Adjuvant therapies

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What does it mean?

It has a clear conotation within oncology!

Adjuvant therapy refers to additional treatment, usually given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to occult disease.

In ART the detectable disease is not removed!

Adjuvant therapy =
enhancing therapeutic strategies in ART

Established enhancing therapeutic strategies in ART:

- Controlled ovarian hyperstimulation
- GnRH – agonist or antagonists for prevention of premature LH – surges
- LPS
- Embryo scoring and selection
- eSET

Non – established enhancing therapeutic strategies in ART:

- **GH**
- **DHEA**
- **Dopamin – agonists (e.g. bromocriptine)**
- **ASS and Prednisolone**
- **LH – supplementation**
- **Luteal – phase GnRH – agonist administration**
- **Hyaluron/recombinant albumin as embryo transfer medium**
- **Aromatase – inhibitors**
- **Preimplantation Genetic Screening (PGS)**

GH

GH: 32 patients; 4 IU GH i.m. per day; GnRH - microdose protocol; 450 IU FSH per day

Table 2 Comparison of Stimulation Parameters for Cycles Using Microdose GnRH-a versus Conventional Protocol With GH*

Parameter	Conventional	Microdose GNRH-a-GH
Cancellation rate† (%)	100	12.5
E_2 day 5 (pg/mL)†‡§	81.8 ± 42.9	303.8 ± 167.6
Follicles day 5†‡	3.6 ± 1.7	10.9 ± 4.2
Ampules of gonadotropins to day 5	24	24
Growth hormone (IU)	24	16

* Conventional protocol consisted of luteal phase initiation of GnRH-a followed by stimulation with exogenous gonadotropins and GH.
† $P < 0.0001$.
‡ Values are means ± SD.
§ Conversion factor to SI unit, 3.67.

Schoolcraft W., Schlenker T., Gee M., Stevens J., Wagley L. (1997): Improved controlled Ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle – stimulating hormone flare, growth hormone protocol. Fertil. Steril.; 67:93 - 97

Table 3 Clinical Parameters of the 28 Microdose GnRH-a-GH Cycles That Progressed to Oocyte Retrieval

Parameter	Result
Ampules of gonadotropins*	53 ± 10.5
LH before hCG (IU/L)*†	2.6 ± 1.6
P before hCG (ng/mL)*†	0.29 ± 0.30
E_2 day of hCG (pg/mL)*†	1295 ± 429
No. of oocytes retrieved*	10.9 ± 4.2
Mean fertilization rate (%)*	51 ± 9
Implantation rate (fetal heartbeat per embryo) (%)	25
Ongoing PR (fetal heartbeat past 13 weeks) (%)	50 (14/28)

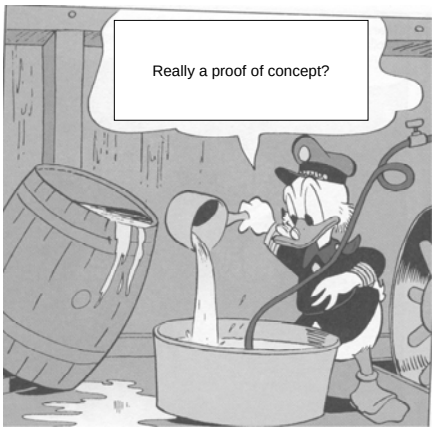
* Values are means ± SD.
† Conversion factors to SI units are as follows: LH, 1.00; P, 3.185; E_2, 3.67.

Schoolcraft W., Schlenker T., Gee M., Stevens J., Wagley L. (1997): Improved controlled Ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle – stimulating hormone flare, growth hormone protocol. Fertil. Steril.; 67:93 - 97

Theoretical Explanation:

- **GH acts via IGF-1**
- **IGF-1 acts synergistically with gonadotrophins**
- **IGF-1 amplifies the FSH induction of LH receptors**
- **IGF – 1 stimulates aromatase activity**
- **IGF – 1 stimulates progesterone secretion**
- **IGF – 1 stimulates Inhibin production by GC**

**Homburg R., Eshel A., Abdala HI, Jacobs HS (1988):
Growth hormone facilitates ovulation induction
By gonadotropins. Clin. Endocrinol.; 29:113 - 117**



GnRHa/HMG/GH:
18 IU of GH on alternate days

• Number of ampoules used:	no difference
• Number of follicles > 14mm:	no difference
• E2 – Levels on the day of HCG:	no difference
• Number of COC retrieved:	no difference
• Number of embryos transferred:	no difference

„No improvement in low responders by GH – supplementation!“

**Dor J., Seidman D.S., Amudai E., Bider D., Levran D., Mashiach S. (1995):
Adjuvant growth hormone therapy in poor responders to in – vitro – fertilization:
A prospective randomized placebo – controlled double – blind study. Hum. Reprod.;10:40 - 43**

DHEA

25 poor responders; 25 mg of DHEA orally three times a day for ~ 17 weeks „ultrashort protocol“

