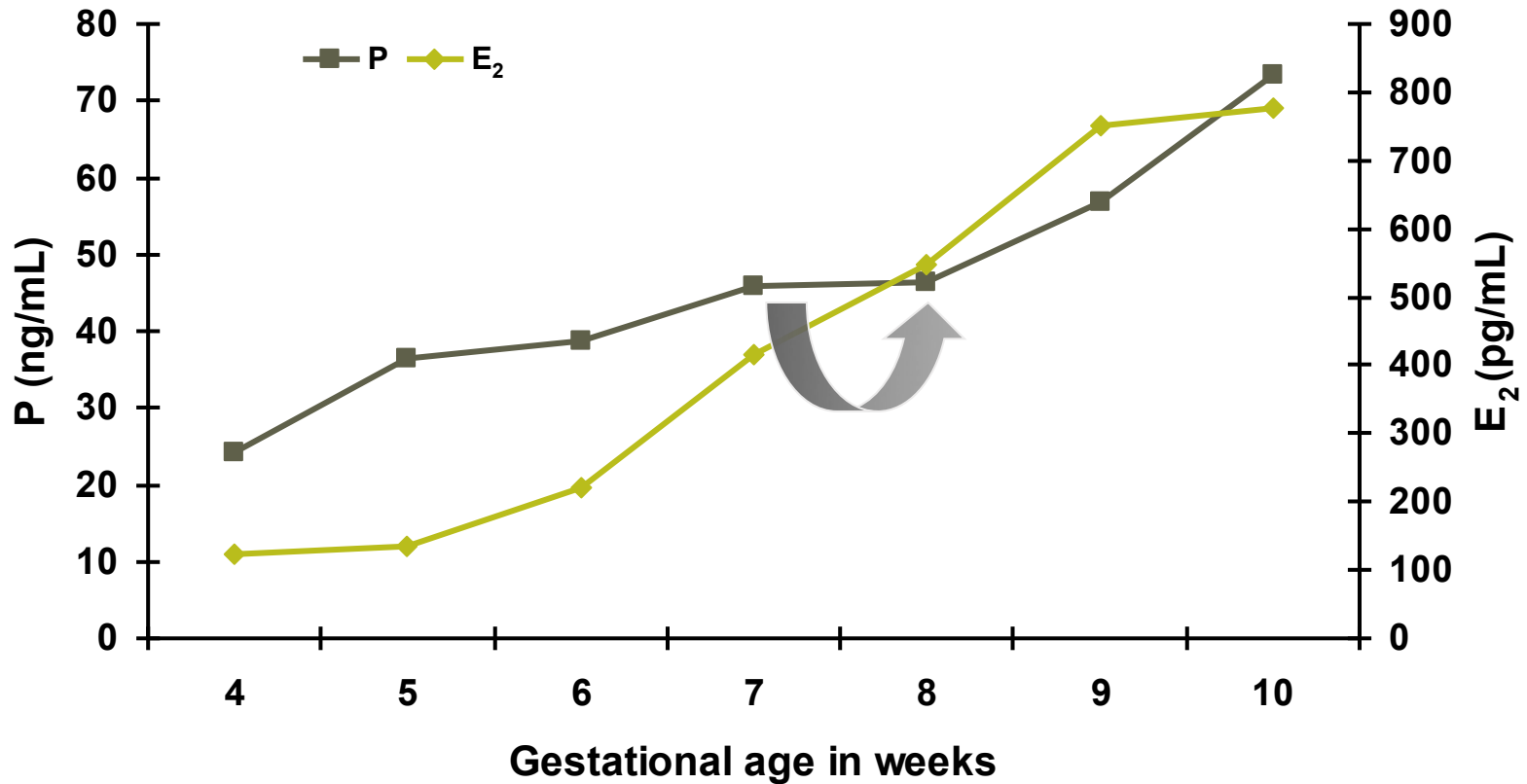


(Fanchin et al, 1998)



UC = uterine contractions.

Luteal-Placental Shift



P = progesterone.

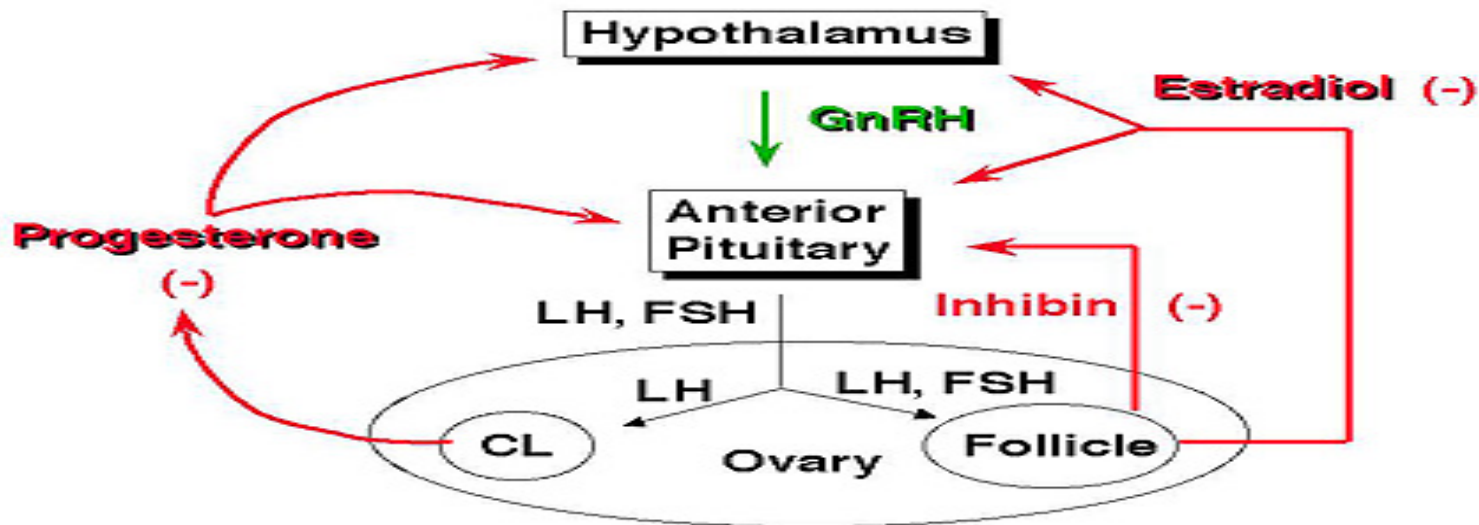
Scott et al. 1991.

Causes of Luteal Phase Defect

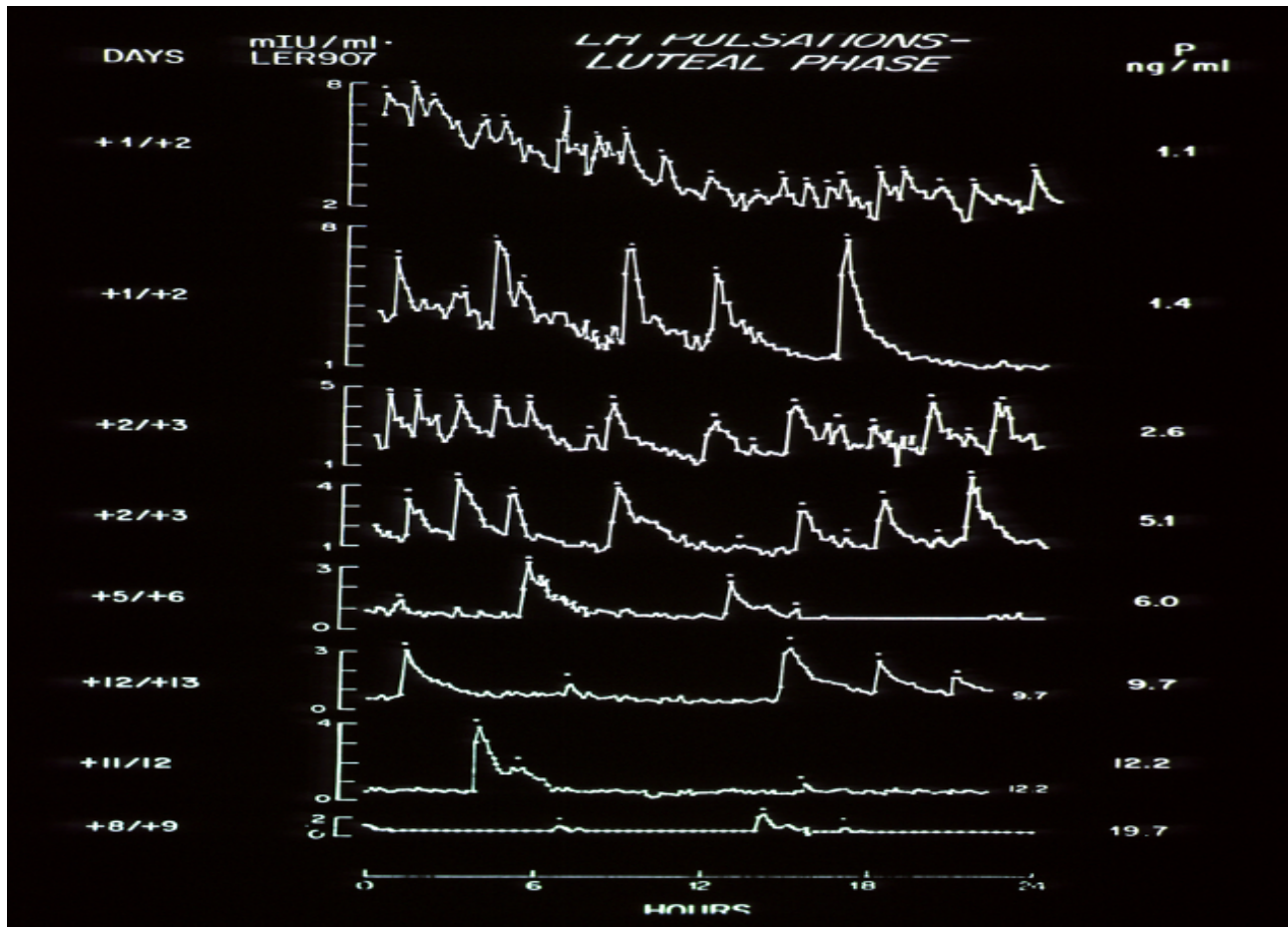
- What is the etiology of the luteal phase defect in stimulated cycles?
 - Oocyte retrieval?
 - GnRH agonist?
 - hCG?
 - Combination of those factors?

