The luteal phase in a natural and stimulated cycle

Christophe Blockeel
UZ Brussel

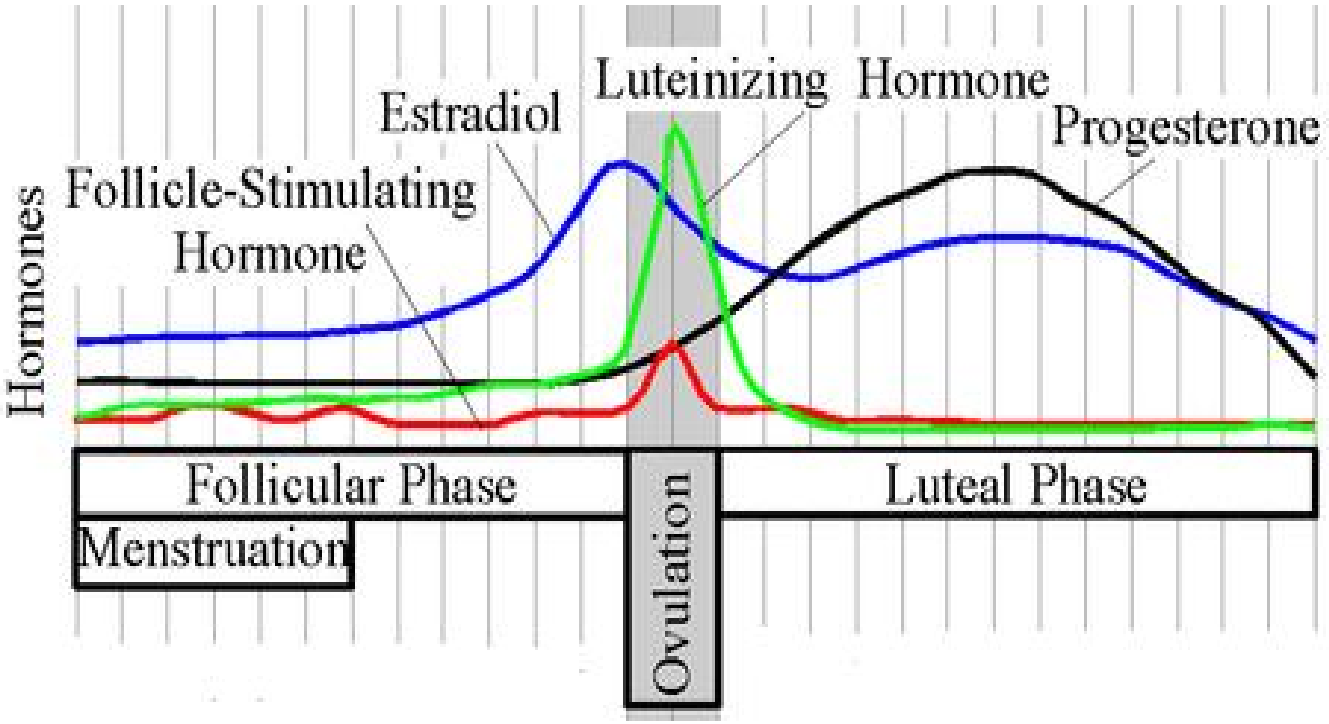
Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Luteal phase in a natural cycle

Which hormones seem to be crucial during the luteal phase in a natural cycle?



Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel
Centrum voor Reproductieve Geneeskunde

The role of LH in the luteal phase

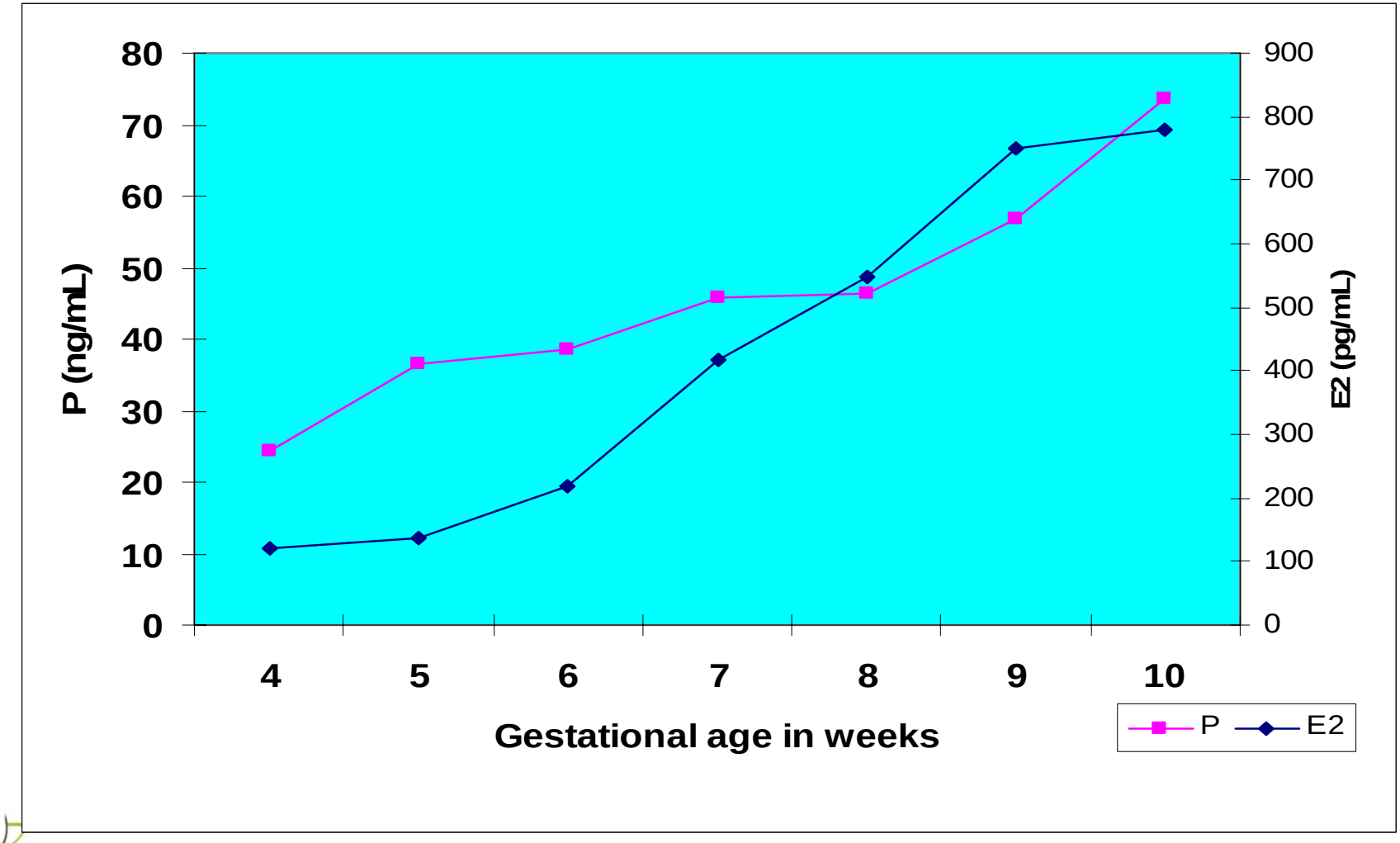
Crucial!

- → 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)

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

Luteo-placental shift



Scott et al.,1991

Luteal phase defect in a natural cycle

- In 1949: premature onset of menses : indication of luteal phase deficiency of progesterone production (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 = **8.1%** (Rosenberg et al., 1980).

Causes of luteal phase defect in a natural cycle

- Disordered folliculogenesis
- Defective corpus luteum function
- Abnormal luteal rescue by the early pregnancy
- A variety of clinical conditions, such as
  - hyperprolactinemia
  - hyperandrogenic states
  - weight loss
  - stress
  - athletic training may result not in oligo- or anovulation, but rather may be manifest as LPD (Ginsburg , 1992).

