Luteal Support in Natural IVF Cycles

Veljko Vlaisavljevic

Professor in Obstetrics and Gynecology at the University of Ljubljana

University Clinical Centre Maribor
Department of Reproductive Medicine
Maribor
SLOVENIA

1

Criteria used for triggering final oocyte maturation

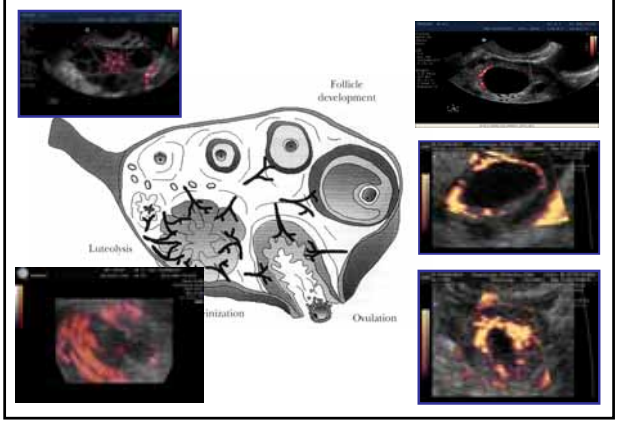
Mean diameter of dominant follicle
≥ 15 mm

&

Serum estradiol level
≥ 0.49 nmol/L

2

Support/supplementation ?



Influence on corpus luteum

- **Evidence of "non influence" of laparoscopic follicle aspiration of bigger preovulatory follicles (23mm in mean diameter) on luteal phase.**

Possible negative effect on corpus luteum function:

- **Ultrasonicaly guided OPU is more traumatic than natural ovulation.**
- **Administratin of hCG in cycles with smaller follicle in mean diameter (15.6-19.6 mm).**
- **Curretage of the inner granulosal cell layers during OPU..**
- **Irrigation and reaspiration of the follicle could remove granulosa cells.**
- **Damage of the fine vascular network of blood vessels in the theca interna leyer..**

Corpus luteum after spontaneous ovulation

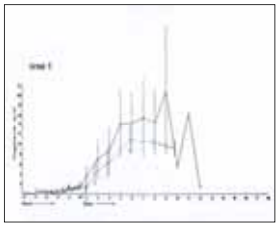
Corpus luteum function after follicle aspiration for oocyte retrieval

- **Normal lutheal phase after follicle aspiration in a spontaneous cycle.**
  Edwards et al. Br.J.Obstet Gynecol 1980;67;669
  Feichtinger et al. Fertil Steril 1982;37:205.
- **The average number of viable granulosa cells in apirate:**
  4.72 million/ aspirate in follicles > 18 mm in diameter
  2.11 million/ aspirate in follicles < 17 mm in diameter
  Garcia et al. Fertil Steril 1981;36:565.
- **The aspiration of a spontaneous preovulatory follicle caused a temporary deficiency in plasma progesterone (p<0.01) on the third day (P+3) following aspiration, then come back to normal on P+6 and P+9..**
  Frydman et al. Fertil Steril 1982; 38:312
- **Significantly lower serum progesteron was noted on day 8 of post oocyte recovery in spontaneous cycle (but all results were within the normal range seen in controlled cycles)**
  Mahmood T & Templeton A., Fertil Steril 1991;55:86

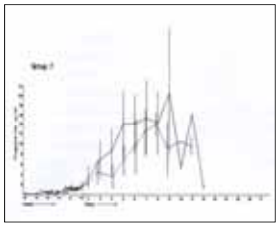
5

Serum progesterone values in cycles after OPU compared with anaspirated control cycles.

Garcia et al. Fertil Steril 1981;36:565-72.



Vigorous aspirations and several washes

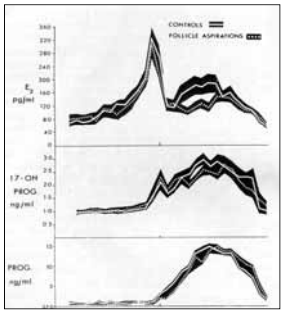


Aspiration of ovulated follicles through the recently ruptured stoma.

Conclusion : There was a statistically significant decrease in the amount of progesterone in the aspirated cycle, as compared with the unaspirated control cycles.

Human luteal phase function following oocyte aspiration in spontaneous ovular cycles.

Kerin et al. Br J Obstet Gynecol 1981;88:1021-8.



