

CORPUS LUTEUM & IVF



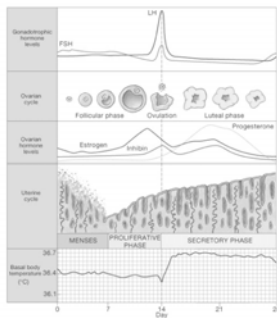
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Brussels, Belgium



Centrum voor
Reproductieve Geneeskunde

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Physiology of the menstrual cycle

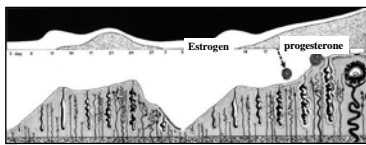


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The role of progesterone

- 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)

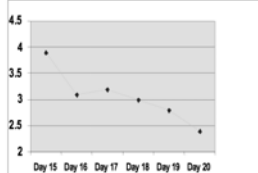
Luteal phase defect: effect on endometrium



E: embryo quality
 U: endometrial receptivity
 IVF pregnancy $1 - [(1-U) + U(1-E)]^n$

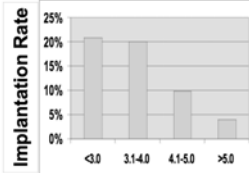
Rogers et al, 1986

(De Ziegler et al., 1996)



UC Frequency /Min

(Fanchin et al., 1998)



UC/Min

The Two cell model is preserved also in the Luteal phase

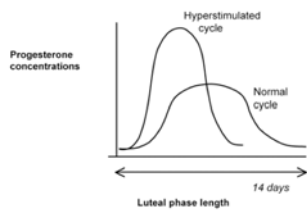
- 30% of luteal cells are steroidogenic (Sanders and Stouffer, 1997)
- Small luteal cells are derived from the theca interna (TI), while large luteal cells are originated from granulosa cell lineage (GC)
 - P₄ and E₂ production are generally greater in GC than in TC, due to aromatase activity (Devoto et al., 2001)
 - TC produce the androgen precursors and 17@OHP that are aromatized by GC. The majority of LH receptors are located on small luteal cells (Retamales et al., 1994)



7 stel

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Luteal Phase defect in stimulated cycles



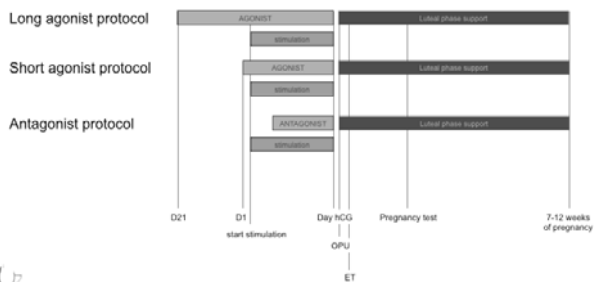
Schematic representation of changes in luteal phase length and progesterone profile induced by ovarian hyperstimulation for IVF (Macklon et al.; 2006)



8 stel

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Stimulated IVF cycles



9 stel

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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	50	5
Late-follicular	60-70	7
Early luteal	100	15
Mid-luteal	150	12
Late luteal	200	8

Adapted from Clinical reproductive medicine and surgery, 2007, page3

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



10 stel

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Why suppressed LH levels in the luteal phase of stimulated IVF cycles?

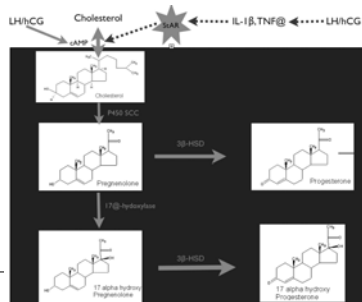
- I What is Etiology of the luteal phase defect in stimulated cycles?
 - Oocyte retrieval?
 - GnRH agonist?
 - hCG?
 - Combination of those factors?
 - Stimulation?



11 stel

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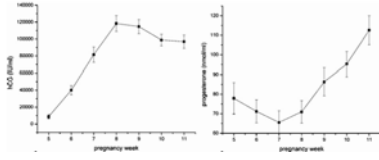
Luteal phase defect:
The importance of StAR



12 stel

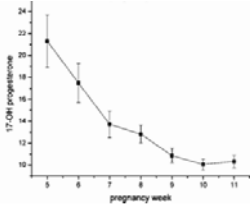
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Endocrine profile of a spontaneous pregnancy



Jaervelae et al., 2008

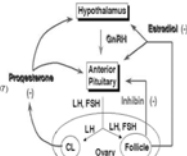
The "real" corpus luteum function



Jaervelae et al., 2008

Luteal Phase defect in stimulated cycles

- iatrogenic luteal phase defect due to supraphysiological steroid levels in stimulated cycles (Eauser and Macklon, 2002 and Estem et al., 2007)



Why suppressed LH levels in the luteal phase of stimulated IVF cycles?



The endocrine profile of the luteal phase in IVF donor cycles with two different luteal treatment schemes: placebo vs. letrozole: a placebo controlled pilot study

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16 *med*

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Table I. Mean estradiol values (pg/mL) in the Letrozole and placebo group in the luteal phase (*: P=significant)

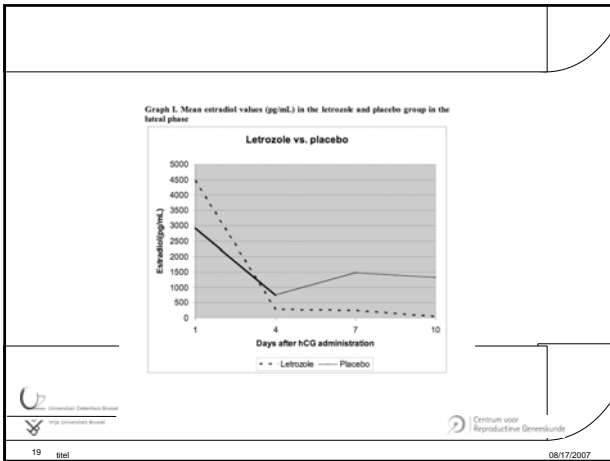
Days after hCG	Letrozole group (pg/mL)	Placebo group (pg/mL)	p value
1	4486±502.3	2916.3±730.3	NS
4	272±65.4	749±27.4	0.008*
7	229±68.9	1457±152.4	0.005*
10	30.7±7.4	1308±87.8	0.004*

Table II. Mean Progesterone and LH values in the Letrozole and placebo groups in the luteal phase

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±0.1	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



Future prospects

- Threshold of LPD ?
- Progesterone antagonist in oocyte donors during the luteal phase?
- Is there a luteal phase defect in cycles stimulated with clomiphene citrate/ recombinant FSH and gonadotropin-releasing hormone antagonist?

20 stel 08/17/2007

Conclusions

- High steroid levels (Progesterone) in stimulated cycles do cause the LPD
- The high steroids (Progesterone) suppresses the LH production
- Without the LH, the StAR gene expression is blocked and the basic substance for steroidogenesis (cholesterol) can not enter the inner site of the mitochondria

21 stel 08/17/2007

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"



22 stel



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