ENDOMETRIAL RECEPTIVITY

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Endometrial advancement pre - hCG injection in GnRH agonist cycles

	Patients	Controls	P
Glandular mitosis	21.2	7.9	< 0.01
Stromal mitosis	10.2	3.2	< 0.01
Basal vacuolated cells	388	97	< 0.01
Glandular diameter	71.1	45.9	< 0.01

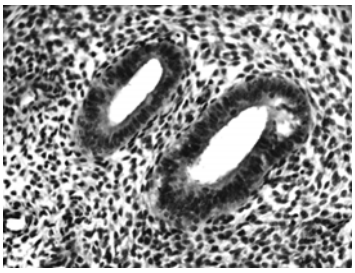
Marchini, Fedele, Bianchi, Losa, Ghisletta, Candiani F S 55 1991

Endometrial biopsy and ovum retrieval

Author	Stimulation	Endometrial advancement		Odds ratio	95 % CI	P
		≤ 3 days	> 3 days			
Clinical pregnancy rate						
Ubaldi (1997)	hMG / agonist	10/32	0/7			
Kolibianakis (2002)	rec-FSH / antagonist	11/49	0/6			
		21/81	0/13	0.22	0.06-0.89	0.03
Ongoing pregnancy rate						
Ubaldi (1997)	hMG/agonist	10/32	0/7			
Kolibianakis (2002)	rec-FSH / antagonist	8/49	0/6			
		18/81	0/13	0.23	0.05-0.98	0.05

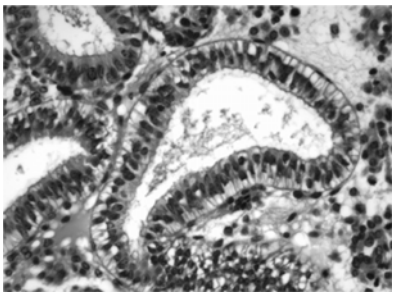
Kolibianakis F S 2002

Endometrial biopsy on the day of ovulation, natural cycle



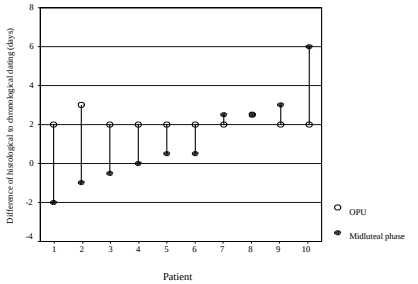
No secretory features

Endometrial biopsy on the day of oocyte retrieval, GnRH agonist and gonadotrophin stimulation cycle

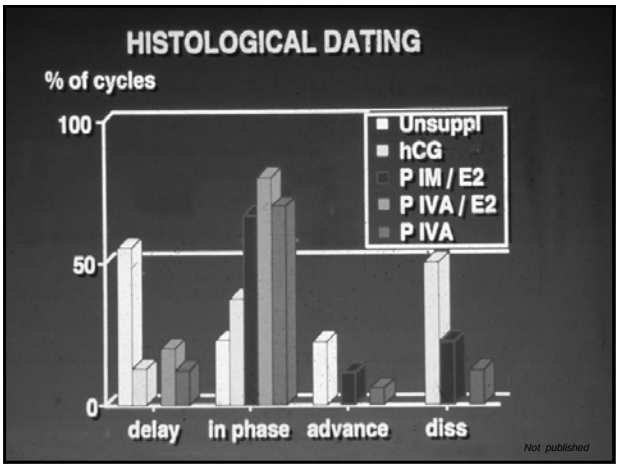


Clear secretory features

Histological regression of endometrium from oocyte retrieval to the midluteal phase



Kolibianakis, Bourgain, Platteau, Albano, Van Steirteghem, Devroey F S in 2003

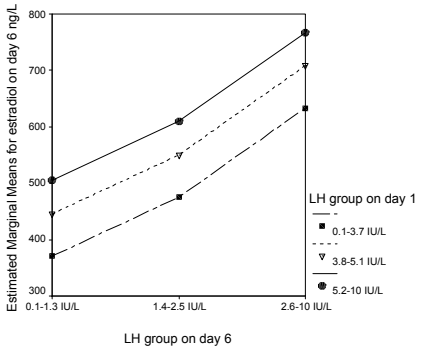


Parameters predicting endometrial advancement at ovum retrieval

Parameters	P
Basal LH	0.02
Days of stimulation prior to antagonist	0.03
Basal FSH	0.45
Starting dose of rec-FSH	0.74
Duration of antagonist treatment	0.43