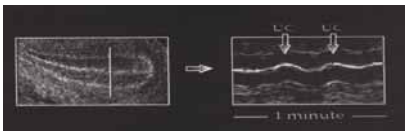
- Comparisons between daily serum steroid levels of women who had their immediate preovular follicle aspirated and women who served as controls.
- Reference point was day 0 (LH peak)
- **Conclusion**: There was no difference in either the follicular and luteal phase between two groups.

7

Progesteron and contractility

- **Progesteron has a uterine-relaxing effect in the nonpregnant uterus. High frequency uterine contractility at the time of ET can affect implantation rates.**

Fanchin et al., Hum Reprod 1998,13,1968-74.



- **Endometrial thickness, endometrial pattern and subendometrial contractility on day of embryotransfer is not predictive for in vitro fertilization outcome in stimulated and unstimulated cycles.**

Vlaisavljević et al., Ultrasound Obstet Gynecol 2000,17;239-44.
Kuder et al. Zdrav Vestn 2002,71;I-31-4.

8

Biomarkers of endometrial receptivity in the natural cycle

Five genses exspressed during the implantation window were all up regulated in the LH+7 samples compared with LH+2:

- Laminin beta3
- Microfibril-associated protein 5
- Angioprotein-like 1
- Endocrine gland-derived vascular endothelial growth factor
- Nuclear localized factor 2

Haouzi et al. Hum Reprod 2009;24:198-205

9

Luteal support in infertility treatment

- **Meta-analysis of the randomized trials**

Pritts EA & Atwood AK, Hum Reprod 2002,17:2287-99.

- **Cochrene review**

Daya S & Gunby J. The Cochrene Library 2004,Issue 3

No data about luteal support in unstimulated cycles !

10

Luteal phase support

- **Luteal support was given after embryotransfer :**

Faulot et al.,1992 ; Paulson et al.,1992 ; Claman et al.,1993 ; Abdulghar et al.,1995, Daya et al.,1995 ; Kim et al.,1996 ; Tomažević et al.,1996 ; Zayed et al.,1997; Basil et al.,1999; Ng et al.,2001

535 ET 14.8% pregnancy rate

- **No luteal support was given after embryotransfer :**

Jahnssens et al.,2000; Ingerslev et al.,2001

70 ET 17.1 % pregnancy rate

It is not clear whether luteal phase support is necessary in natural cycles.

11

Role of hCG in "resque" of the corpus luteum

- **The natural developing follicles contain more hCG stained granulosa cells than the stimulated ones.**

Gersak K et al.,FS 1996;65:608-13.

- **Progesteron secretion 3h after hCG administration to "in vitro" corpora lutea is significantely higher in middle luteal phase than in early and late luteal phase**

Vega et al., JCEM 1987;65:747-52.

- **Progesterone concentrations depend on the preovulatory bolus of hCG and become very low in the middle luteal phase in COH.**
- **Only hCG, but not endogenous LH, has the capacity to prolong corpus luteum half-life. The dose neccessary to support the corpus luteum has not been defined.**

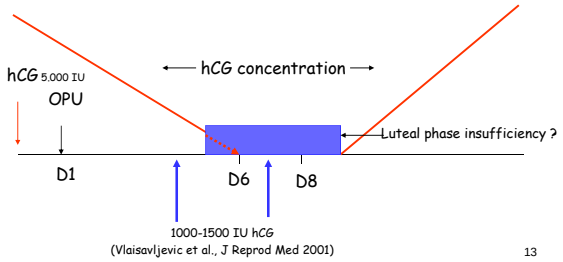
Beckers et al., EJE 2006,155:355-63.

12

Luteal phase insufficiency after IVF

Luteal support is given to cover the "gap" when the exogenous hCG support disappears (day 5-6) and the time when endogenous hCG from the early pregnancy start to rise (day 9-12) after transfer.

Beckers et al., HR 2000, CEM2003



13

Luteal phase support (Maribor IVF)

- **Didrogesteron** (Dabroston 30 mg, Duphare):

  96 embryos — 12 (13.0%) implantations, 8 (8.0 %) deliveries

- **hCG** (1500 IU, Pregnyl, Organon) on day 3 and day 7:

  158 embryos — 37 (23.0%) implantations, 25 (16.0 %) deliveries

Vlaisavljević et al., J Reprod Med 2001;46:892-8.

14

Conclusions (Luteal supplementation)

- Luteal supplementation in natural IVF/ICSI cycles is not evidence based and not universal.
- The luteal support does not seem mandatory, but specific information is still lacking.
- We believe that some patients may benefit from support of corpus luteum with hCG administered following ET between days 3 and 7 after OPU.

15