How to define a luteal phase defect in a natural cycle?

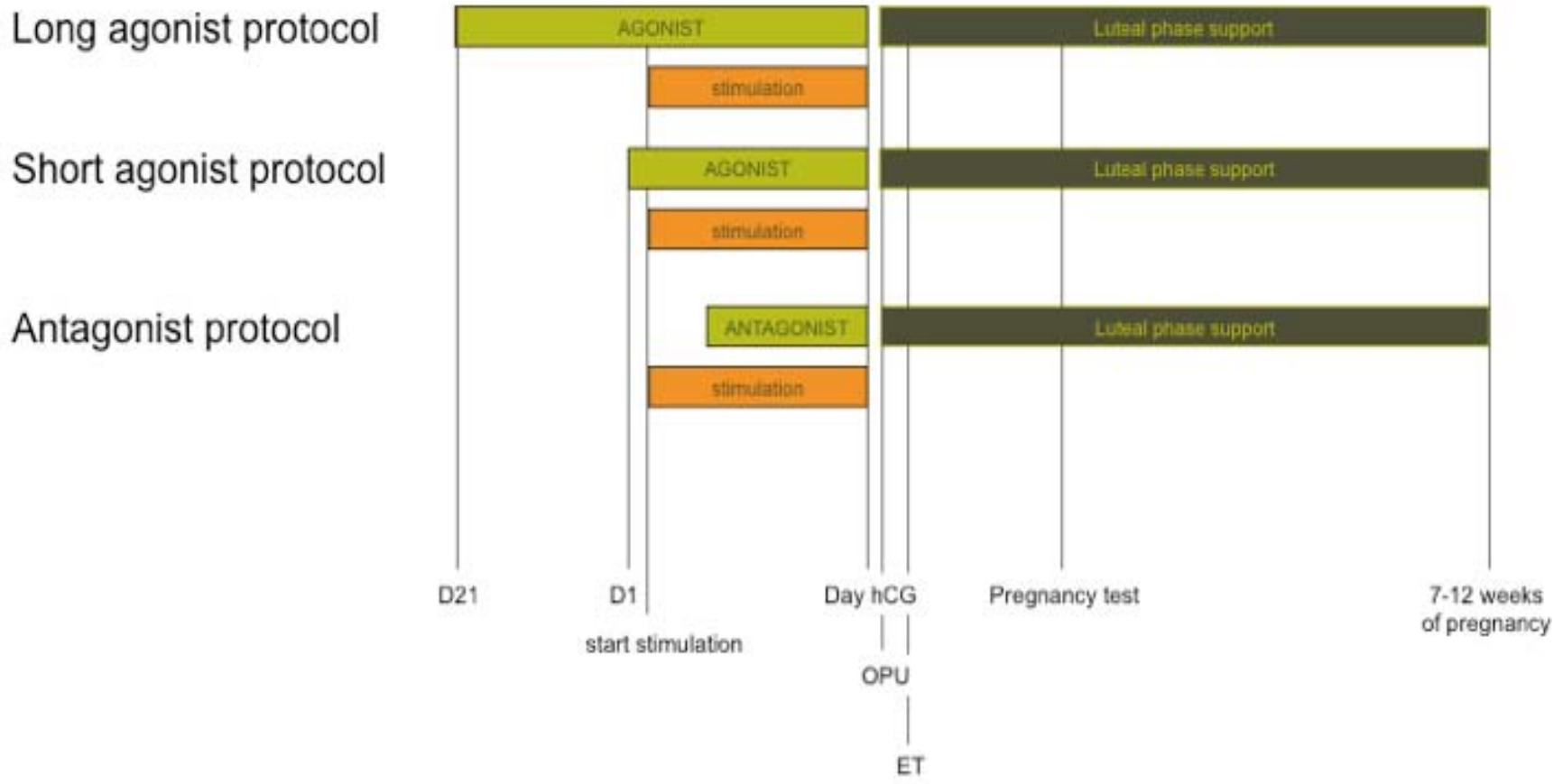
- Serum mid-luteal progesterone levels < 10ng/ml (Jordan et al.,1994)

- Mid-luteal progesterone levels do not always reflect the endometrial maturation (Batista et al., 1994)

- “Most reasonable” consensus =

  a lag of more than two days in endometrial histological development compared to the expected day of the cycle (Jones, 1991; Dawood, 1994).