Kolibianakis, Bourgain, Albano, Osmanagaoglu, Smitz, Van Steirteghem, Devroey F S 78 2002

Positive correlation between LH levels and E_2 levels in the early follicular phase



Kolibianakis, Albano, Camus, Tournaye, Van Steirteghem, Devroey RBM Online 2003

Ongoing pregnancy rate and ongoing implantation rate across groups of patients with increasing LH levels according to percentile analysis

Groups of patients according to LH levels on day 8				Ongoing pregnancy rate per oocyte retrieval	Ongoing implantation rate	Pregnancy loss after hCG detection before 12 weeks
	LH level on day 8			% (n)	% (n)	% (n)
	mean	min	max			
0 - 25th	0.3	0.1	0.5	56.0 (14/25)	39.1 (18/46)	6.7 (1)
25 - 75th	1.0	0.6	1.9	40.3 (25/62)	24.6 (31/126)	7.4 (2)
75 - 100th	3.3	1.9	8.4	24.1 (7/29)	15.7 (8/51)	12.5 (1)
				P < 0.010*	P < 0.018*	P < 0.71*

** Exact Chi-square for trend*

Kolibianakis HR 2004

E_2 at hCG N = 416	Ongoing Pregnancy rate %	Ongoing Implantation rate %
< 600	50 (11/22)	32.5
600 - 1200	35.7 (27/76)	22.1
1200 - 1800	36.0 (49/136)	22.1
1800 - 2600	36.8 (39/92)	22.8
> 2600	31.1 (28/90)	15.4

Unpublished data

Is exposure to LH and E_2 in the early follicular phase affecting pregnancy rates

Fixed versus flexible protocol

AUC	Pregnant	Non-pregnant	p
LH	15.3 ± 1.1	24.0 ± 1.5	0.001
E_2	1081 ± 171	2023 ± 139	0.01
P	3.4 ± 0.34	3.9 ± 0.2	0.1

Kolibianakis, Albano, Kahn, Camus, Tournaye, Van Steirteghem, Devroey FS 79 2003

Randomization

Patients received 10.000 IU of hCG

as soon as ≥3 follicles ≥17mm were present in ultrasound

early-hCG group, 208 patients

or

2 days later after this criterion was met

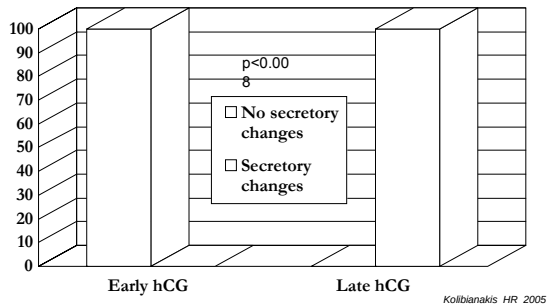
late-hCG group, 205 patients

Kolibianakis Albano Camus Tournaye Van Steirteghem Devroey Fertil Steril 2004

	Early hCG	Late hCG	P
Embryos transferred	2	2	NS
Ongoing pregnancy rate / OPU %	35.6 69/194	25 44/196	0.02
Ongoing pregnancy rate / ET %	39 69/176	28 49/177	0.02
Ongoing implantation rate %	23 87/385	15 58/383	0.009

Kolibianakis, Albano, Camus, Tournaye, Van Steirteghem, Devroey FS 2004

Prolongation of follicular phase results in secretory changes of endometrium at OPU



Kolibianakis HR 2005

LH concentration during the luteal phase (post hCG) in agonist gonadotrophin stimulated cycles

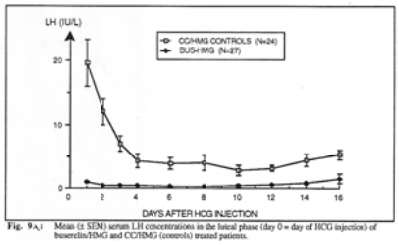
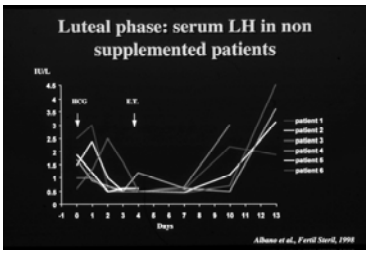


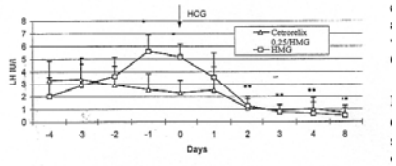
Fig. 9.A.1 Mean (± SEM) serum LH concentrations in the luteal phase (day 0 = day of HCG injection) of buserelin/HMG and CC/HMG (controls) treated patients.

