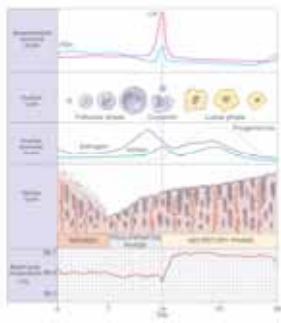


“Luteal supplementation in midly stimulated and natural cycles”

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Physiology of the menstrual cycle



2 Titel 08/17/2007

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 G, 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 CL (Csapo et al., 1973)

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(De Ziegler et al., 1996)

UC Frequency /Min

(Fanchin et al., 1998)

Implantation Rate (%)

UC/Min

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Endocrine profile of a spontaneous pregnancy

Jaervela et al., 2008

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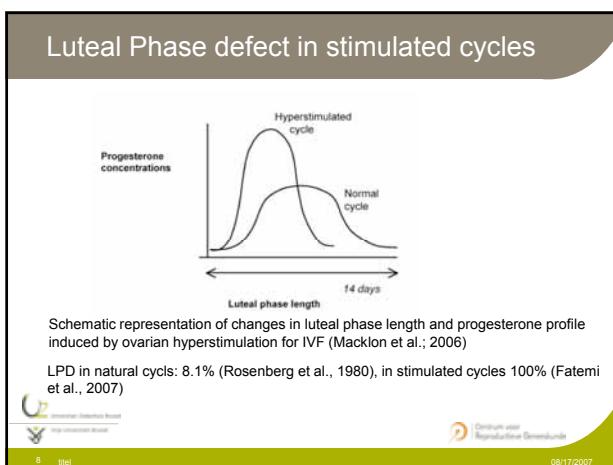
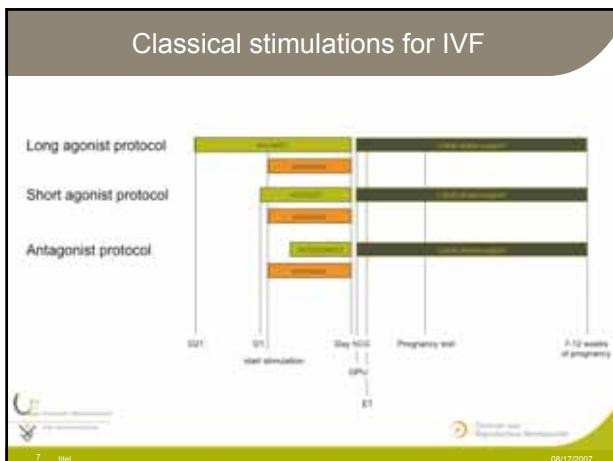
Luteal phase defect: effect on endometrium

E: embryo quality
U: endometrial receptivity

IVF pregnancy = $1 - [(1-U) + U(1-E)]$

Rogers et al, 1986

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- Why suppressed LH levels in the luteal phase of stimulated IVF cycles?**
- What is Etiology of the luteal phase defect in stimulated cycles?
 - Oocyte retrieval?
 - GnRH agonist?
 - hCG?
 - Stimulation?
 - Combination of those factors?
- Source: Dernstuhl West Reproductive Sciences
- 9 Met 08/17/2007

What is the cause of the luteal phase defect in stimulated cycles?

Menstrual cycle variation in LH pulse Frequency and Amplitude

Cycle Phase	Mean frequency (minutes)	Mean Amplitude (mIU/ml)
Early follicular	90	6.5
Mid-follicular	70	5
Late-follicular	60-70	7
Early luteal	100	15
Mid-luteal	130	12
Late luteal	200	8

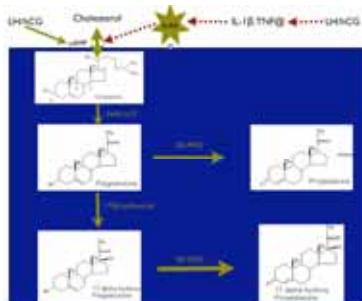
Adapted from Clinical reproductive medicine and surgery, 2007, page3



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**Luteal phase defect:
The importance of StAR**



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stimulated cycles?

Days after hCG	Letrozole		Placebo		p value
	Pregnentriol (ng/ml)	LH (IU/L)	Pregnentriol (ng/ml)	LH (IU/L)	
0	3.8±1.9	1.3±0.4	3.5±1.2	1.1±0.2	NS
4	27.3±2.7	0.2±0.1	46.9±6.1	0.2±0.1	NS
7	40.0±6.0	0.1±0.0	43.2±7.0	0.1±0.0	NS
10	33.3±17.8	0.1±0.0	32.3±15.8	0.1±0.0	NS

* : The highest level of serum pregnentriol measured was 46 ng/ml.

② : LH below the detection limit.

In stimulated cycles: severely suppressed LH levels
(Fatemi et al., 2007& 2008)



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LPD and mild stimulation?

