"Luteal supplementation in midly stimulated and natural cycles"

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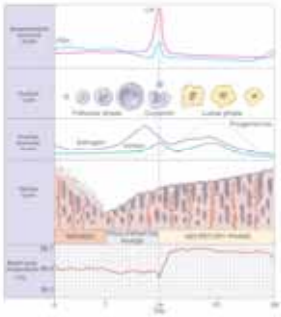
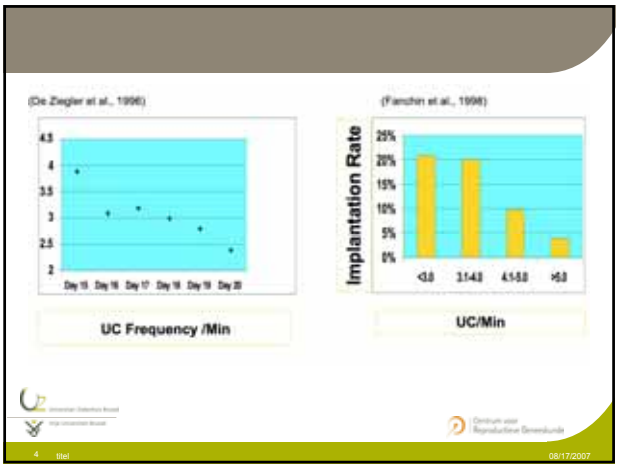
Physiology of the menstrual cycle

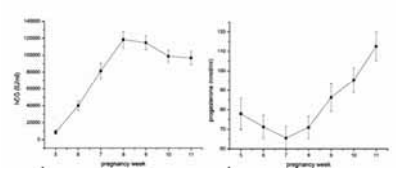


The role of progesterone

- 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)

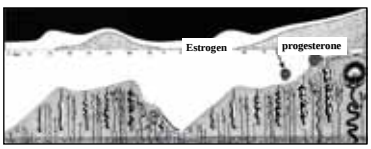


Endocrine profile of a spontaneous pregnancy



Jaervelae et al., 2008

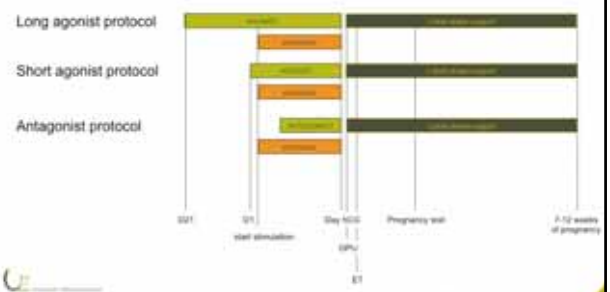
Luteal phase defect: effect on endometrium



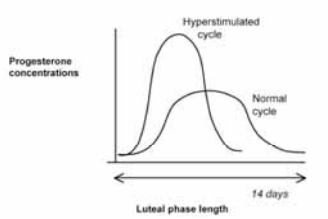
E:	embryo quality
U:	endometrial receptivity
IVF pregnancy	1-[(1-U)+U(1-E)n]

Rogers et al, 1986

Classical stimulations for IVF



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)

LPD in natural cycls: 8.1% (Rosenberg et al., 1980), in stimulated cycles 100% (Fatemi et al., 2007)

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

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

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

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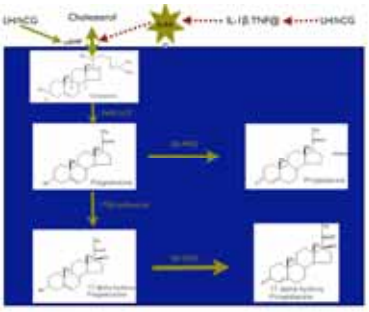
Luteal phase defect: The importance of StAR



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stimulated cycles?

Days after hCG	Letrozole: Progesterone (ng/mL)	Letrozole: LH (IU/L)	Placebo: Progesterone (ng/mL)	Placebo: LH (IU/L)	p value
1	1.8±1.9	1.1±0.4	3.3±1.2	1.9±0.8	NS
4	37.3±23.7	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	53.13±15.9	0.1*±0.0	52.3±13.6	0.1*±0.0	NS

• : The highest level of serum progesterone measured was 60 ng/mL

✪ : LH below the detection limit

In stimulated cycles: severely suppressed LH levels

(Fatemi et al., 2007& 2008)

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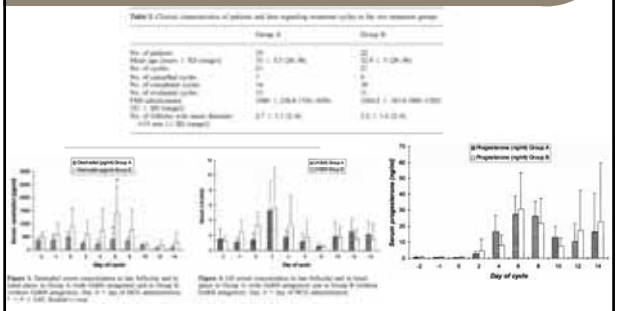
LPD and mild stimulation?

Ermed et al, IN PRESS

LPD and mild stimulation?

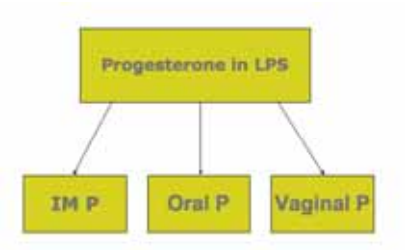


Ragni et al.2001

How to support the luteal phase? By cooking?

LPS

Means of progesterone administration



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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

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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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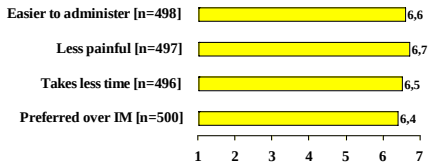
Patients Prefer vaginal over IM progesterone



Levin et al., 2000

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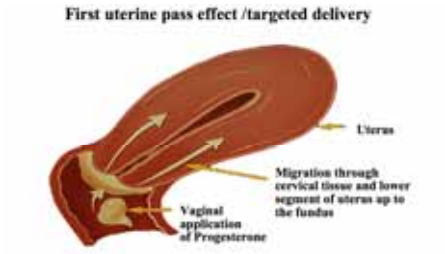
First uterine pass effect /targeted delivery



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

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- 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 bioavailibility of this hormone, if taken orally.

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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 άv (Honda et al., 1997) and relaxin (lutel 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 (Buvat 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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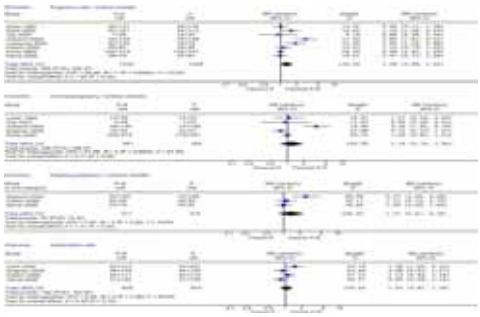
Progesterone + E2: A systematic review Gelbaya et al.2008



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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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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"