Impact of Controlled Ovarian Hyperstimulation on Endometrial Receptivity

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I. Clinical aspect of endometrial receptivity in COH cycle

1. High estradiol concentrations on the day of human chorionic gonadotropin (HCG) administration are detrimental to endometrial receptivity (from Simon et al., 1995).

Table 1. In-vitro fertilization outcome in normal responder versus high responder patients

	Normal responders	High responders
No. of cycles	114	63
Age (years)	33.1±3.8	30.3±2.8*
Oestradiol (pg/ml) on the day of HCG	1410±780	3194±1637*
Progesterone (pg/ml) on the day of HCG	0.5±0.4	0.9±0.7*
No. of oocytes retrieved	8.5±2.8	25.7±9.6*
Fertilization rate (%)	65.5±24.1	59.6±25.2
No. of embryo transferred per cycle	3.7±1.2	4.1±0.9*
No. of pregnancies per cycle (%)	38/114 (33.3)	10/63 (16.4)*
No. of embryo implanted (%)	48/432 (11.1)	14/258 (5.4)*

Values are given as mean ± SD.
HCG = human chorionic gonadotropin.
*Significantly different to normal responder ($p<0.05$).

2. Endometrial receptivity was improved in high responder patients using step-down regimen.

3. When endometrial biopsies are obtained during the late luteal phase in the patients undergoing controlled ovarian hyperstimulation (COH), there is a significant dys-synchrony in the maturation of the glandular epithelium and the stroma (from Benadiva and Metzger, 1994).

57% in COH cycle
13% in unstimulated cycle

Table 2. Reproductive outcome of the previous failed cycle compared with step-down and standard protocols (from Simon et al., 1998)

	Previous cycle (n=24)	Step-down (n=24)	Previous cycle (n=62)	Standard (n=62)
Age(years)	31.1±1.4	31.6±1.2	33.1±0.4	33.8±0.3
Oestradiol(pg/ml)	5770±650	1919±477[b]	4035±489	5271±613
Retrieved oocyte (No.)	24.0±1.9	18.1±2.1[b]	22.9±0.9	23.1±1.6
Fertilization rate (%)	71.2	74.2	77.9	76.1
Implantation rate (%)	0	29.3[a,b]	0	8.5[a]
Pregnancy rate (%)	0	64.2[a,b]	0	24.2[a]

Values are given as mean ± SE.
[a] Significantly different versus their previous cycle ($p<0.05$).
[b] Significantly different versus the respective previous cycle and standard protocol ($p<0.05$).

4. Human endometrial maturation is markedly improved after luteal supplementation of GnRH (gonadotropin-releasing hormone) analogue / HMG (human menopausal gonadotropin) stimulated cycle (from Bourgain et al., 1994).

5. The early luteal phase of cycle undergoing controlled ovarian hyperstimulation characterized the markedly elevated serum progesterone levels during the peri-ovulatory period. The high levels of progesterone in the early luteal phase cause premature endometrial luteinization and a premature appearance of the implantation window, thus providing an explanation for the observed decrease in endometrial receptivity (from Kolb and Paulson, 1997).

6. Cycles with COH are associated with high early luteal P levels and advanced endometrial histology. Low doses of RU486 may correct the precocious luteinization and restore endometrial receptivity (from Paulson et al., 1997).

7. When stimulated cycles associated with gland-stroma dys-synchrony were compared with stimulated cycles associated with coordinated development of the glands and stroma, no significant differences were observed in E2 level on the day of hCG, midluteal serum P, midluteal E2 level, or P:E2 ratios. This may reflect the degree of responsiveness of an individual woman's endometrium rather than a result of the hormonal milieu (from Benadiva and Metzger, 1994).

II. The endometrial receptivity and markers

1. Definition of endometrial receptivity and its markers

– Endometrial receptivity:

Window of time when the uterine environment is conductive to blastocyst acceptance and subsequent implantation.