Luteal Phase in ART Cycles

- Iatrogenic luteal phase defect due to supraphysiological steroid levels in stimulated cycles



The Importance of LH



Filicori et al. *J Clin Endocrinol Metab.* 1986;62:1136.

Fatemi et al, 2009

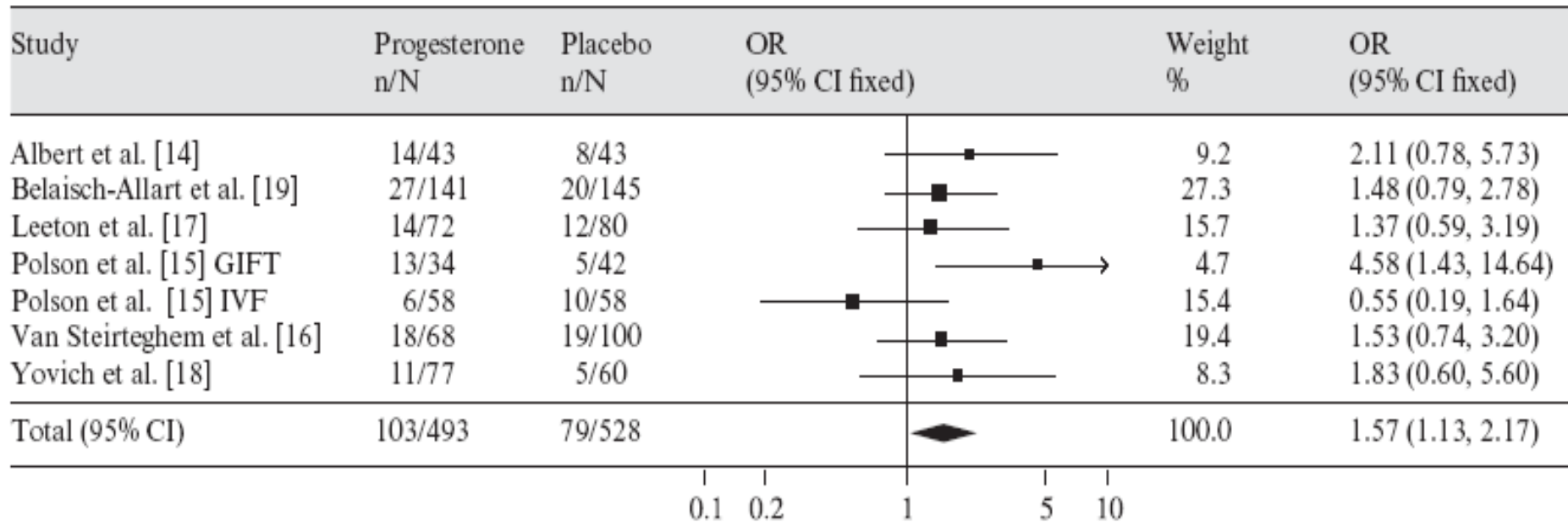
Days After hCG	Letrozole		Placebo		P Value
	Progesterone (ng/mL)	LH (IU/L)	Progesterone (ng/mL)	LH (IU/L)	
1	5.8±1.9	1.1±0.4	3.5±1.2	1.0±0.6	NS
4	57.3±2.7	0.2±0.01	40.9±6.3	0.2±0.1	NS
7	60.0*±0.0	0.1 [†] ±0.0	60.0*±0.0	0.1 [†] ±0.0	NS
10	33.13±15.8	0.1 [†] ±0.0	32.2±12.6	0.1 [†] ±0.0	NS

*The highest level of serum progesterone measured was 60 ng/mL.

[†]LH below the detection limit.

The Use of Progesterone in IVF

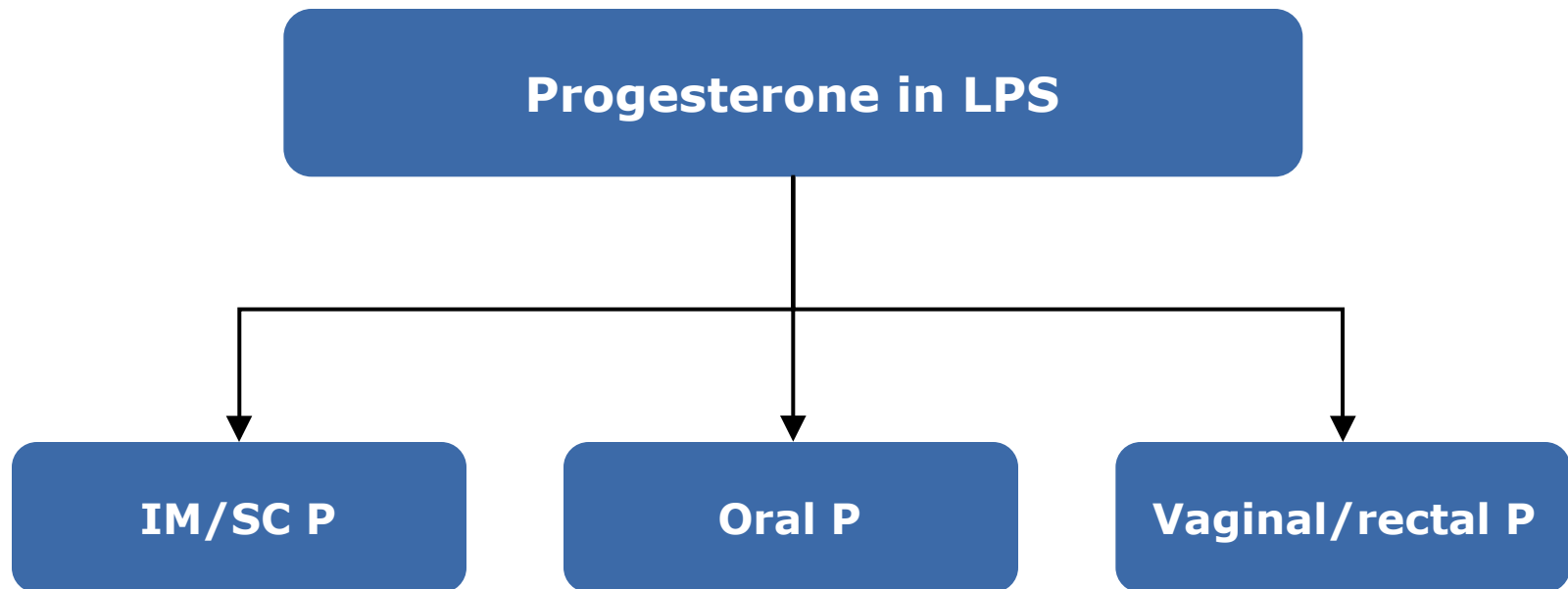
Meta-analysis of the relative risk and 95% CI of patients using various routes of progesterone vs. placebo



Test for heterogeneity: $\chi^2 = 7.35$, d.f. = 6, $p = 0.29$.

Test for overall effect: $z = 2.70$, $p = 0.007$.

LPS: In which form?



LPS = luteal phase support

IM Progesterone

- Effective
- Physiological serum levels
- Painful (long, thick needles)
- Occasional sterile abscess
- Occasional allergic reaction (oil vehicle)
- Needs to be administered by nurse, husband
- Acute eosinophilic pneumonia associated with IM administration of progesterone as luteal phase support after IVF: 6 case reports
- Not FDA approved for use in IVF

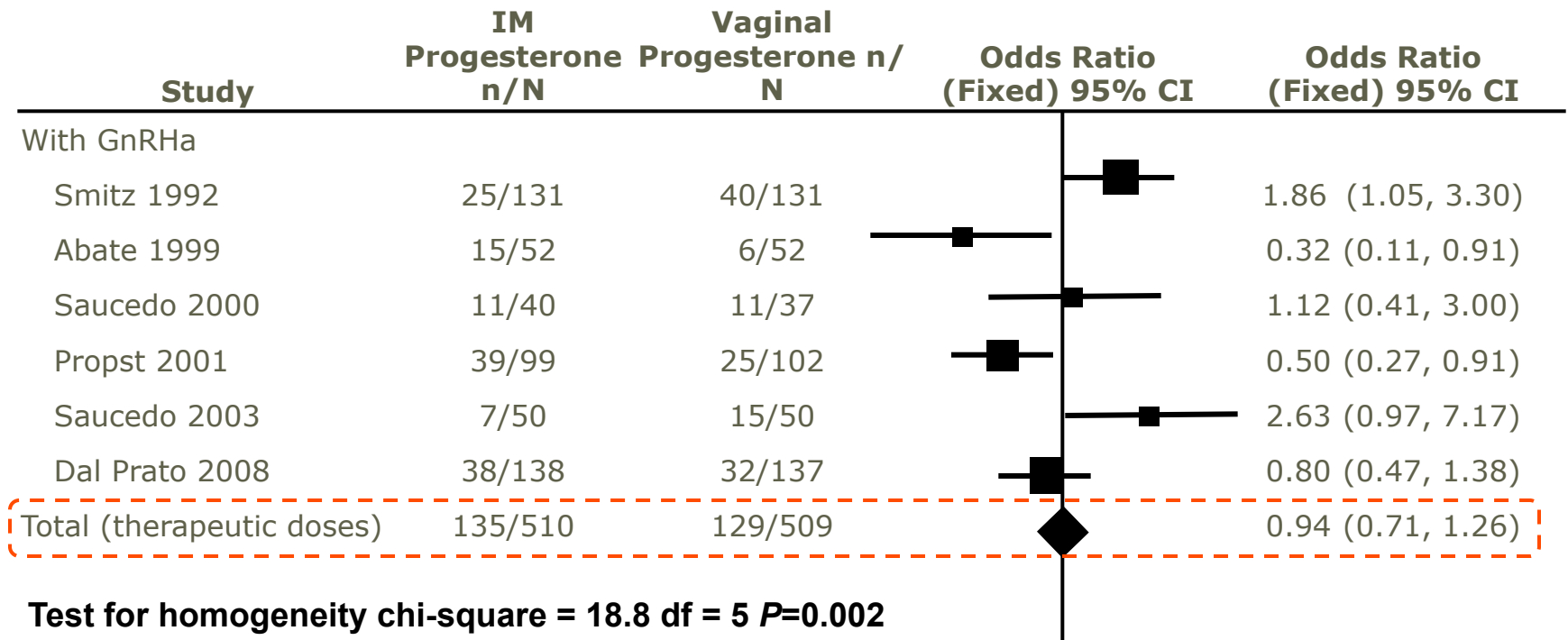
SC Progesterone

Table III Pregnancy and implantation rates by treatment group (in per cent), calculated for both the per-protocol (PP) and intent-to-treat (ITT) cohorts (PP/ITT, $n = 392/400$ for Prolutex, $n = 390/400$ for Endometrin).