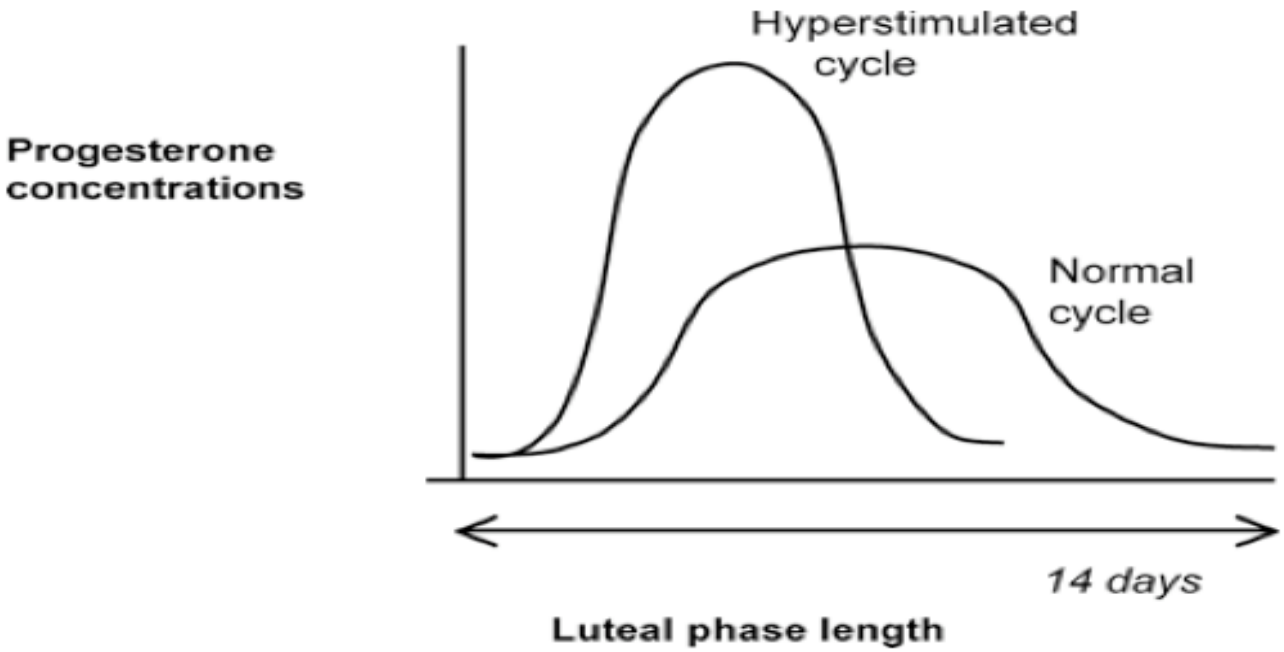
The luteal phase in stimulated cycles



Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

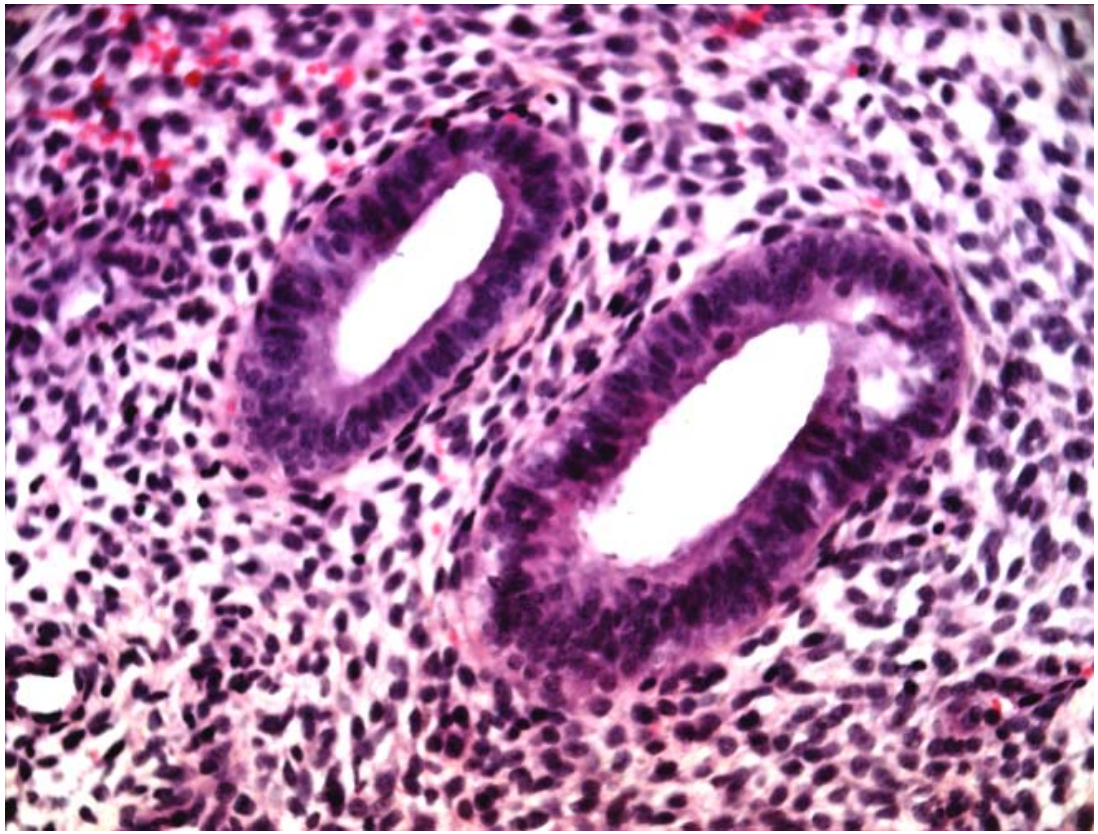
Centrum voor
Reproductieve Geneeskunde

Luteal phase defect in all stimulated cycles



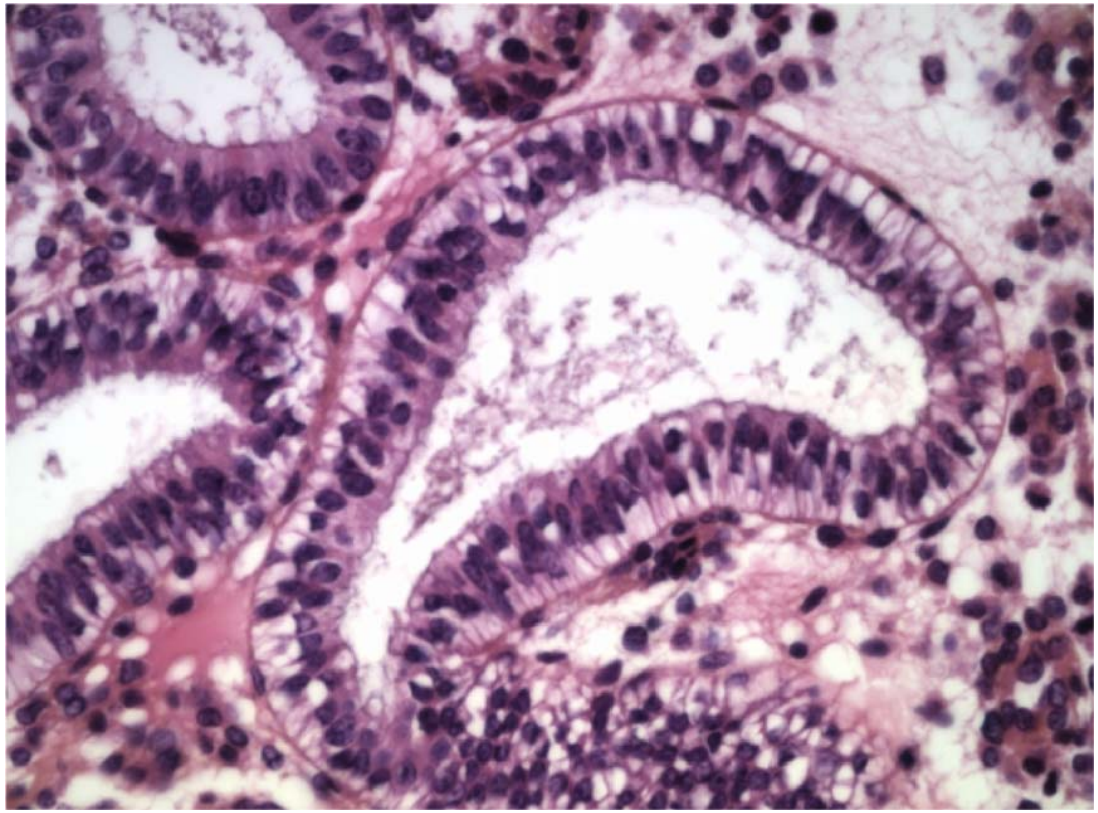
Schematic representation of changes in luteal phase length and progesterone profile induced by ovarian hyperstimulation for IVF (Macklon et al., 2006)

Endometrial biopsy on the day of ovulation, natural cycle



No secretory features

Endometrial biopsy on the day of oocyte retrieval, GnRH agonist and gonadotrophin stimulation cycle



Clear secretory features

Etiology of luteal phase defect

- Oocyte retrieval?
  - Removal of granulosa cells
- hCG?
  - Suppressing LH
- GnRH agonist? GnRH antagonist?
- Combination of these factors?

LH concentration during the luteal phase (post hCG) in GnRH agonist and gonadotrophin stimulation cycles