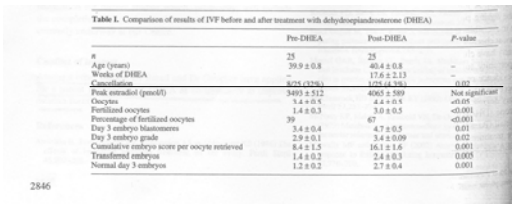
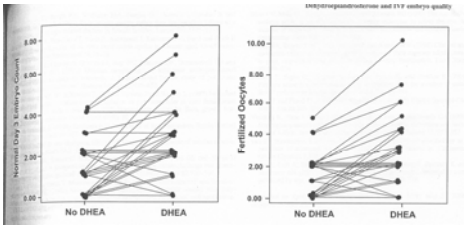


Table I. Comparison of results of IVF before and after treatment with dehydroepiandrosterone (DHEA)

	Pre-DHEA	Post-DHEA	*P*-value
n	25	25	
Age (years)	39.9 ± 0.8	40.4 ± 0.8	–
Weeks of DHEA	–	17.6 ± 2.13	–
Cancellation	8/25 (32%)	1/25 (4.3%)	0.02
Peak estradiol (pmol/l)	3493 ± 512	4065 ± 589	Not significant
Oocytes	3.4 ± 0.5	4.4 ± 0.5	<0.05
Fertilized oocytes	1.4 ± 0.3	3.0 ± 0.5	<0.001
Percentage of fertilized oocytes	39	67	<0.001
Day 3 embryo blastomeres	3.4 ± 0.4	4.7 ± 0.5	0.01
Day 3 embryo grade	2.9 ± 0.1	3.4 ± 0.09	0.02
Cumulative embryo score per oocyte retrieved	8.4 ± 1.5	16.1 ± 1.6	0.001
Transferred embryos	1.4 ± 0.2	2.4 ± 0.3	0.005
Normal day 3 embryos	1.2 ± 0.2	2.7 ± 0.4	0.001

2846

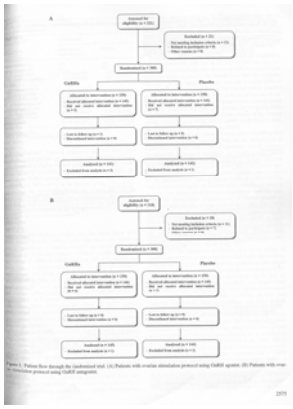
Barad D., Gleicher N. (2006): Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum. Reprod.;11:2845 - 2849



Barad D., Gleicher N. (2006): Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum. Reprod.;11:2845 - 2849

Up to now no further data...

„Administration of 0,1 mg of GnRH – agonist triptorelin on day 6 after ICSI led to a significant improvement of implantation and live – birth after ICSI compared with Placebo.“



Tesarik J., Hazout A., Mendoza – Tesarik R., Mendoza N., Mendoza C. (2006): Beneficial effect of luteal – phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist – treated ovarian stimulation cycles. Hum. Reprod.;21:2572 - 2579

Tesarik J., Hazout A., Mendoza – Tesarik R., Mendoza N., Mendoza C. (2006): Beneficial effect of luteal – phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist – treated ovarian stimulation cycles. Hum. Reprod.;21:2572 - 2579

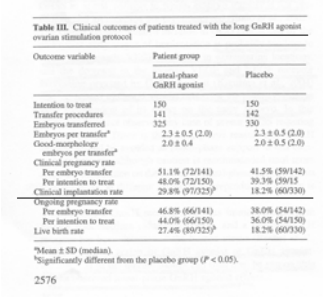


Table III. Clinical outcomes of patients treated with the long GnRH agonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Intention to treat	150	150
Transfer procedures	141	142
Embryos transferred	325	330
Embryos per transfer[a]	2.3 ± 0.5 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer[a]	2.0 ± 0.4	2.0 ± 0.5 (2.0)
Clinical pregnancy rate		
Per embryo transfer	51.1% (72/141)	41.5% (59/142)
Per intention to treat	48.0% (72/150)	39.3% (59/15
Clinical implantation rate	29.8% (97/325)[b]	18.2% (60/330)
Ongoing pregnancy rate		
Per embryo transfer	46.8% (66/141)	38.0% (54/142)
Per intention to treat	44.0% (66/150)	36.0% (54/150)
Live birth rate	27.4% (89/325)[b]	18.2% (60/330)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

2576

Tesarik J., Hazout A., Mendoza – Tesarik R., Mendoza N., Mendoza C. (2006): Beneficial effect of luteal – phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist – treated ovarian stimulation cycles. Hum. Reprod.;21:2572 - 2579

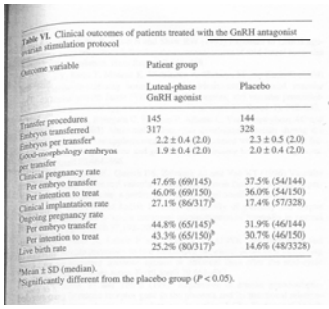


Table VI. Clinical outcomes of patients treated with the GnRH antagonist ovarian stimulation protocol