	Prolutex	Endometrin	Difference versus vaginal (95% CI) (non-inferiority margin = 10%)
Initial serum β -hCG positive			
PP	56.4 (221/392)	59.0 (230/390)	-2.6 (-9.5, 4.3)
ITT	55.3 (221/400)	57.5 (230/400)	-2.2 (-9.1, 4.6)
Clinical pregnancy (6–7 weeks of gestation)			
PP	42.6 (167/392)	46.4 (181/390)	-3.8 (-10.8, 3.2)
ITT	41.8 (167/400)	45.3 (181/400)	-3.5 (-10.4, 3.4)
Ongoing pregnancy (12 weeks of gestation—primary efficacy variable)			
PP	41.6 (163/392)	44.4 (173/390)	-2.8 (-9.7, 4.2)
ITT	40.8 (163/400)	43.3 (173/400)	-2.5 (-9.4, 4.4)
Live birth			
PP	41.1 (161/392)	43.1 (168/390)	-2.0 (-8.9, 4.9)
ITT	40.3 (161/400)	42.0 (168/400)	-1.7 (-8.6, 5.1)
Take-home baby			
PP	41.1 (161/392)	42.6 (166/390)	-1.5 (-8.4, 5.4)
ITT	40.3 (161/400)	41.5 (166/400)	-1.3 (-8.1, 5.6)

IM vs Vaginal Progesterone

Intramuscular vs vaginal P administration: ongoing pregnancy per ET



Test for homogeneity chi-square = 18.8 df = 5 P=0.002
 Test for overall P=0.676.

Endometrial Diffusion: Vaginal Progesterone

One hour after application



Four hours after application



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

Oral Progesterone Ineffective?

- ✓ Progesterone administered orally
 - Degradation to its 5 α - and 5 β -reduced metabolites (Penzias, 2002)
- ✓ Bourgain (1990) and Devroey (1988) reported absence of any secretory transformation of the endometrium in patients treated with oral micronized progesterone compared to IM or vaginal micronized progesterone

Oral Progesterone Ineffective?

- DG, a retroprogesterone with good oral bioavailability, has an antiestrogenic effect on the endometrium, causing a secretory transformation (Whitehead, 1980)
- Chakravarty et al (2005) in a prospective, randomized study compared the efficacy of vaginal micronized progesterone with oral DG as luteal phase support after IVF
- Both DG and micronized progesterone were associated with similar rates of successful pregnancies (24.1% vs 22.8%, respectively; $P=0.81$)

DG = dydrogesterone.

Oral Progesterone Ineffective?

- A RCT Comparison of oral dydrogesterone with progesterone gel and micronized progesterone in 1,373 women
- The overall pregnancy rate and miscarriage rate were comparable

Oral Progesterone Ineffective?

- However, a relatively retarded endometrial development in artificial cycles treated with oral DG has been reported in several studies

(Pellicer et al, 1989; Li et al, 1994; Fatemi et al, 2007)

Oral DG vs Vaginal Progesterone

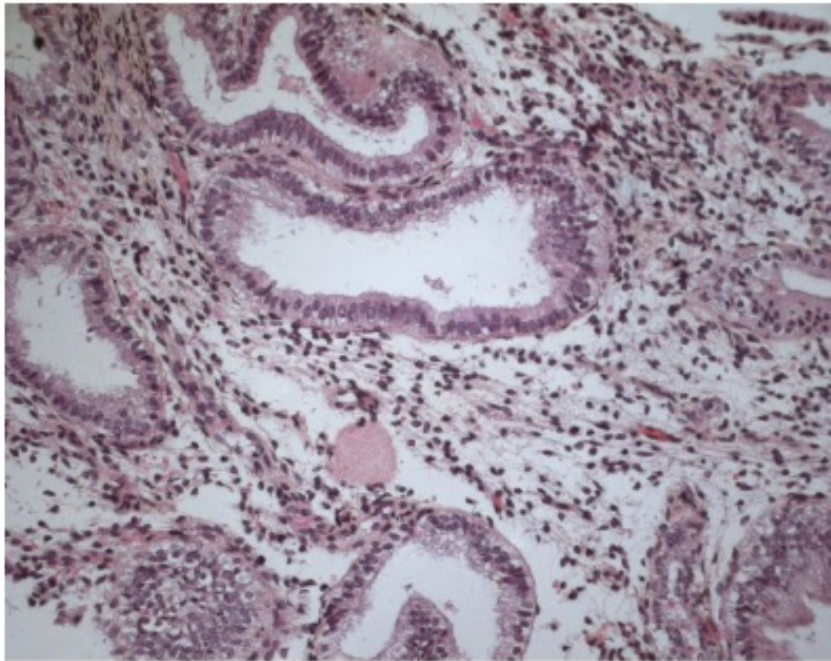


Figure 1. Representative endometrial biopsy on day 21 of an artificial cycle after micronized progesterone. Patients with premature ovarian failure received estrogen from days 1 to 21 and vaginal progesterone from days 15 to 21. (Coiled glands with active secretion and minimal residual vacuoles. Stromal oedema.) Absence of mitotic activity. The maturation corresponds to day 6 of the luteal phase (haematoxylin and eosin staining, $\times 200$).

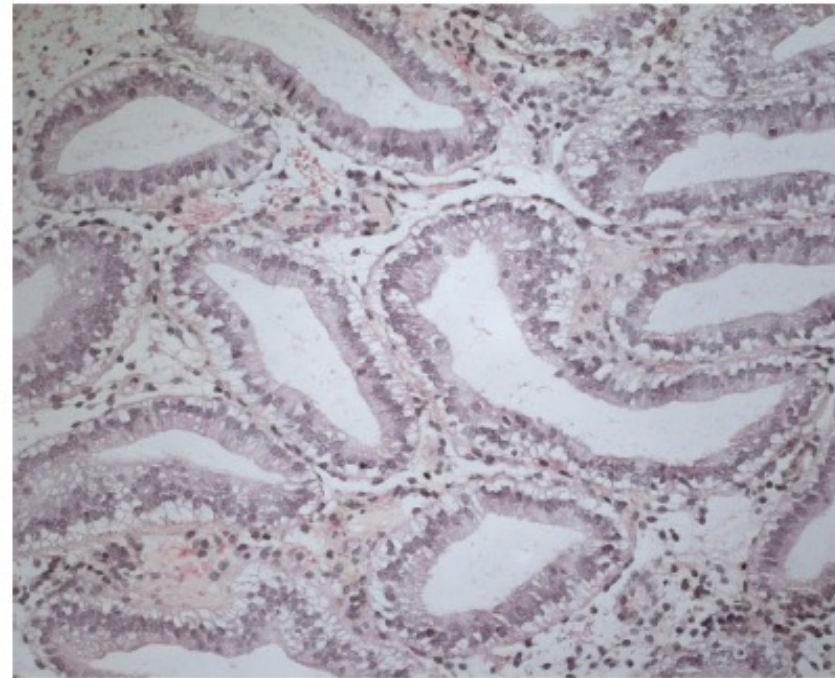
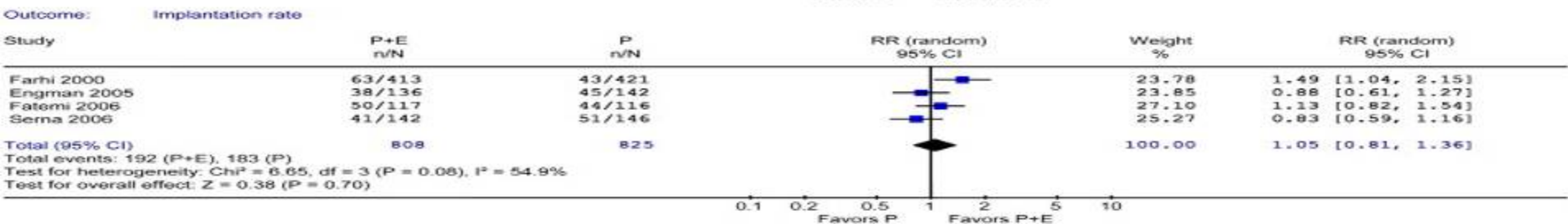
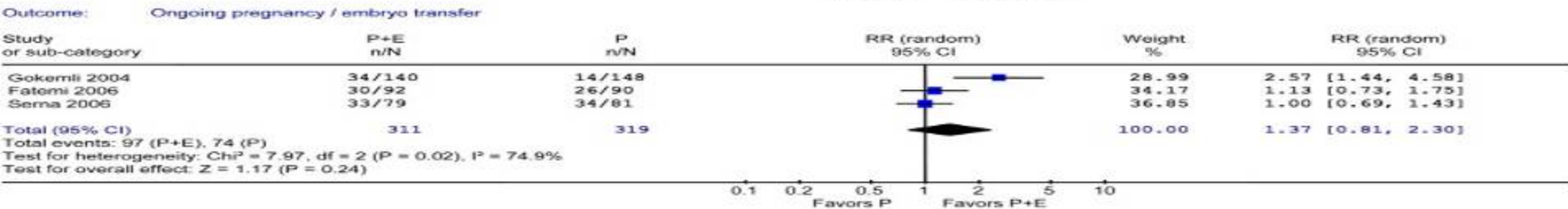
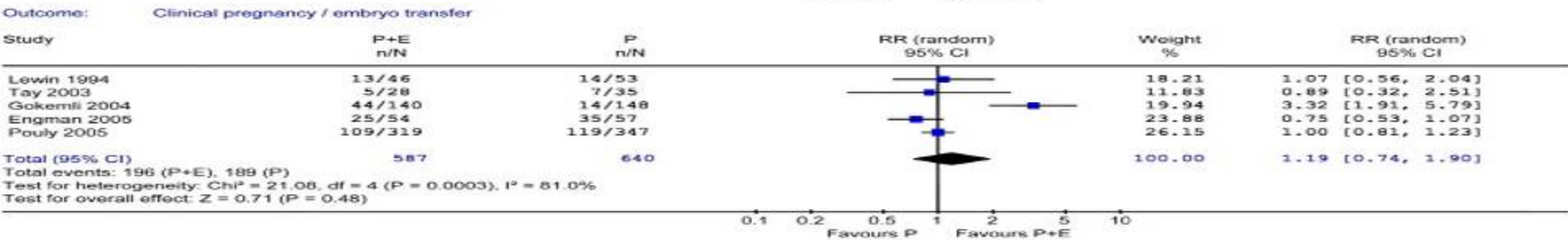
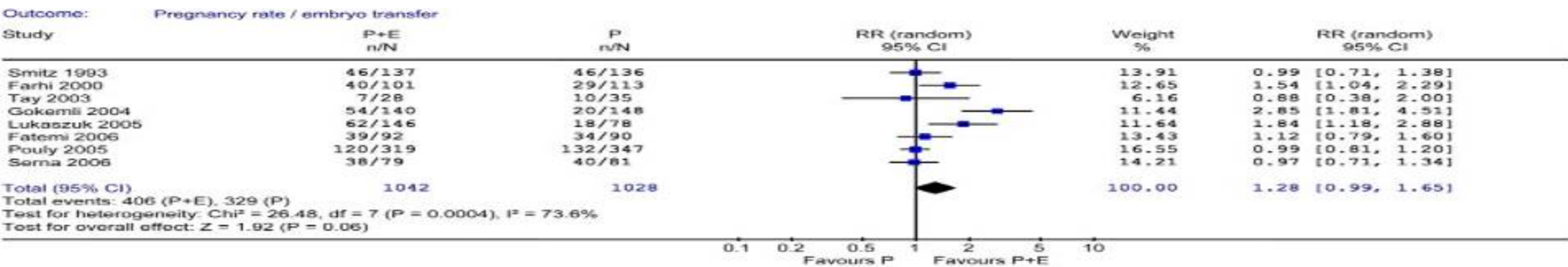