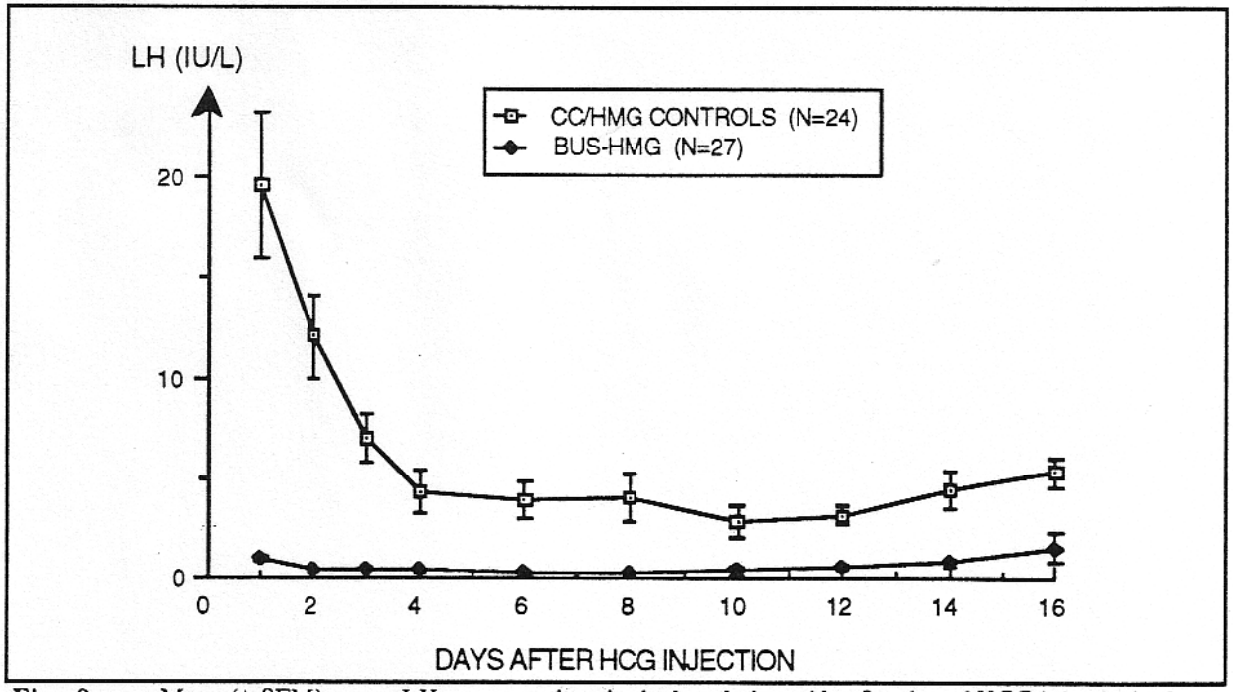


Fig. 9.x: Mean (± SEM) serum LH concentrations in the luteal phase (day 0 = day of HCG injection) of buserelin/HMG and CC/HMG (controls) treated patients.

Smitz HR 1988

Statement

GnRH antagonist can be safely administered in gonadotrophin stimulated IUI cycles without luteal phase supplementation

Ragni HR 2001

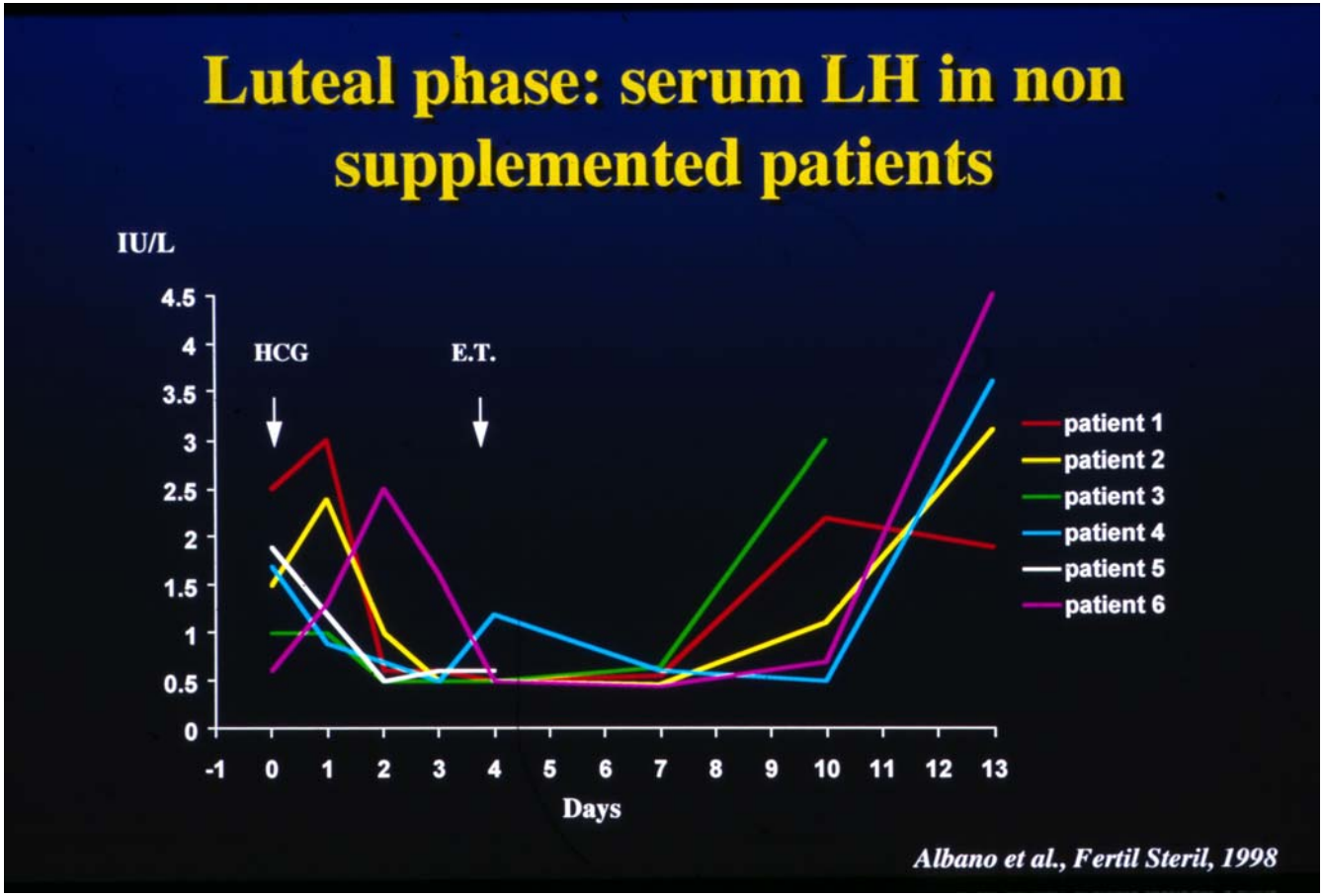
Is this statement in contradiction with the lecture ?

Answer : **No**

Stimulation	FSH + antagonist	FSH alone
Mean no of follicles	2.7	3.2
FSH units	1080	1054
E2 (ng/ml) (pre hCG)	500	900
LH (U / L) (day 4 post hCG)	1.8	2.5

Ragni HR 2001

Is the luteal phase LH concentration (post hCG) in antagonist – gonadotrophin cycles normal or decreased ?



Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Is luteal support necessary in GnRH antagonist cycles?

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)
No. patients achieving embryo transfer[b]	9	11	14
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)

Support of corpus luteum function remains mandatory after ovarian stimulation for IVF with GnRH antagonist co treatment

Beckers et al 2003 JCEM

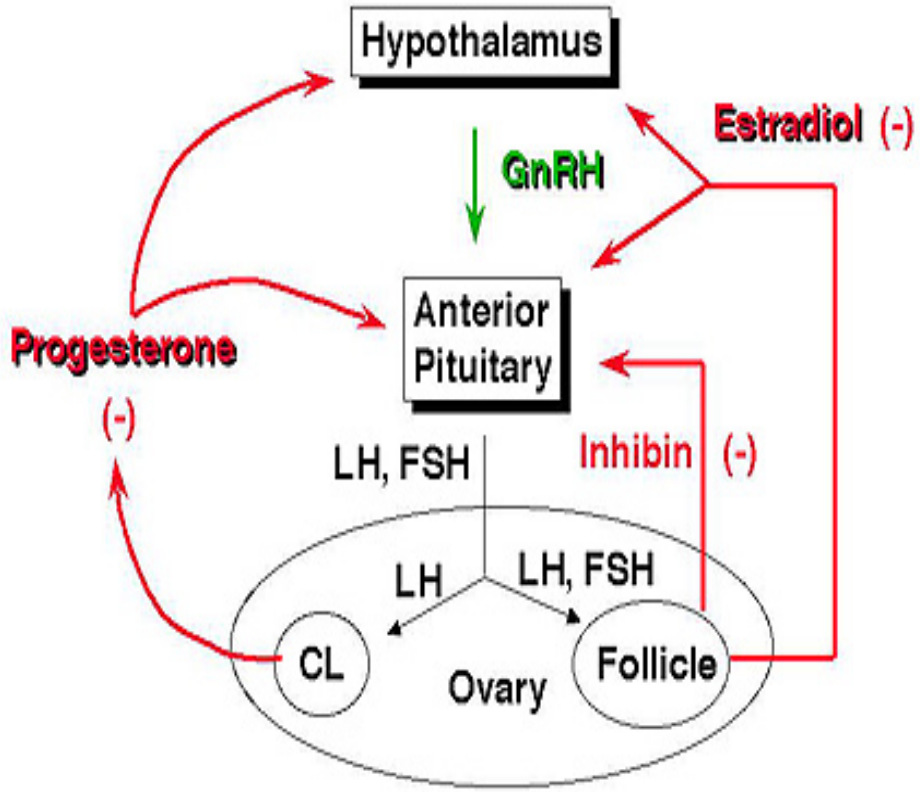
Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Etiology of luteal phase defect in ART cycles