– Markers of endometrial receptivity:

Molecules or phenomena that specifically appear or take place during implantation window

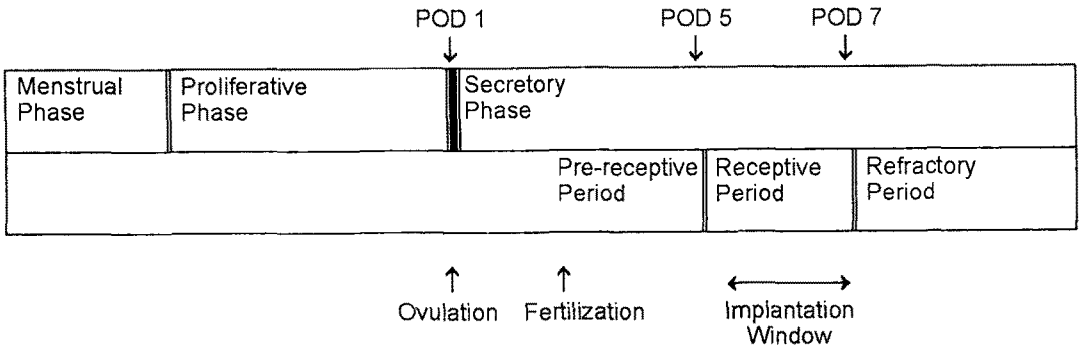

Figure 1. Receptive and non-receptive periods of the human menstrual cycle:

2. Histological changes in endometrium during implantation window
   - In glandular epithelium, the mitotic activity ceases and the diameter of the glandular lumen increases and the secretory activity of the glands reaches its maximum. Also, the cells show three characteristic structural changes, such as giant mitochondria, glycogen deposit and nuclear channel system.
   - In surface epithelium, the main anatomical landmark is the appearance of microprotrusions from the apical surface of the epithelium towards the uterine lumen (pinopod).
   - In stroma, edematous change begins and the fibroblasts are transformed into pseudo-decidual cells, which appear as large cells with dark round nuclei. Also, stromal leukocytes begin to appear and spiral arterioles begin to coil and be prominent.
   - Around the time of implantation, the permeability of stromal vessels is increased dramatically at the implantation site.
   - In extracellular matrix (ECM), the interstitial collagen fibers are loosely dispersed and the ECM becomes less viscous and rich in de-polymerized substance. The ECM provides a static framework within which the events of cell recruitment, migration, implantation, placentation and fetal growth occur.

3. Endometrial markers for endometrial receptivity
   1) pinopod
   2) Integrin
   3) Cytokines: LIF (Leukemia inhibitory factor), EGF (epithelial growth factors)
   4) Interleukin-1
   5) MAC

6) MUC-1

7) Endometrial receptors for estradiol and progesterone

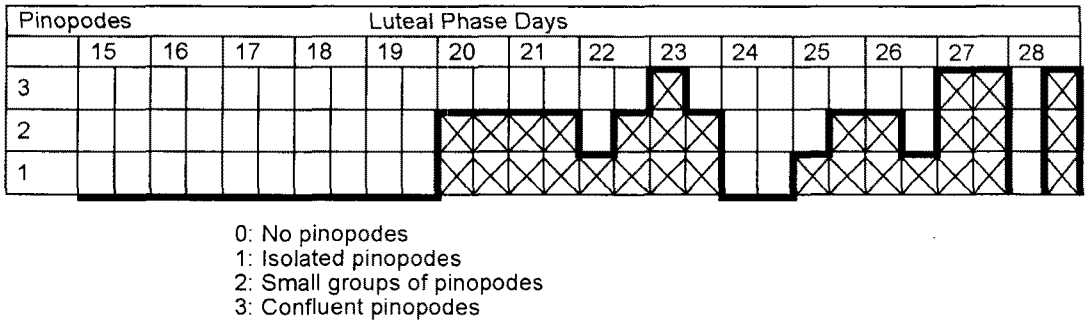

Figure 2. Graphic representation of the characteristics and expression of pinopodes during the luteal phase (the two half panels in each day represent the two different volunteers).