Figure 2. Representative endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and persistent homogeneous subnuclear vacuoles and pseudostratified nuclei. (No stromal edema. Focal mitotic activity.) The maturation corresponds to days 2–3 of the luteal phase (haematoxylin and eosin staining, $\times 200$).

A Systematic Review: P+E₂ vs. P (Gelbaya et al, 2008)



Is hCG in the Luteal Phase Superior to Progesterone?

- hCG does not provide better results than progesterone and is associated with a greater risk of OHSS

When do you Start Progesterone?

1. Day of hCG
2. Day of OR
3. Day of ET (day 3)
4. Day of ET (day 5)

What Is the Best Timing of Luteal Support?

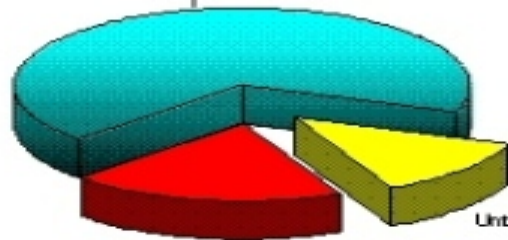
- There appears to be a window for P start time between the evening of oocyte retrieval and day 3 after oocyte retrieval.

How long should progesterone be administered?

1. Positive hCG
2. Up to 7 wks pregnancy
3. Up to 12 wks pregnancy
4. During the whole pregnancy

Analysis of >25,000 cycles

Until 10-12 weeks of gestation
67%

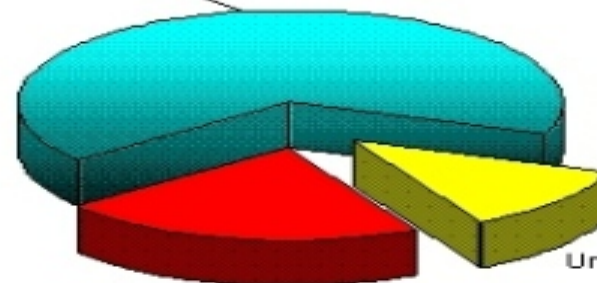


Until FHR is recognized
20%

Until b-hCG is positive
13%

Analysis of >50,000 cycles

Until 10-12 weeks of gestation
66%



Until FHR is recognized
22%

Until b-hCG is positive
12%

What Is the Best Length of Luteal Support?

- Does prolongation of luteal support during early pregnancy influence the delivery rate after IVF?
 - 200 mg vaginal progesterone three times daily during 14 days from the day of transfer until the day of a positive HCG test. In the study group (n = 150), vaginal progesterone was withdrawn from the day of positive HCG. The control group (n = 153) continued receiving vaginal progesterone during the next 3 weeks of pregnancy

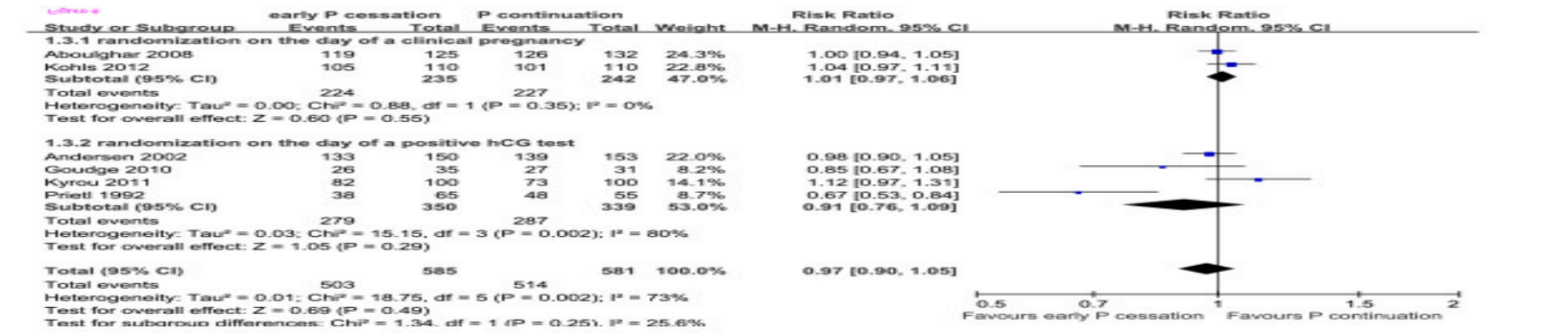
Liu et al, 2012



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



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



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

What Is the Best Length of Luteal Support?

- Prolongation of progesterone supplementation in early pregnancy has no influence on the miscarriage rate, and thus no effect on the delivery rate
- Progesterone supplementation can safely be withdrawn at the time of a positive hCG test

GnRH agonist for Luteal Support?

Hum Reprod Update. 2011 Nov-Dec;17(6):734-40. Epub 2011 Jul 6.

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

Kyrou D, Kolibianakis EM, Fatemi HM, Tarlatzi TB, Devroey P, Tarlatzis BC.

Unit for Human Reproduction, Department of Obstetrics and Gynaecology, Medical School, Papageorgiou General Hospital, Aristotle University of Thessaloniki, Nea Efkarpia Peripheral Road, Thessaloniki 54603, Greece. mimikyrou@yahoo.gr

The best available evidence suggests that GnRH agonist addition during the luteal phase significantly increases the probability of live birth rates.

Kyrou et al., Hum Reprod update. 2011

Luteal phase support in normo-ovulatory women stimulated with CC for intrauterine insemination: need or habit?

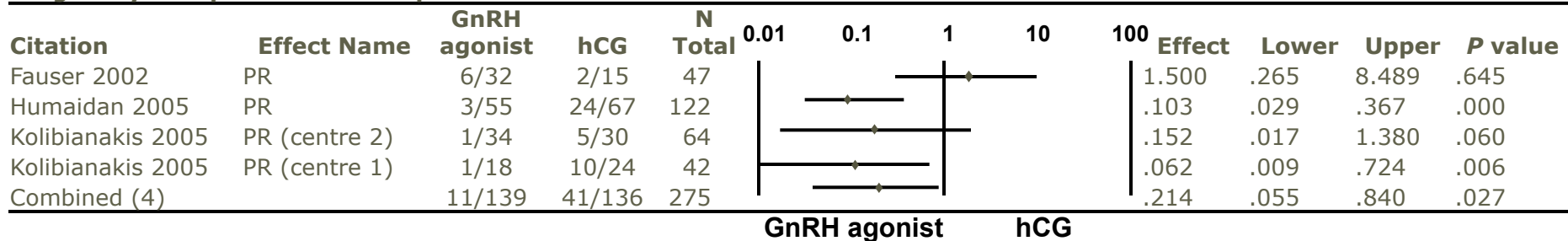
- $n = 468$
 - CC with Progesterone for LPS
 - CC without Progesterone for LPS
- No difference was observed in ongoing pregnancy between patients who did, or did not, receive vaginal progesterone as luteal support