Smitz HR 1988

Is the luteal phase LH concentration (post hCG) in antagonist - gonadotrophin cycles normal or decreased ?

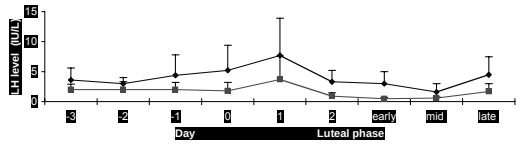


Are the luteal phase concentrations (post hCG) similar in gonadotrophin alone versus antagonist gonadotrophin stimulated cycles ?



Tavaniotou HR 2001

Luteinizing hormone serum concentrations in Clomid gonadotrophin antagonist or gonadotrophin antagonist cycles



Tavaniotou F S 77 2002

Is luteal support necessary in GnRH antagonist cycles?

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)
No. patients achieving embryo transfer[b]	9	11	14
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)

Support of corpus luteum function remains mandatory after ovarian stimulation for IVF with GnRH antagonist cotreatment

Beckers et al 2004 JCEM

If non - supplemented luteal phase after induction of ovulation with rechCG , recLH or GnRH - agonist luteolysis starts prematurely human embryonic implantation is almost nihil

Beckers JCEM 2003

Centrum voor Reproductieve Geneeskunde

Myth :

Luteal phase supplementation corrects always luteal phase defect on stimulated cycles

OVARIAN STIMULATION

- Day 2
- Puregon 200 U (unchanged)
- Orgalutran 0.25 mg from day 6 stimulation onwards
- Final egg maturation as soon as ≥ 3 follicles of 17 mm of diameter at ultrasound
- Computer generated list
  - either 10.000 U hCG
  - either 0.2 mg Triptorelin

  (the decision was only made on ultrasound)

CYCLE OUTCOME

	Brussels (Centre 1)		Luebeck (Centre 2)	
	Agonist	hCG	Agonist	hCG
Stimulation (n patients)	18	24	34	30
OPU (n)	18	24	32	30
ET (n)	15	20	29	28
Ongoing pregnancy rate / started cycle	1/18 (5.6%)	10/24 (41.7%)	1/34 (2.9%)	5/30 (16.7%)

Odds ratio (95% CI) 0.11 (0.02 - 0.52)
P level = 0.005

PRESENTED DATA AGONIST - HCG IN GNRH ANTAGONIST CYCLES

	Agonist (n : 48)	hCG (n : 48)
Clinical pregnancy rate	7.5 %	39 %
Pregnancy loss	79 %	11 %

Humaidan HR 2005

- Westergaard
  - 0.5 mg Busereline
  - Discontinuation of luteal support at pregnancy
  - Progesterone
- Our study (Kolibianakis)
  - 0.2 mg Triptorelin
  - No discontinuation of luteal support
  - Progesterone + Progynova

GnRH agonist to induce oocyte maturation

	GnRH agonist	hCG
OHSS (%)	0/30	10/29 (34)
Embryotransfer (mean)	2.0	2.2
Inplantation rate (%)	22/61 (36)	20/64 (31)
Ongoing pregnancy rate (%)	16/30 (53)	14/29 (48)

Engmann FS 2008

Advanced endometrial maturation on the day of oocyte retrieval correlates with altered gene expression

- Background
  - Endometrium exceeding > 3 days never resulted in an ongoing pregnancy
- Results of gene expression
  - Discriminates between the advanced and non advanced endometria between the occurrence of pregnancy
  - Upregulated genes were found in the non pregnant patients exceeding > 3 days (SERPINB6 SOX17 CDC42 FOX03A)

Van Vaerenbergh I HRS 2008

Is it ethically acceptable to replace fresh embryos in a stimulated cycle ?

- Yes if there is no other solution
- No if there are other solutions
- Science has to progress

Vitrification of all zygotes after triggering with GnRH agonist (n:19)

Days of stimulation (n)	10
Total FSH (IU)	1926
COC (n)	16
2 PN cryopreserved	10
Survival rate	78 %

Griesinger et al HR 2007

Pregnancy outcome after vitrification

Ongoing pregnancy rate per	
first ET	6 / 19 (31 %)
per patient	7 / 19 (37 %)

Griesinger et al HR 2007

CODA

- Ovarian stimulation makes human endometrium irreceptive for embryonic implantation

Proposed strategy

- In GnRH antagonist cycle
- Replacing hCG by GnRH agonist
- Vitrification of all zygotes / embryos
- Replacement one by one after thawing
- Avoidance of
  - Multiple pregnancies
  - Ovarian hyperstimulation syndrome