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

(Fatemi et al, HRU, 2007)



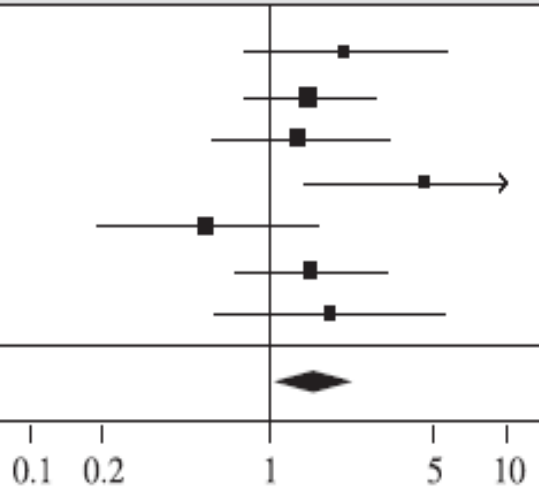
Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

The use of progesterone in IVF

Table 5. Meta-analysis of the relative risk and 95% CI of patients using various routes of progesterone vs. placebo

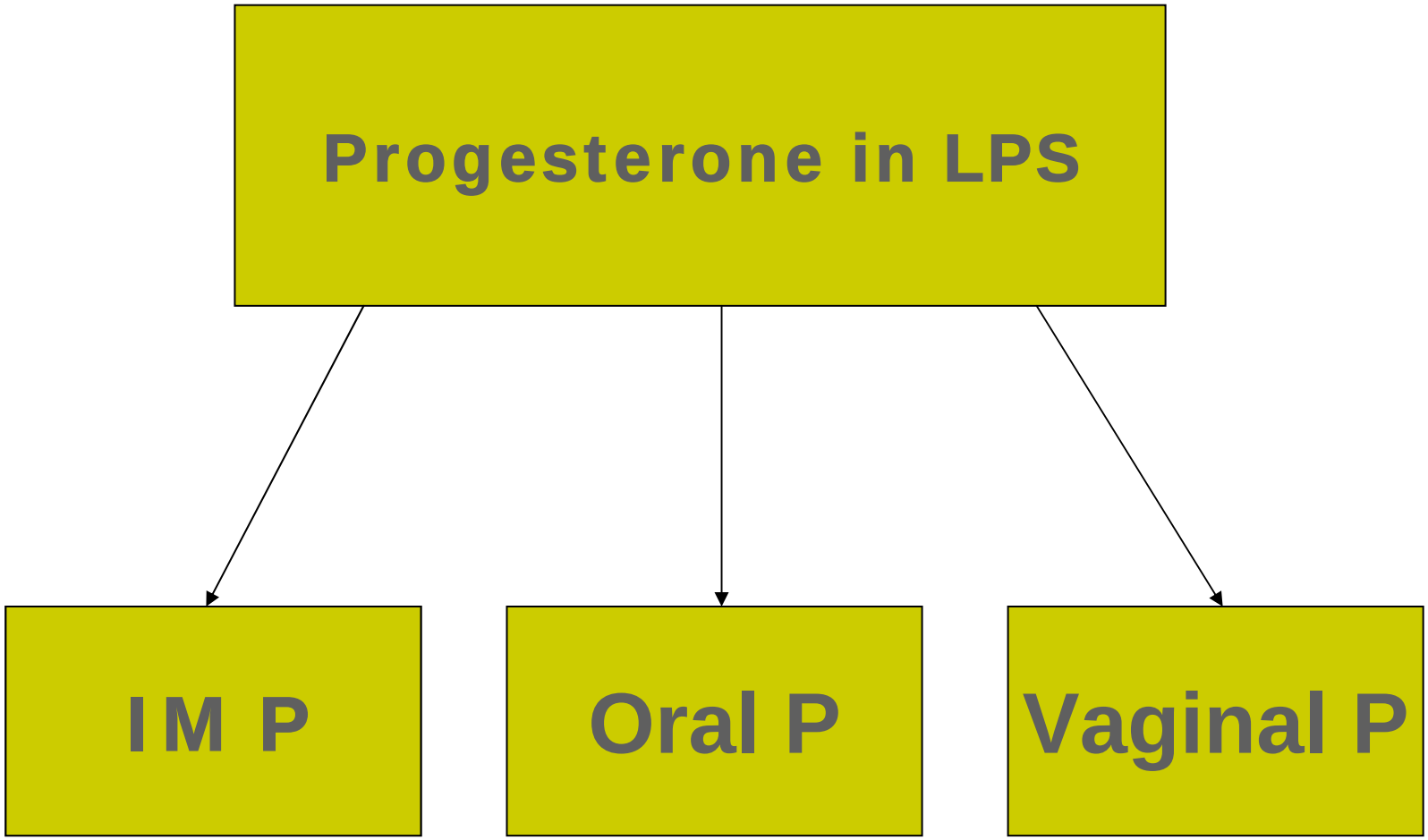
Study	Progesterone n/N	Placebo n/N	OR (95% CI fixed)	Weight %	OR (95% CI fixed)
Albert et al. [14]	14/43	8/43		9.2	2.11 (0.78, 5.73)
Belaisch-Allart et al. [19]	27/141	20/145		27.3	1.48 (0.79, 2.78)
Leeton et al. [17]	14/72	12/80		15.7	1.37 (0.59, 3.19)
Polson et al. [15] GIFT	13/34	5/42		4.7	4.58 (1.43, 14.64)
Polson et al. [15] IVF	6/58	10/58		15.4	0.55 (0.19, 1.64)
Van Steirteghem et al. [16]	18/68	19/100		19.4	1.53 (0.74, 3.20)
Yovich et al. [18]	11/77	5/60		8.3	1.83 (0.60, 5.60)
Total (95% CI)	103/493	79/528		100.0	1.57 (1.13, 2.17)



Test for heterogeneity: $\chi^2 = 7.35$, d.f. = 6, p = 0.29.
Test for overall effect: z = 2.70, p = 0.007.