Table 1 Demographic data of patients undergoing treatment with study group or placebo control group
Original manuscript.pdf

	Study group	Control group
No. of patients	228	228
Age (yrs)	36.1 ± 3.6	36.1 ± 3.6
Body mass index (kg/m ²)	25.1 ± 3.6	25.1 ± 3.6
No. of previous cycles	1.1 ± 1.1	1.1 ± 1.1
Total no. of cycles	36.0 ± 36.0	36.0 ± 36.0
No. of embryos transferred	1.0 ± 0.0	1.0 ± 0.0
No. of live births	10.0 ± 10.0	10.0 ± 10.0

Table 2 Cycle characteristics of patients undergoing treatment with study group or without control group
Original manuscript.pdf

	Study group	Control group
Cumulative no. of embryos	36.0 ± 36.0	36.0 ± 36.0
No. of transfers per cycle	1.0 ± 0.0	1.0 ± 0.0
No. of oocytes retrieved	12.0 ± 12.0	12.0 ± 12.0
No. of embryos transferred	1.0 ± 1.0	1.0 ± 1.0
Number of eggs per cycle	1.0 ± 1.0	1.0 ± 1.0
Number of embryos per cycle	1.0 ± 1.0	1.0 ± 1.0
Number of live births per cycle	1.0 ± 1.0	1.0 ± 1.0
Number of embryos per live birth	1.0 ± 1.0	1.0 ± 1.0

Ermel et al, IN PRESS

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LPD and mild stimulation?

Table 3 Clinical characteristics of patients and day reporting measure used in the two treatment groups

	Group A	Group B
No. of patients	100	100
Median age (years) (IQR range)	36.0 (31.0–38.0)	36.0 (31.0–38.0)
No. of previous cycles	1	0
No. of successful cycles	100	100
No. of unsuccessful cycles	0	0
Mean number of eggs per cycle	14.00 (1.00–15.00)	14.00 (1.00–15.00)
No. of embryos per cycle	1.00 (1.00–1.00)	1.00 (1.00–1.00)
No. of oocytes per live birth	1.00 (1.00–1.00)	1.00 (1.00–1.00)

Figure 3 Testosteron concentrations at day 10 follicular and at basal phase in Group A (study group) and in Group B (placebo group). In Group A median testosterone was significantly lower than in Group B (Mann-Whitney U-test, $P = .001$).

Ragni et.al.2001

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**How to support the luteal phase?
By cooking?**

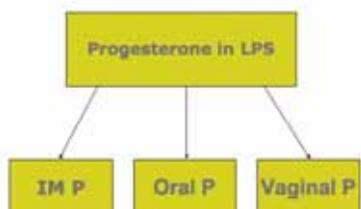


LPS

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Means of progesterone administration



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Dtsch Gesellschaft für
Reproduktive Medizin

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 report



International Federation of
Gynaecology and Obstetrics



World Health Organization

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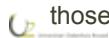
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Dtsch Gesellschaft für
Reproduktive Medizin

IM Progesterone

- Vaginal and intramuscular progesterone has comparable implantation and clinical PRs (Penzias, 2002, Nosarka, 2005, n=1675 cycles)
- Levin et al., 2000 in a multicenter U.S. study involving almost 2,000 women, found that, pregnancy rates were comparable between women who had used i.m. progesterone and those who had used vaginal gel



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Patients Prefer vaginal over IM progesterone

Reason	n	Score
Easier to administer	498	6,6
Less painful	497	6,7
Takes less time	496	6,5
Preferred over IM	500	6,4

Levin et al., 2000

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Denkraum voor Reproductieve Gezondheid

First uterine pass effect /targeted delivery

Vaginal progesterone, Yes, but what dose???
O'Chanson et al., 1996?

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Denkraum voor Reproductieve Gezondheid

- Progesterone administered orally is subjected to first-pass prehepatic and hepatic metabolism. This metabolic activity results in progesterone degradation to its 5α - and 5β -reduced metabolites. (Penzias, 2002)
- Bourgain (1990) and Devroey (1988) reported absence of any secretory transformation of the endometrium in patients treated with oral micronised progesterone compared to patients treated with intra muscular injections or vaginal micronised progesterone, suggesting a reduced bioavailability of this hormone, if taken orally.

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Denkraum voor Reproductieve Gezondheid

HCG as a first line LPS?

- Progesterone and estradiol are hormone supplementations, whereas hCG is used to stimulate these hormones in the corpora lutea.
- Placental protein 14 (Anthony et al., 1993), integrin αv (Honda et al., 1997) and relaxin (luteal peptide hormone) concentrations, which has been shown to increase at the time of implantation are higher with hCG support (Ghosh and Sengupta, 1998)
- Limitations: OHSS. Luteal support with hCG should be avoided:
 - If E2 >2700pg/ml (Buvinet et al., 1990)
 - If Number of follicles is >10 (Araujo et al., 1994)
- progesterone is as effective as hCG for luteal phase support but provides a higher safety with regard to ovarian hyper-stimulation syndrome (Ludwig and Diedrich, 2001)



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Progesterone + E2: A systematic review Gelbaya et al.2008



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Title



conclusions

- High steroids are the cause of LPD in stimulated cycles
- Luteal phase support with hCG or progesterone after assisted reproduction results in an increased pregnancy rate. (Fatemi et al, 2007)
- Co-administration of E2 does not increase the ongoing pregnancy rates (Gelbaya et al., 2008)
- HCG is associated with a greater risk of OHSS.
- Natural micronised progesterone is not efficient if taken orally (Bourgain 1990 and Devroey 1988)
- Vaginal and intra muscular progesterone seem to have comparable implantation and clinical PRs and DR (Nosarka et al.,2005)



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Title



Conclusion

- “Since the cause of luteal phase defect in IVF appears to be related to the ovarian stimulation and more and more countries are going towards SET, milder stimulation protocols should be considered in order to overcome the luteal phase defect”



European Society of Human Reproduction and Embryology



Dutch Society for Reproductive Medicine

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