GnRH agonist triggering

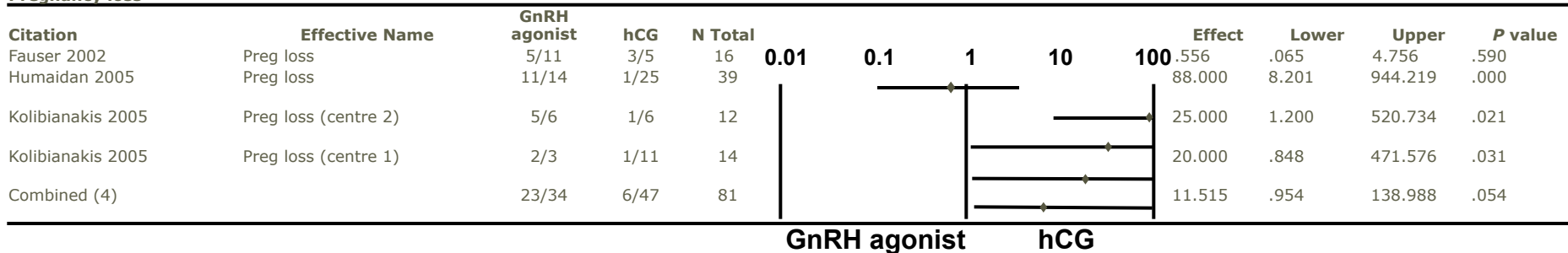
- Administration of a bolus of GnRH agonist induces release of LH from the pituitary gland similarly to a spontaneous mid-cycle LH surge:
 - Alternative to HCG in ovarian stimulation protocols
- GnRH α displaces the GnRH antagonist from the GnRH receptors in the pituitary triggering a surge of both LH and FSH