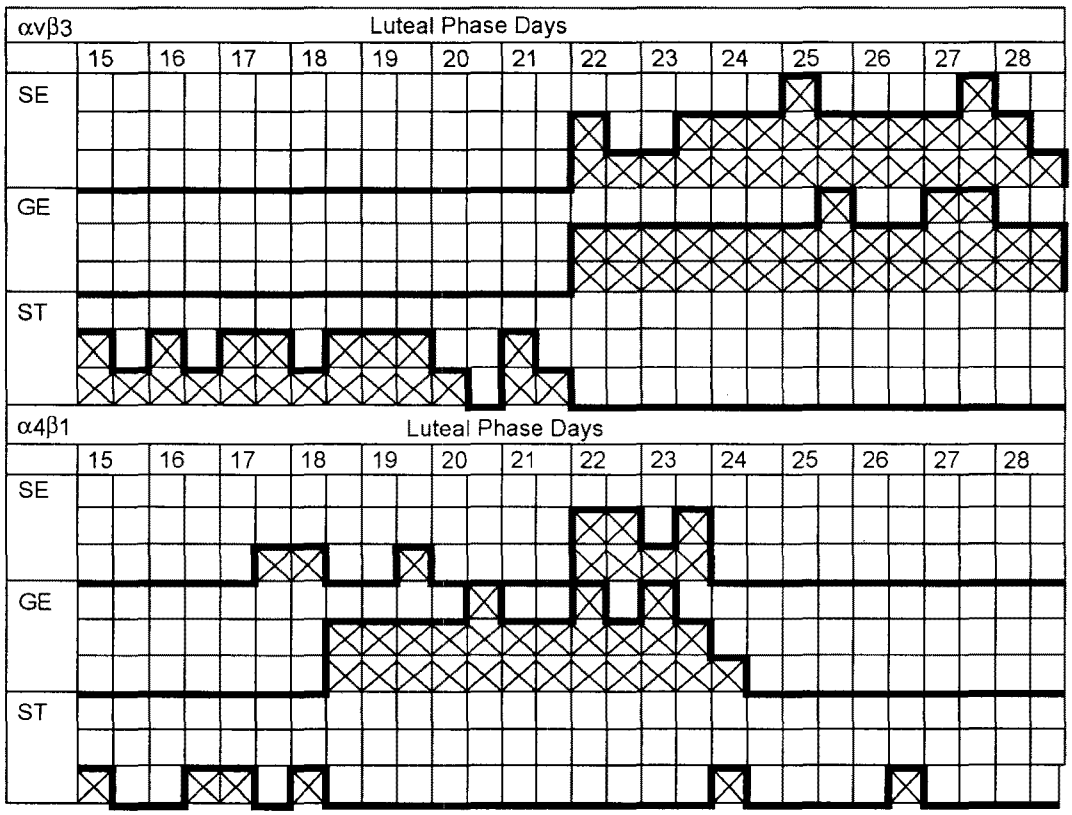

Figure 3. Graphic representation of integrin expression (αvβ3 and α4β1) in superficial and glandular epithelium and in the stroma during the luteal phase. SE= superficial epithelium; GE = glandular epithelium; ST = stroma

III. Changes of the markers of endometrial receptivity in COH cycle

1. In human cycles stimulated for ovulation with gonadotropin releasing hormone (GnRH) agonizes and human menopausal gonadotropin (HMG), a luteal phase defect has been described. In non-supplemented cycles all endometrial features were consistent with an impaired progesterone bioavailablilty. After supplementation of the luteal phase, fewer signs of luteal phase deficiency were visible, especially with the intravaginal route of progesterone administration (from Bourgain et al., 1994).