Nosarka et al., 2005

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel
Centrum voor Reproductieve Geneeskunde


Progesterone in LPS
I M P
Oral P
Vaginal P

IM Progesterone

Effective

Physiological serum levels

Painful (long, thick needles)

Occasional sterile abscess

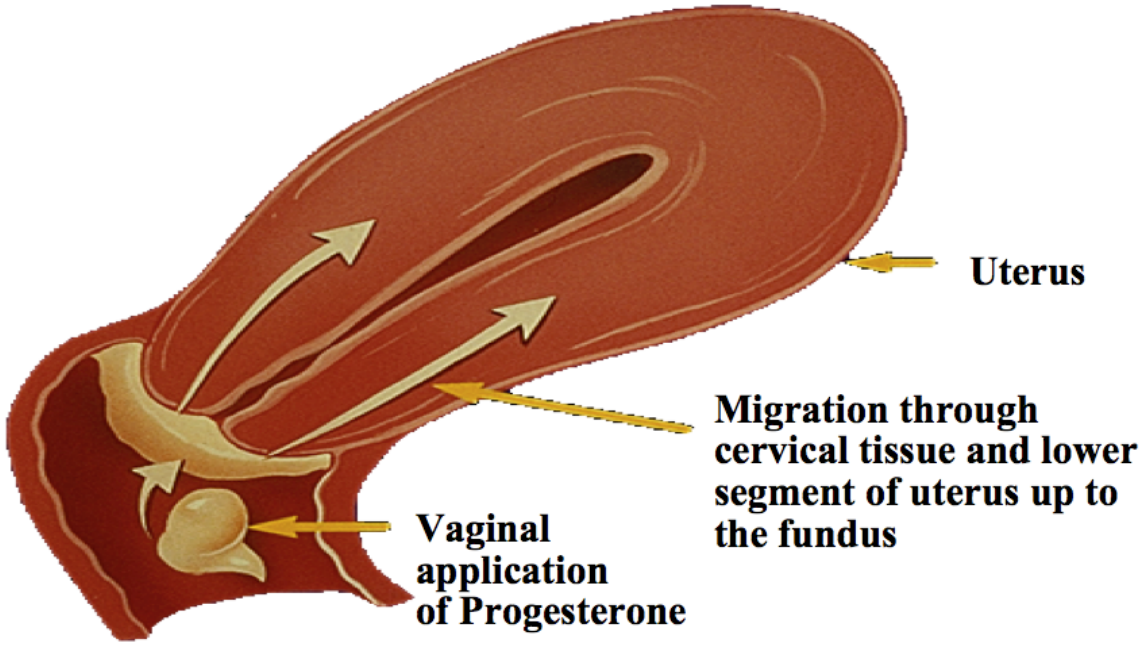
Occasional allergic reaction (oil vehicle)

Needs to be administered by nurse, husband

Acute eosinophilic pneumonia associated with IM administration of progesterone as luteal phase support after IVF: 4 case reports

Vaginal progesterone

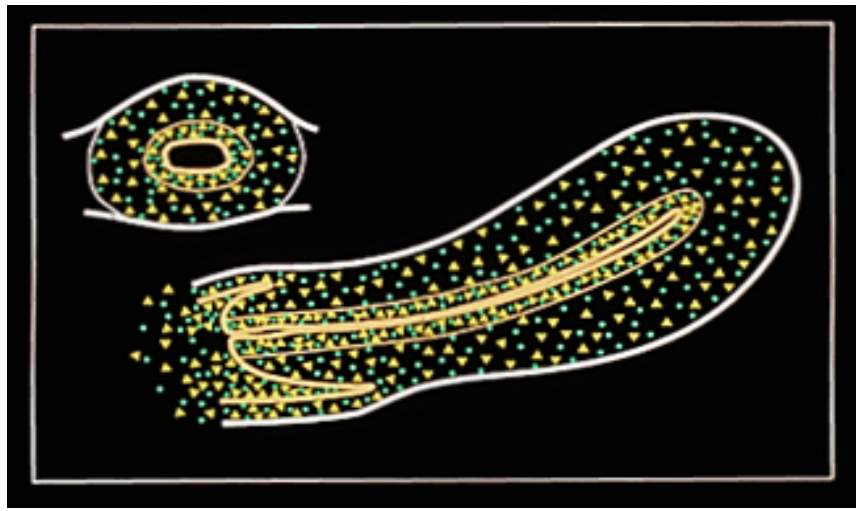
First uterine pass effect /targeted delivery



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

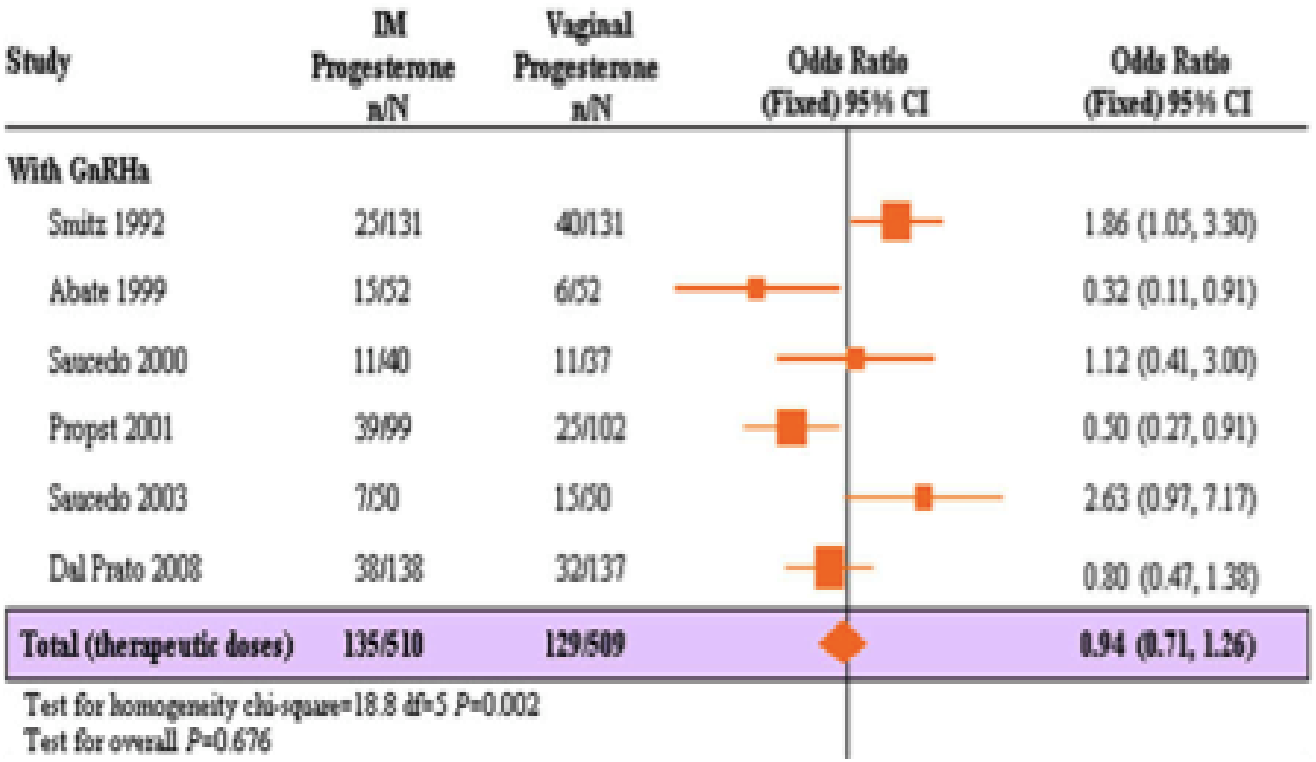
Bulletti et al. Hum Reprod. 1997;12:1073-9

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

IM vs Vaginal progesterone

Intramuscular versus vaginal P administration: ongoing pregnancy per ET.