Agonist trigger: Outcome

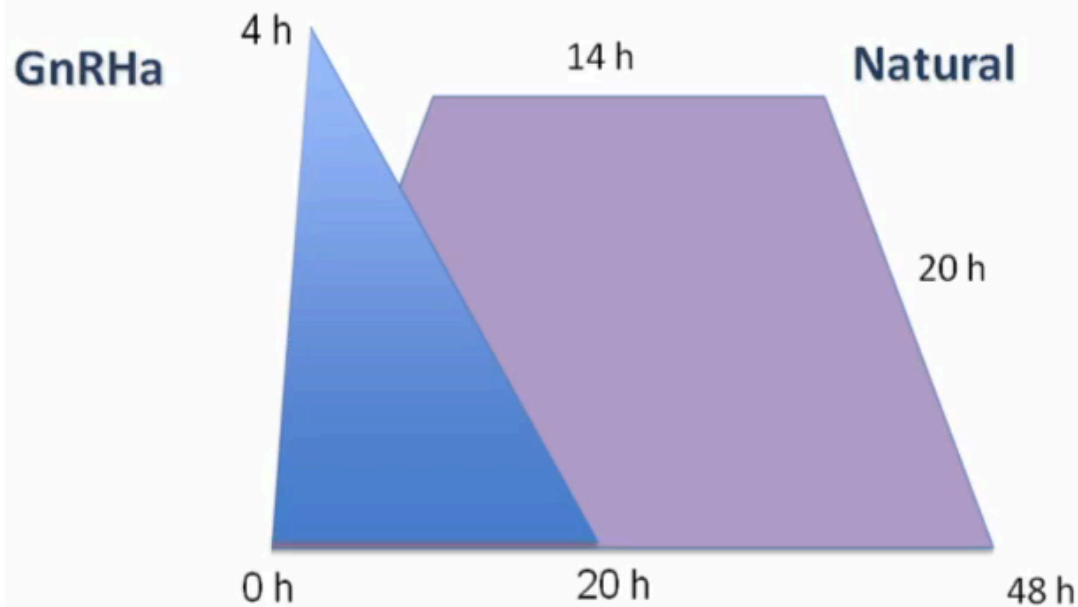
Pregnancy rate per randomized patient



Pregnancy loss

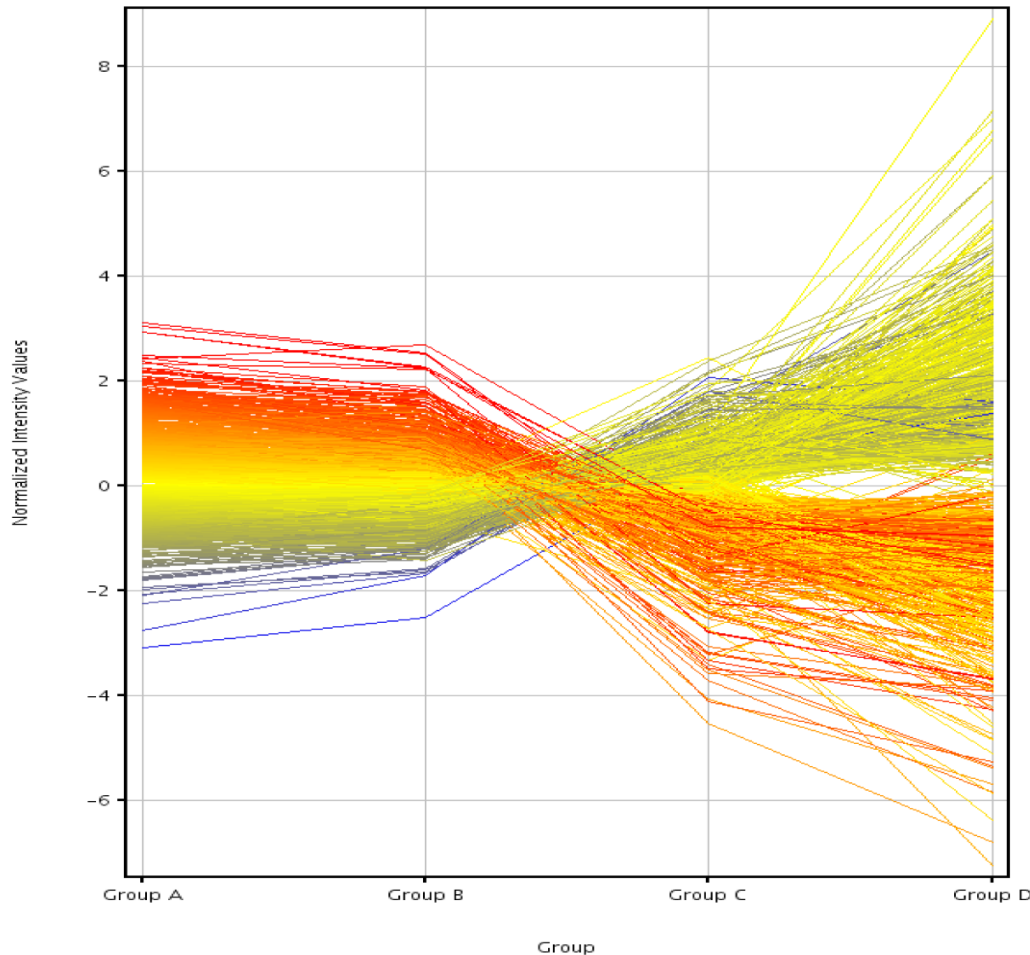


LH surge: GnRHa vs natural



Hoffer, 1983; Gonen, 1990; Itskovitz, 1991

Humaidan and Fatemi, HR 2013

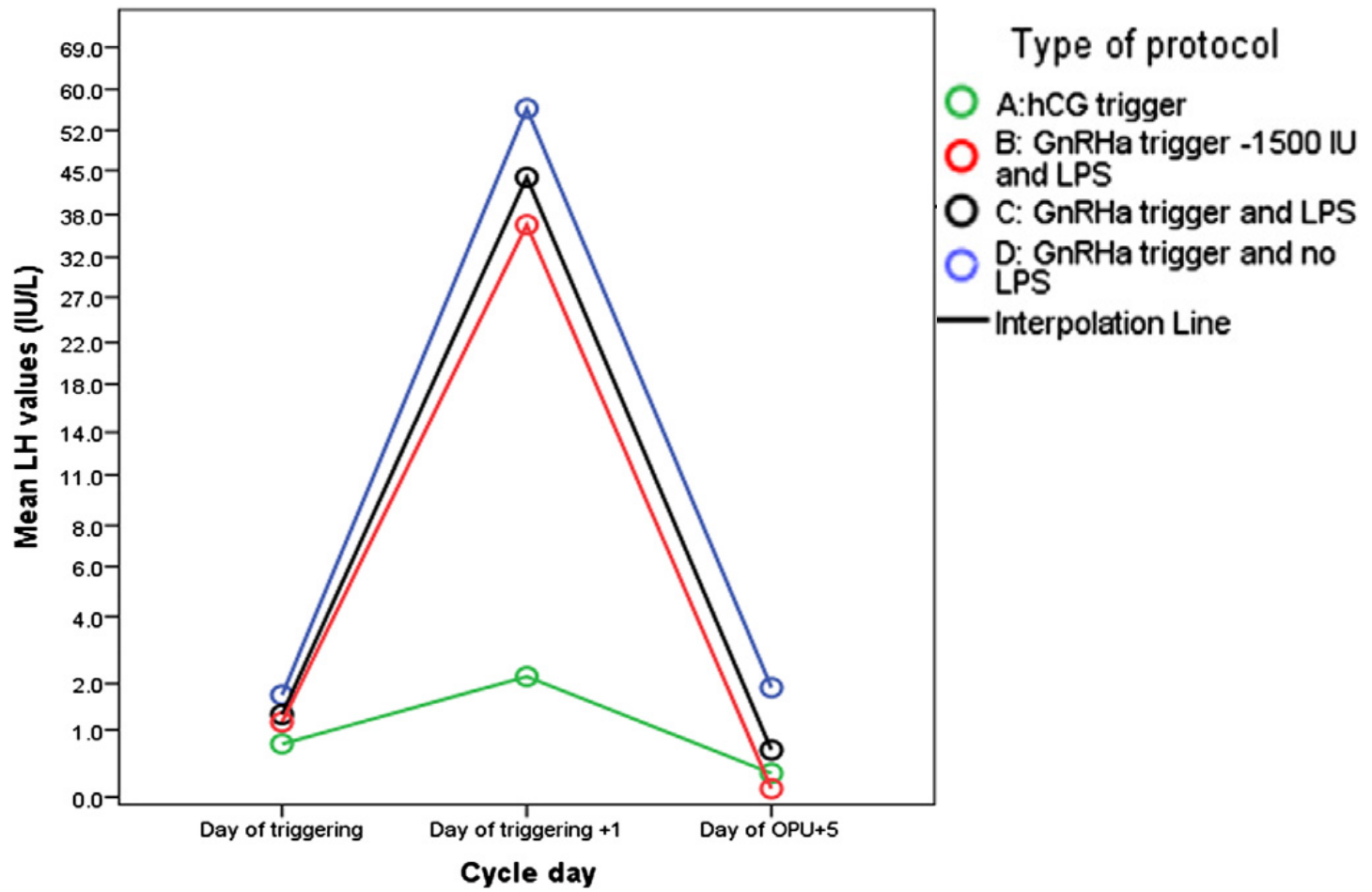


Group A: 10.000 IU hCG –
control group

Group B: 0,2 mg Triptorelin sc +
1.500 IU Pregnyl 1 h
before OPU

Group C: 0,2 mg Triptorelin

Group D: 0,2 mg Triptorelin no
luteal support

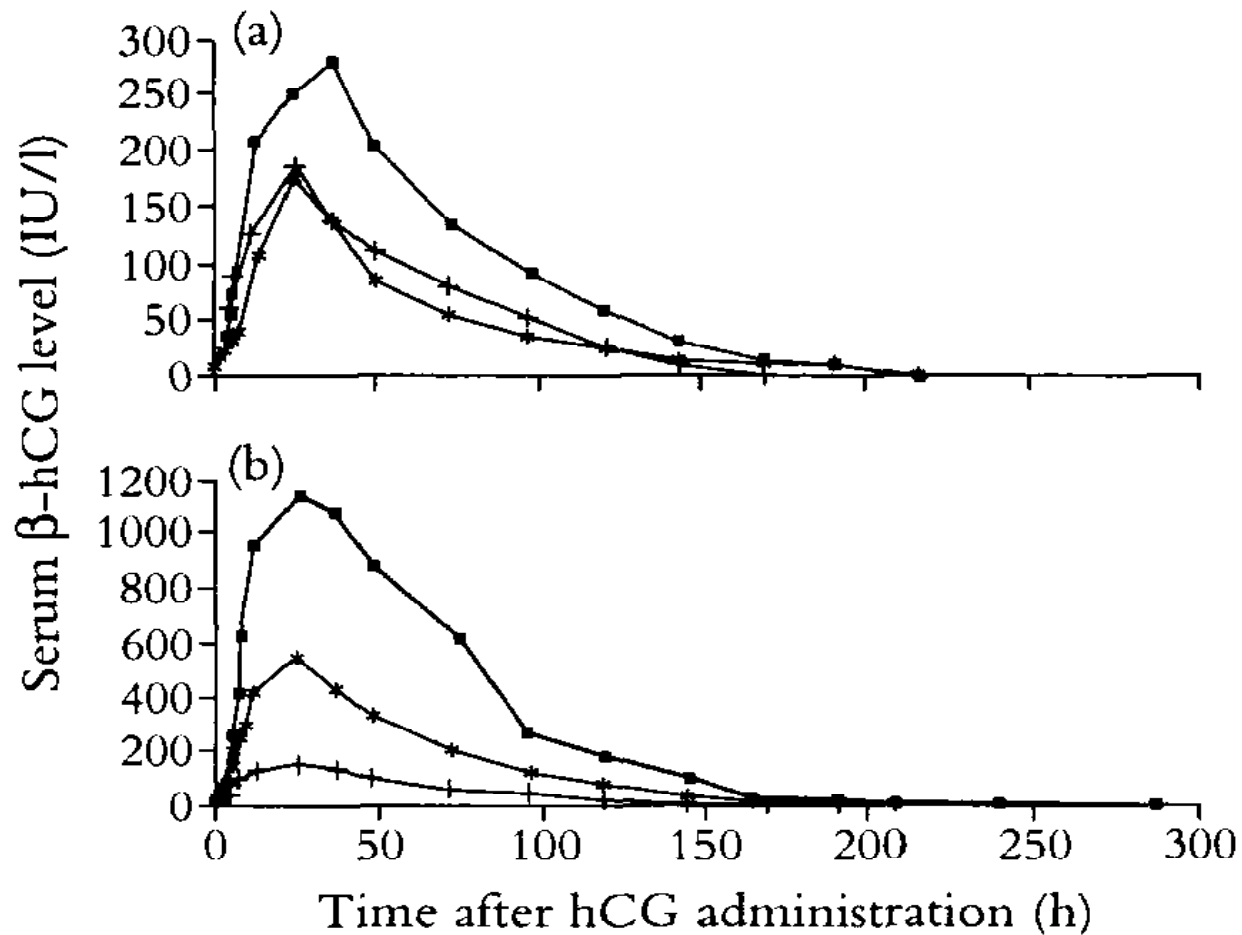


- As it has been established in primates as well as in humans, the duration of the LH/FSH surge is critical for a normal luteal function
- Short LH surge:
 - Normal oocyte maturation
 - Whereas the luteal phase length is reduced significantly
 - Implying that luteal support is required under these conditions
- An LH increment of too short a duration prevents the granulosa cells from completing luteinization, leading to a corpus luteum with impaired secretory function and a shortened lifespan

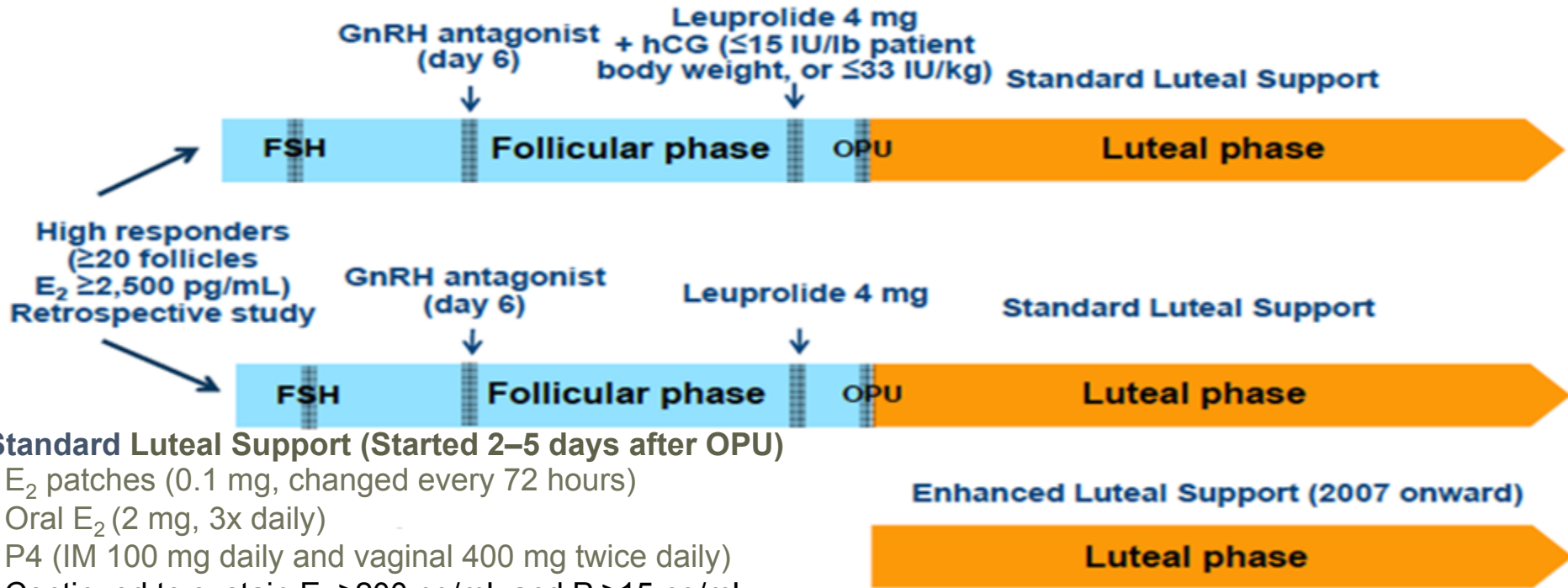
Why hCG?

- 60's: LH measured to calculate ovulation
- 70's: Agonist triggering described (Nakano, 1973)
- 80's: hCG binds on LH receptors(Kessler, 1979)
 - Good timing OPU
 - OHSS!

hCG triggering



GnRH agonist + low-dose hCG vs GnRH agonist with enhanced luteal support



Standard Luteal Support (Started 2–5 days after OPU)

- E₂ patches (0.1 mg, changed every 72 hours)
- Oral E₂ (2 mg, 3x daily)
- P4 (IM 100 mg daily and vaginal 400 mg twice daily)
- Continued to sustain E₂ ≥200 pg/mL and P ≥15 ng/mL until levels indicated placental production at ≈ 10 weeks' gestation

Enhanced Luteal Support

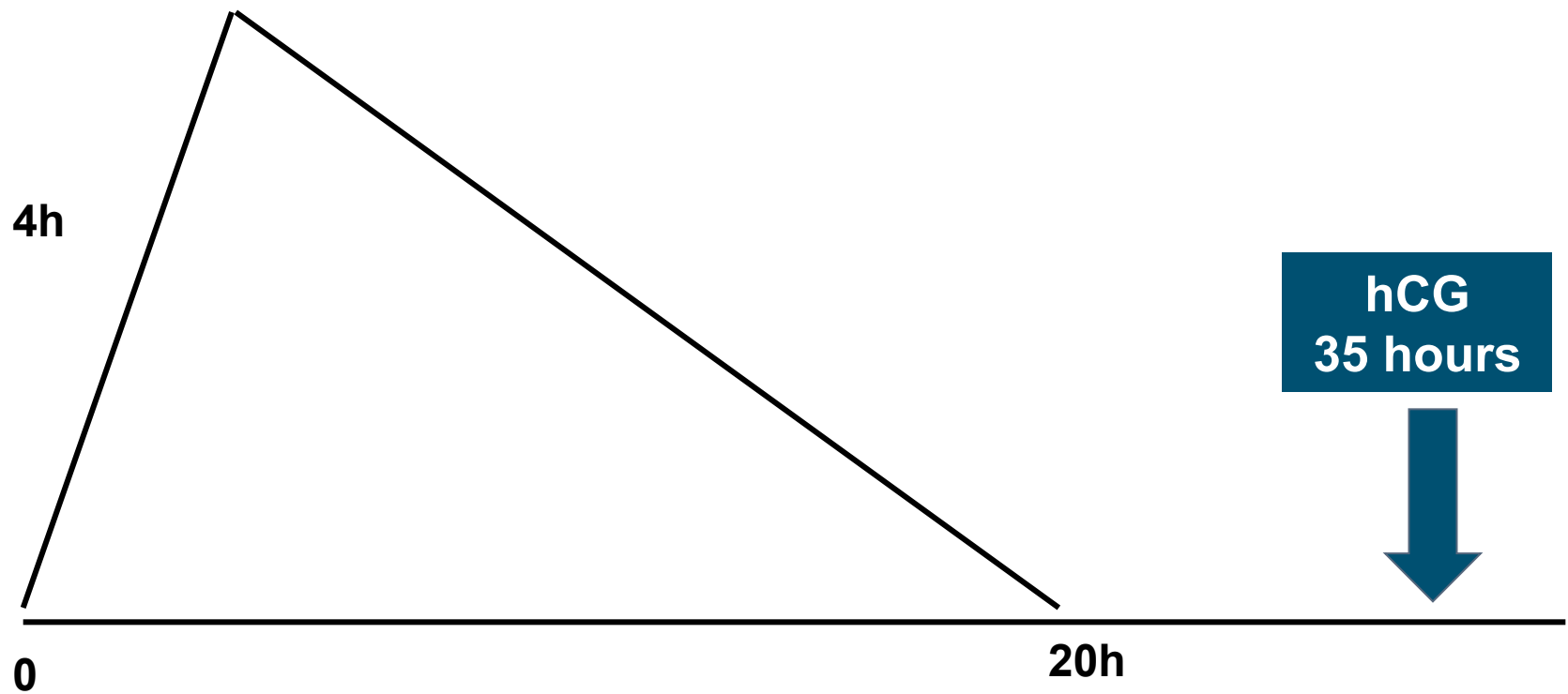
- E₂ and P as in standard support but initiated immediately after OPU