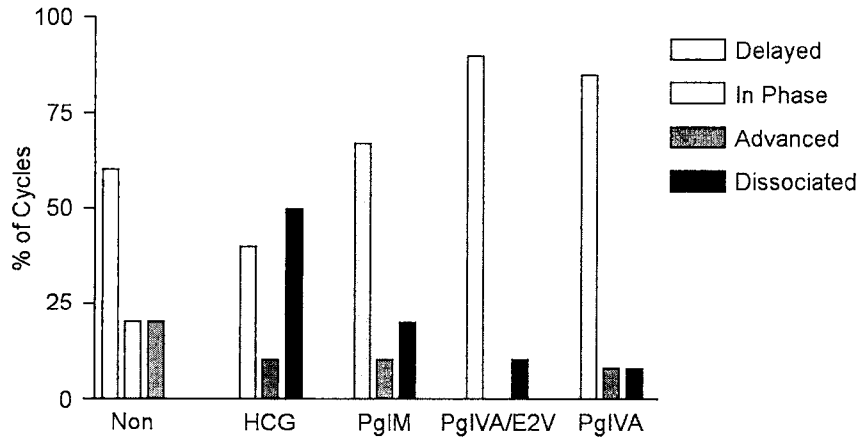

Figure 4. Histological endometrial maturation in non-supplemented cycles and in supplemented cycles during controlled ovarian hyperstimulation.

Non; non-supplementation
HCG; human chorionic gonadotrophin 5000 IU on days 3,6 and 9
PgIM; natural progestrone i.m. 2 x 50mg / day
PgIVA; natural progesterone intravaginally 3 x 200mg / day
PgIVA/E2V; natural progesterone intravaginally with oestradiol valerate

2. Many controlled ovarian hyperstimulation cycles are associated with synchronous early expression of the expected pattern of histologic features, estrogen and progesterone receptors and pinopodes (from Develioglu et al., 1999).

3. Ovarian stimulation does not affect endometrial pinopodes formation in terms of their quantity and short life span. The cycle days when pinopodes form greatly vary between women and on average, they occur 1 - 2 days earlier in ovarian stimulation cycle the in natural cycle (from Nikas et al., 1999)

4. Advanced endometrial histology in glands and stroma was noted in COH cycles. Significant positive correlations of E2 and P4 were noted IGFBP-1 and -3, but not with advanced endometrial morphology in the COH cycles (from Brown et al., 2000).

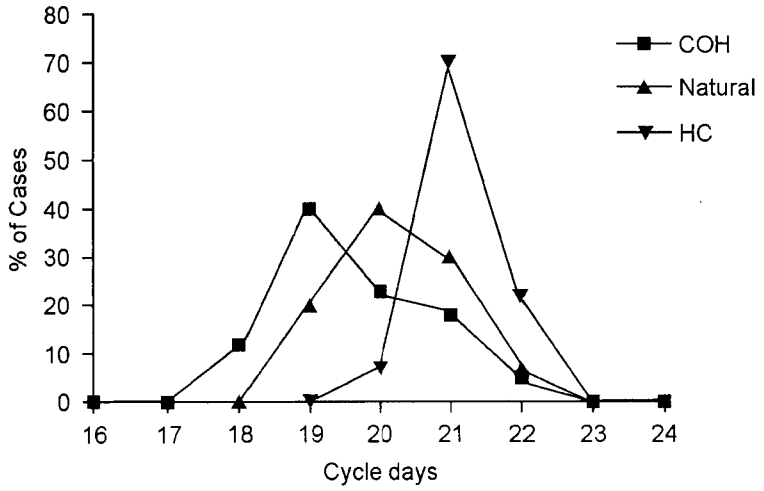

Figure 5. Differential expression of pinopodes in controlled ovarian hyperstimulation (COH), natural and hormone replacement cycles (HC).

5. Controlled ovarian hyperstimulation with HMG and simultaneous administration of a GnRH antagonist did not affect the immune system (Giuliani et al., 1998).

IV. The impact of COH on endometrial receptivity

High level of estradiol in proliferative phase and high level of progesterone in early luteal phase may cause premature endometrial luteinization and a premature appearance of the implantation window, thus providing an explanation for the observed decrease in endometrial receptivity. However, the changes of markers related to implantation in COH cycle as well as natural cycle should be further elucidated.

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