Study	IM Progesterone n/N	Vaginal Progesterone n/N	Odds Ratio (Fixed) 95% CI	Odds Ratio (Fixed) 95% CI
With GnRHa				
Smitz 1992	25/131	40/131		1.86 (1.05, 3.30)
Abate 1999	15/52	6/52		0.32 (0.11, 0.91)
Saucedo 2000	11/40	11/37		1.12 (0.41, 3.00)
Propst 2001	39/99	25/102		0.50 (0.27, 0.91)
Saucedo 2003	7/50	15/50		2.63 (0.97, 7.17)
Dal Prato 2008	38/138	32/137		0.80 (0.47, 1.38)
Total (therapeutic doses)	**135/510**	**129/509**		**0.94 (0.71, 1.26)**

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

Zarutskie et al., FS, 2009

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

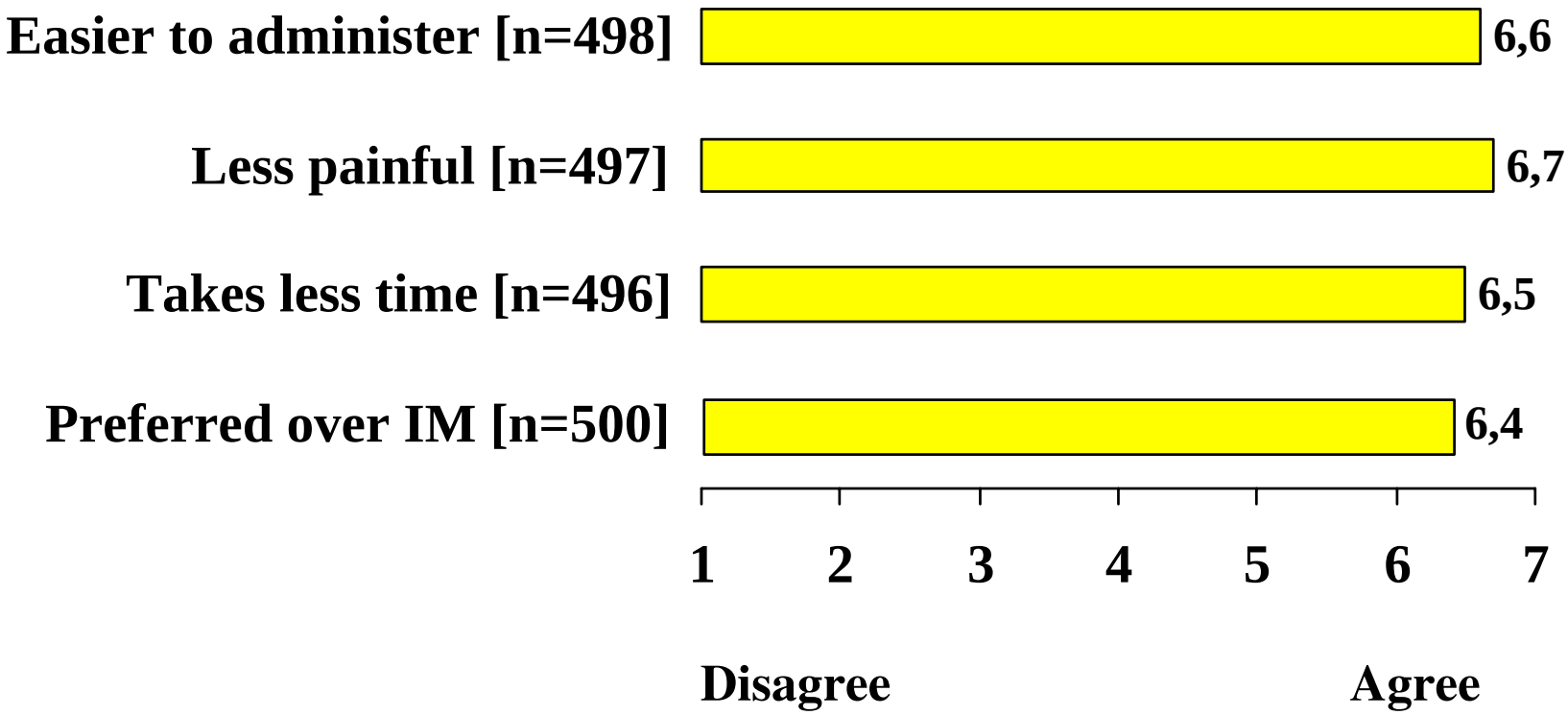
Vaginal vs IM Progesterone

- 544 women undergoing GnRH agonist long luteal phase IVF-ET
- 399 women IM P4
- 145 women vaginal micronized P4

- No difference in clinical pregnancy rates or in pregnancy loss rates

Mitwally et al, Fertil Steril, 2010

Patients prefer Vaginal progesterone over IM



Levine H., 2000

Oral progesterone ineffective?

- ✓ Progesterone administered orally:
  - degradation to its 5α- and 5β-reduced metabolites. (Penzias, 2002)

- ✓ Bourgain (1990) and Devroey (1988):

  absence of any secretory transformation of the endometrium in patients treated with oral micronised progesterone compared to I.M. or vaginal micronised progesterone

Oral progesterone ineffective?

- Dydrogesterone (DG), a retroprogesterone with good oral bioavailability, which has an anti-estrogenic effect on the endometrium causing a secretory transformation (Whitehead, 1980)

- Chakravarty *et al*. (2005) in a prospective, randomised study compared the efficacy of vaginal micronised progesterone with oral dydrogesterone as luteal phase support after IVF

  Both dydrogesterone (DG) and micronised progesterone (P) were associated with similar rates of successful pregnancies (24.1% vs. 22.8%, respectively; p=0.81).

Oral progesterone ineffective?

- Relatively retarded endometrial development in artificial cycles treated with oral dydrogesterone has been reported in several studies

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

- The oral DG might be sufficient for luteal supplementation in IVF cycles, however; more large randomized controlled trails are needed, before a conclusion can be made.

Oral DG versus Vaginal progesterone

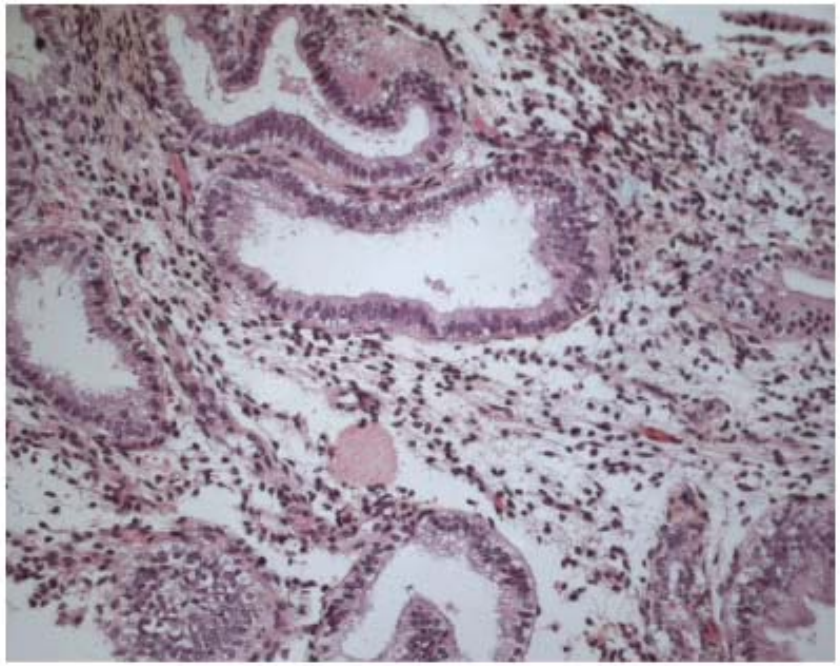


Figure 1. Representative endometrial biopsy on day 21 of an artificial cycle after micronized progesterone. Patients with premature ovarian failure received estrogen from days 1 to 21 and vaginal progesterone from days 15 to 21. (Coiled glands with active secretion and minimal residual vacuoles. Stromal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