GnRH agonist + low dose hCG vs GnRH agonist with enhanced luteal support

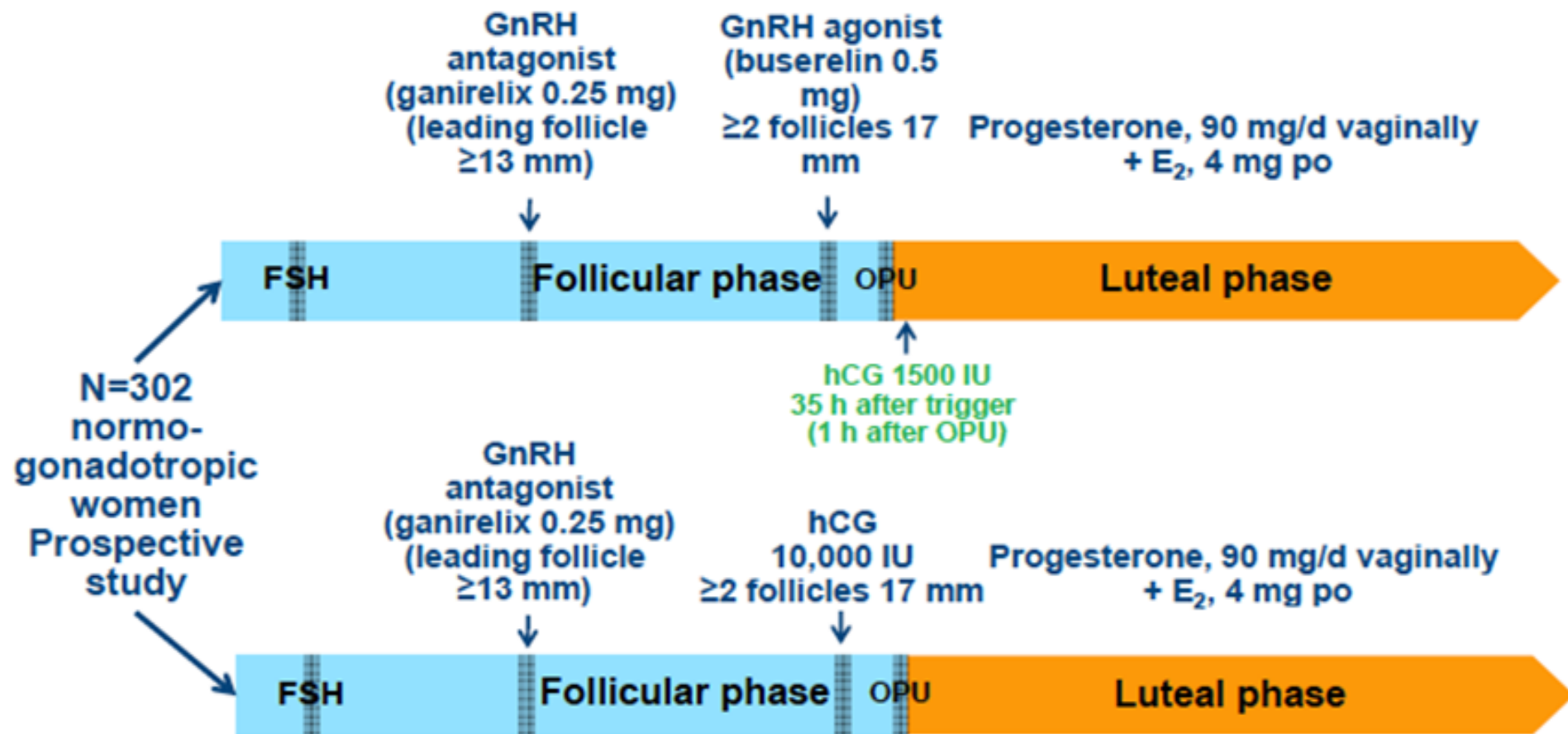
	Group 1 GnRH agonist + hCG standard luteal (n=182)	Group 2 GnRH agonist standard luteal (n=91)	Group 3 GnRH agonist enhanced luteal (n=24)	P value
Oocytes retrieved, n	20.4 ± 6.2	27.1 ± 11.2	25.4 ± 10.3	<0.001
Bipronuclear oocytes	13.7 ± 4.8 ^a	18.7 ± 9.0	16.8 ± 8.1	<0.001
Implantation rate (%)	48.8 ^a	20.6	37.8 ^a	<0.001
OPR (%)	57.7 ^a	25.3	50.0 ^a	<0.001
Early pregnancy losses (%)	23.4 ^a	58.2	20.0 ^a	<0.001
OHSS, n (%)	1 (0.55)	0	0	0.723

^aSignificantly different from group 2 in two-way comparison

Rescue of corpus luteum function with periovulatory hCG supplementation



GnRH agonist triggering + low-dose single-bolus hCG vs hCG: Protocol



GnRH agonist triggering + low-dose single-bolus hCG vs hCG: Results

	GnRH agonist (n=152)	hCG (n=150)	Odds Ratio (95% CI)	P value
Oocytes, mean no.	8.9 ± 5.4	9.3 ± 5.0	-	0.23
MII/ICSI, n (%)	465/546 (85.2)	468/574 (81.5)	-	0.06
Clinical pregnancy rate per patient (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	0.29
OPR per patient (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	0.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	0.16
OHSS	0	3		

Dual trigger

- Patients <40 years
 - E2 \geq 4,000 pg/mL at risk of OHSS
- Triggered
 - GnRHa or
 - GnRHa plus 1,000 IU hCG (dual trigger)

Dual trigger

TABLE 3

Outcome of IVF cycle.

Variable	GnRHa alone	Dual trigger	P value
Biochemical miscarriage rate (%)	14/43 (32.6)	4/26 (15.4)	NS
Clinical miscarriage rate (%)	6/43 (14.0)	3/26 (11.5)	NS
Implantation rate (%)	27/122 (22.1)	26/62 (41.9)	< .01
Clinical pregnancy rate (%)	25/68 (36.8)	20/34 (58.8)	.03
Live birth rate (%)	21/68 (30.9)	18/34 (52.9)	.03
OHSS rate (%)	0/68 (0)	1/34 (2.9)	NS

Note: OHSS = ovarian hyperstimulation syndrome.

Griffin. Dual GnRHa/hCG trigger in IVF. *Fertil Steril* 2012.

hCG (1,500IU) day 3 post OPU

Haas *et al. Journal of Ovarian Research* 2014, **7**:35
<http://www.ovarianresearch.com/content/7/1/35>

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Table 1 Comparison between IVF cycles with intense luteal support only versus additional luteal hCG

	hCG group (n = 5)	Intense luteal support group (n = 6)	p values
Age (yrs)	31.6 ± 4.6	29.8 ± 5.1	ns
BMI (kg/m ²)	23.65 ± 3.8	23.0 ± 2.5	ns
Length of stimulation (days)	9 ± 2.1.8	10.3 ± 3.8	ns
Number of gonadotropin ampoules used	17.1 ± 3.4	22.0 ± 11.5	ns
Peak E2 levels on day of hCG administration (pmol/L)	10597 ± 669	13064 ± 3019	ns
Peak progesterone levels on day of hCG administration (nmol/L)	2.1 ± 0.2	2.3 ± 0.5	ns
Number of oocytes retrieved	18.4 ± 3.5	19.6 ± 3.0	ns
Mid-luteal progesterone levels (nmol/L)	>127	42.1 ± 14.5	<0.0001
Pregnancy rate	2/5(40%)	1/6(16.6%)	ns

Luteolysis: how long to “reanimate”?

- Corpus luteum function can be rescued if gonadotrophin therapy is reinitiated within 3 days (Hutchison and Zeleznik, 1985).
- Rescue of the corpora lutea for longer period than 3 days is hcg dose dependent , i.e. ≥ 1500 IU (Dubourdieu et al, 1991, Weosman et al, 1996).
- After GnRH agonist trigger, Corpus luteum is capable of recovering even after 7 days if supra-physiologic doses of hCG are administered.
(Weisman et al.1996)

What options do we have for hCG administration?

- 1,500 IU with OPU (Humaidan et al, 2006)
- 1,000 IU with trigger (Griffin et al, 2011)
- 1,500 IU 3 days post OPU (Haas et al, 2014)

What about safety of corpora lutea stimulation?

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Human
Reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG

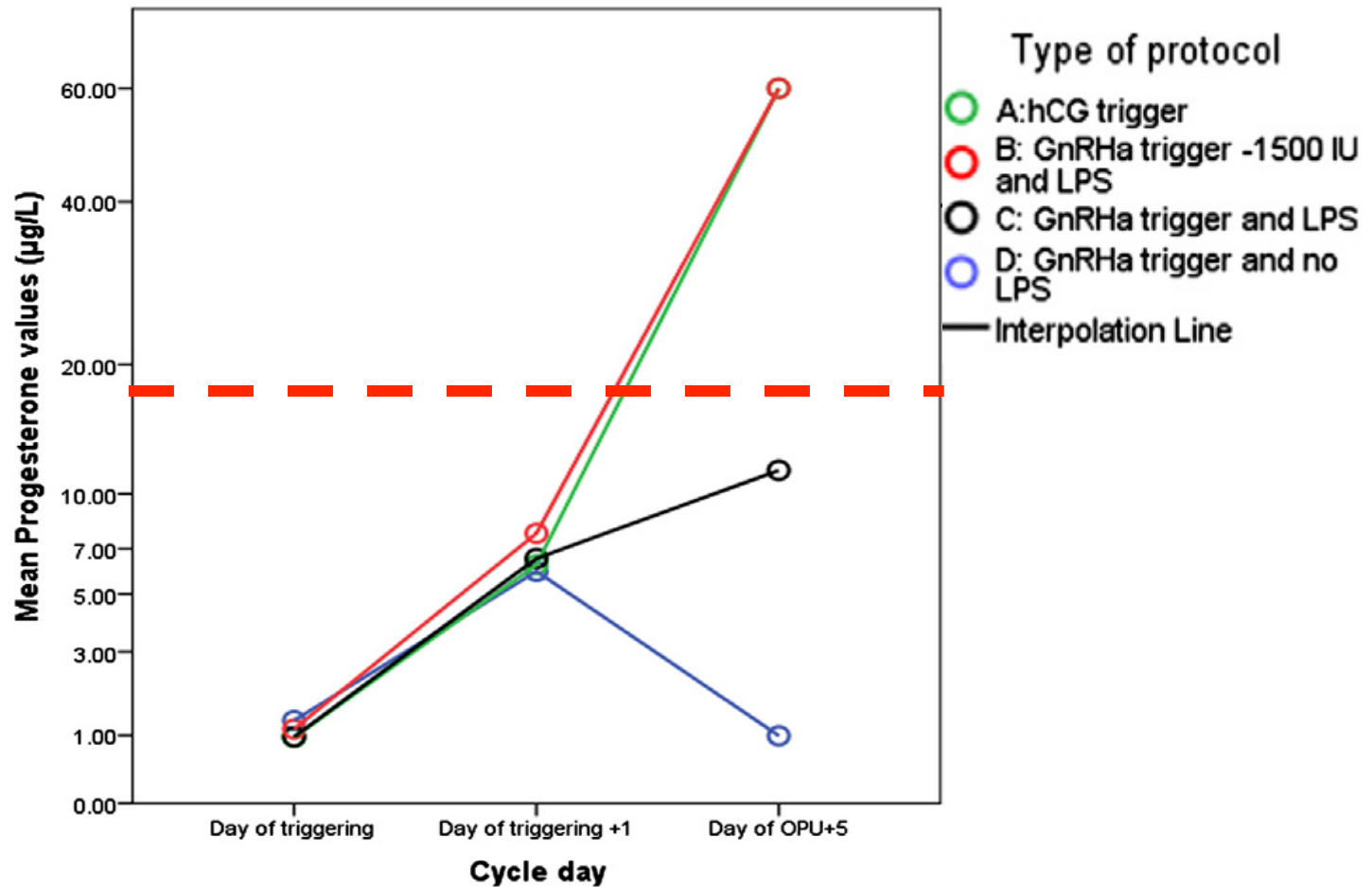
Ayse Seyhan^{1,2,†}, Baris Ata^{1,2,3,†}, Mehtap Polat⁴, Weon-Young Son¹, Hakan Yarali⁴, and Michael H. Dahan^{1,2,*}

¹Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, McGill University, Montreal, QC H3A 1A1 ²McGill University Health Centre Reproductive Centre, Montreal, QC, Canada H3A 1A1 ³Assisted Reproduction Unit, Uludağ University, Bursa 16059 Turkey ⁴Anatolia IVF Centre, Ankara 06690 Turkey

*Correspondence address. Royal Victoria Hospital, 687 Pine Avenue West, Women's Pavilion, F6.58, Montreal, QC, Canada H3A 1A1
Tel: +1-514-843-1650; Fax: +1-514-843-1496; E-mail: michael.dahan@muhc.mcgill.ca



Fatemi et al, 2013, FS



ARTICLE IN PRESS

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and “freeze-all” approach in GnRH antagonist protocol

Human Mousavi Fatemi, M.D., Ph.D.,^a Biljana Popovic-Todorovic, M.D., Ph.D.,^b Peter Humaidan, M.D., D.M.Sc.,^c Shahar Kol, M.D., Ph.D.,^d Manish Banker, M.D.,^e Paul Devroey, M.D., Ph.D.,^a and Juan Antonio García-Velasco, M.D., Ph.D.^f

^a Center for Reproductive Medicine, Dutch-Speaking Free University Brussels, Brussels, Belgium; ^b Special Gynecology Hospital “Ivanovic,” Belgrade, Serbia; ^c Fertility Clinic, Skive Regional Hospital and Faculty of Health, Aarhus University, Aarhus, Denmark; ^d Department of Obstetrics and Gynecology, IVF Unit, Rambam Medical Center, Haifa, Israel; ^e NOVAIVI, Ahmadabad, India; and ^f Instituto Valenciano de Infertilidad-MADRID, Madrid, Spain

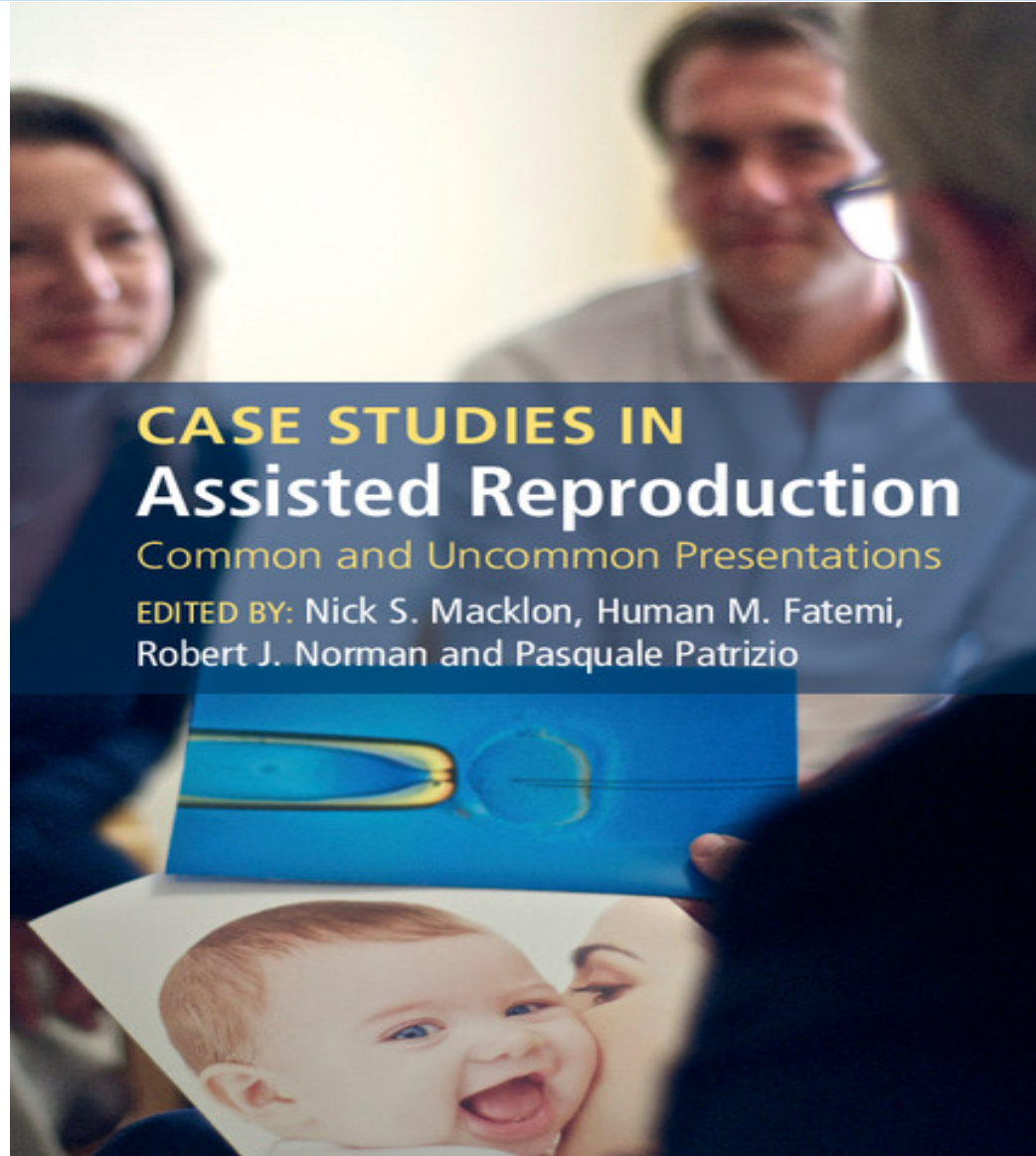
Summary

- Need luteal support whenever gonadotropins with multiple follicle recruitment and ovulation
- Vaginal progesterone most popular form of luteal support
- IM/SC and vaginal progesterone are equivalent
 - IM should not be the first choice
- Duration of luteal support?
- No benefit of E2 in the luteal phase
- Further need for RCTs to confirm the possible benefit of oral dydrogesterone for LPS

Summary

- In GnRH antagonist cycles triggered by GnRH agonist: need for hcg/high dose of steroids
- Other strategies for enhanced luteal support, such as enhanced steroid support, may also provide good pregnancy rates
 - however, further research is needed
 - Individualisation of LPS

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CASE STUDIES IN
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Common and Uncommon Presentations

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