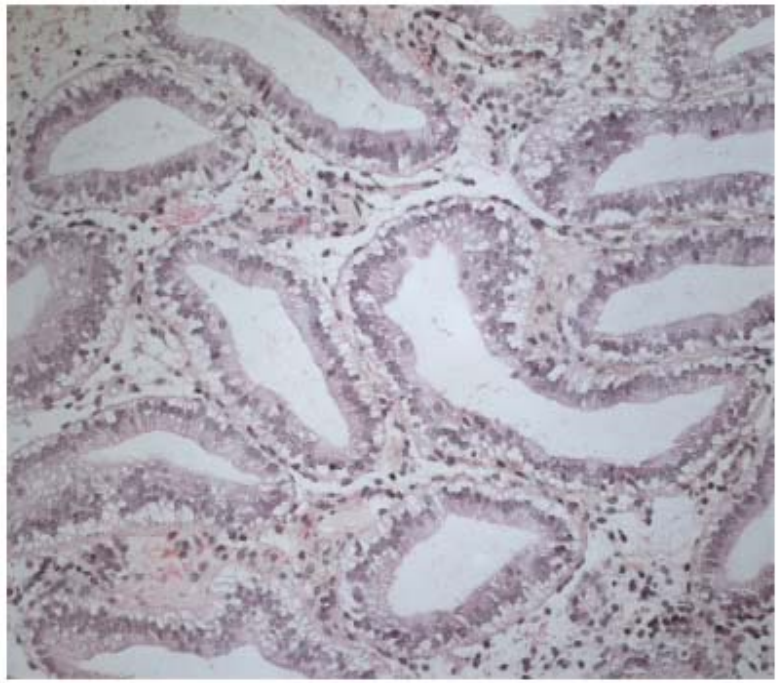


Figure 2. Representative endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and persistant homogeneous subnuclear vacuoles and pseudostratified nuclei. (No stromal edema. Focal mitotic activity.) The maturation corresponds to days 2–3 of the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

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Vaginal progesterone versus vaginal progesterone + E_2V (RCT)

	Vaginal prog	Vaginal prog + E_2V
ET (n)	183	195
Pregnancies (n)	65	64
%	35	32

Smitz HR 1993

Estradiol supplementation - RCT

Pilot trial RCT n = 176

Ongoing pregnancy rate	
Prog (200 mg bid)	34 / 81 (42 %)
Prog + E2 patches (100 μg / day, twice / week)	33 / 79 (42 %)

Serna FS 2008

Similar in meta-analysis Gelbaya FS 2008

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Vaginal progesterone (Utrogestan) versus vaginal progesterone and estradiol valerate (E_2)

	Vaginal progesterone	Vaginal progesterone + E_2
Age (mean) (years)	32	32
Days of stimulation (mean)	9	9
FSH units (mean)	1796	1807
COC (mean)	12.3	11.9
Embryos transferred	1.3	1.3

Fatemi HR 2006

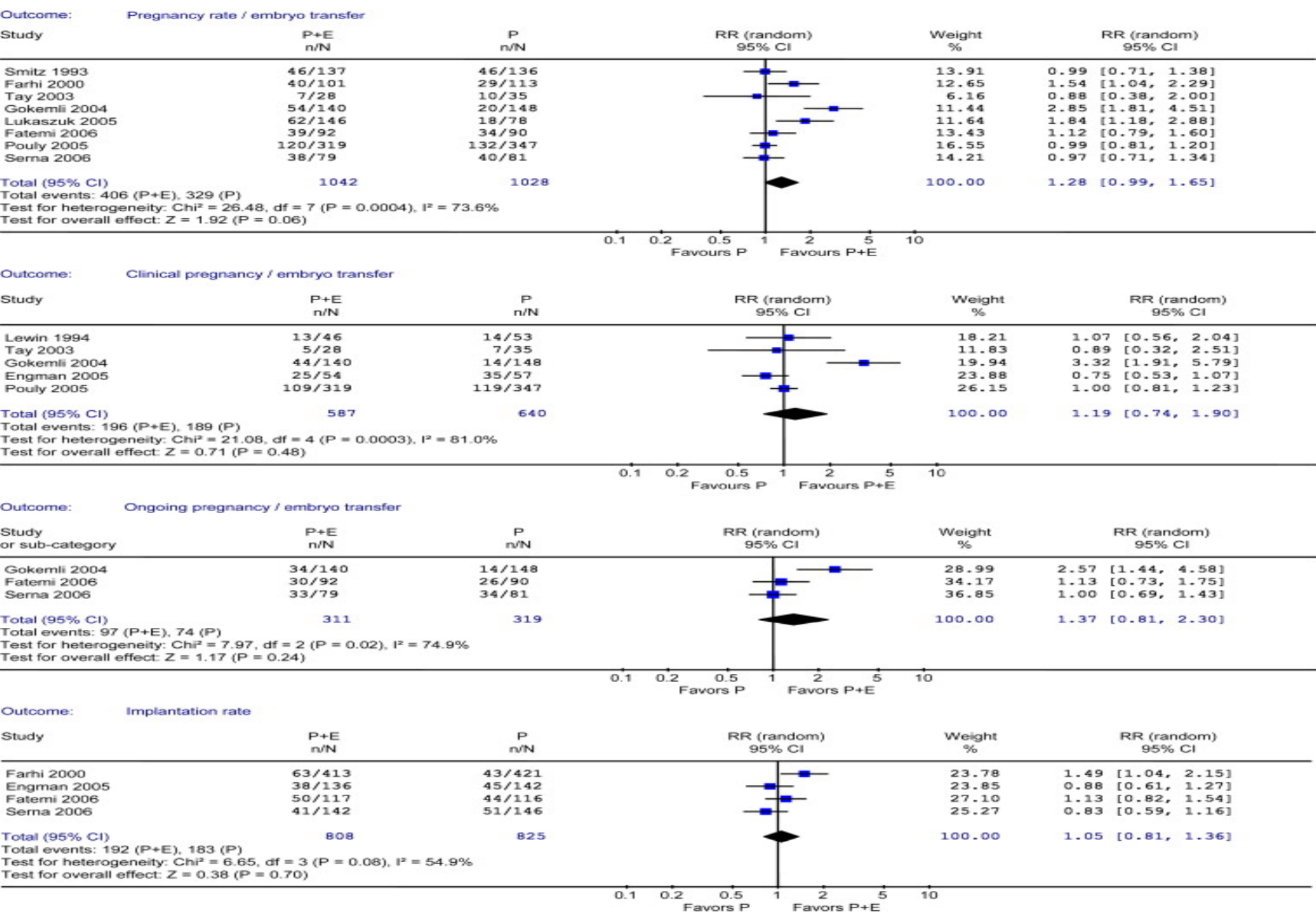
Pregnancy outcome in GnRH antagonist cycles

	Vaginal prog	Vaginal prog + E_2
Ongoing pregnancies per rand. patients (%)	26 /126 (26.0)	30 /101 (29.7)
egg retrieval (%)	26 / 97 (26.8)	30 / 99 (30.3)
ET (%)	26 / 90 (29.9)	30 / 92 (32.6)

Fatemi HR 2006

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde



A systematic review Gelbaya et.al, FS, 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.

- **Daya S, Gunby JL., Cochrane Database Syst Rev. 2008 Jul 16;(3):**

What is the best timing of luteal support?

- The administration of progesterone before oocyte retrieval is associated with a lower pregnancy rate than the administration of progesterone after oocyte retrieval. (Sohn *et al*., 1999)

- Decrease of 24% was seen when luteal phase support was delayed until 6 days after OR compared to 3 days after OR (Williams *et al*., 2001)

- No difference was found when luteal phase support was started at OR compared to starting at ET (Baruffi *et al*., 2003)

Luteal support: How long?

200 mg vaginal progesterone three times daily during 14 days from the day of transfer until the day of a positive HCG test. The study group (n = 150) withdrew vaginal progesterone from the day of positive HCG. The control group (n = 153) continued administration of vaginal progesterone during the next 3 weeks of pregnancy.

Prolongation of progesterone supplementation in early pregnancy has <u>no</u> 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.

Andersen et al., 2002

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Reproductieve Geneeskunde

Conclusions

- Ovarian stimulation destroys luteal phase receptivity
- Role of supraphysiological levels of steroids
- Vaginal progesterone and progesterone IM do provide similar pregnancy rates
- There is no benefit of addition of estrogens