Outcome variable	Patient group	
	Luteal-phase GnRH agonist	Placebo
Transfer procedures	145	144
Embryos transferred	317	328
Embryos per transfer[a]	2.2 ± 0.4 (2.0)	2.3 ± 0.5 (2.0)
Good-morphology embryos per transfer	1.9 ± 0.4 (2.0)	2.0 ± 0.4 (2.0)
Clinical pregnancy rate		
Per embryo transfer	47.6% (69/145)	37.5% (54/144)
Per intention to treat	46.0% (69/150)	36.0% (54/150)
Clinical implantation rate	27.1% (86/317)[b]	17.4% (57/328)
Ongoing pregnancy rate		
Per embryo transfer	44.8% (65/145)[b]	31.9% (46/144)
Per intention to treat	43.3% (65/150)[b]	30.7% (46/150)
Live birth rate	25.2% (80/317)[b]	14.6% (48/3328)

[a]Mean ± SD (median).
[b]Significantly different from the placebo group ($P < 0.05$).

Unfortunately….

- Nobody could repeat these results and confirm them by publication (so far)
- Nevertheless the „implantation injection“ became popular (even in Germany)

Ata B. et al. (2008): GnRH – agonist protocol administration in the luteal phase in ICSI – ET cycles stimulated with the long GnRH agonist protocol: randomized, controlled double blind study. Hum. Reprod.; 23: 668 - 673

Improvement of uterine receptivity…

„Embryo glue“:
Hyaluronic Acid (HA) enriched transfer medium containing recombinant Human albumin

51 patients with repeated (> 4) implantation failures

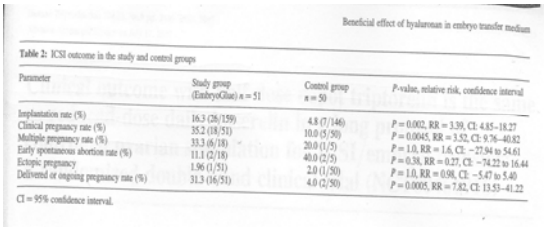
Friedler *et al.*

Table 1: Clinical characteristics of the treatment cycles comparing the study and control groups

Parameter	Study group (EmbryoGlue) $n = 51$ mean (SD)	Control group $n = 50$ mean (SD)
Age (years)	33.1 (5.1)	31.7 (5.6)
Number of previous cycles	5.8 (2.6)	5.2 (1.4)
hCG-day estradiol level (pg/ml)	2252 (1309)	2187 (1327)
hCG-day progesterone level (ng/ml)	1.0 (0.61)	1.0 (0.57)
Number of ova retrieved per patient	12.0 (7.3)	13.3 (6.2)
Number of mature (2PN) ova injected per patient	10.3 (6.6)	10.6 (5.0)
Number of mature (2PN) ova fertilized per patient	7.0 (4.2)	7.0 (3.6)
Fertilization rate (%)	70.0 (16.1)	68.0 (19.0)
Number of embryos cleaved	6.9 (3.9)	6.8 (4.0)
Number of embryos transferred	3.1 (0.73)	2.9 (0.63)
Mean embryo quality		
Number of cells		
Day 2	3.77 (1.10)	3.88 (1.03)
Day 3	7.81 (0.62)	7.59 (1.02)
Morphology grade		
Day 2	1.89 (0.59)	1.88 (0.53)
Day 3	1.57 (0.54)	1.70 (0.56)

Friedler S., Schachter M., Strassburger D., Kasterstein E., Ron – El R., Raziel A. (2007): A randomized clinical trial comparing Recombinant hyaluron / recombinant albumin versus human tubal fluid for cleavage stage embryo transfer in patients with Multiple IVF – embryo transfer failure. Hum Reprod.; 22:2444 - 2448

„Embryo glue“:
Hyaluronic Acid (HA) enriched transfer medium containing recombinant Human albumin



Beneficial effect of hyaluronan in embryo transfer medium

Table 2: ICSI outcome in the study and control groups

Parameter	Study group (EmbryoGlue) $n = 51$	Control group $n = 50$	P-value, relative risk, confidence interval
Implantation rate (%)	16.3 (26/159)	4.8 (7/146)	$P = 0.002$, RR = 3.39, CI: 4.85–18.27
Clinical pregnancy rate (%)	35.2 (18/51)	10.0 (5/50)	$P = 0.0045$, RR = 3.52, CI: 9.76–40.82
Multiple pregnancy rate (%)	33.3 (6/18)	20.0 (1/5)	$P = 1.0$, RR = 1.6, CI: −27.94 to 54.61
Early spontaneous abortion rate (%)	11.1 (2/18)	40.0 (2/5)	$P = 0.38$, RR = 0.27, CI: −74.22 to 16.44
Ectopic pregnancy	1.96 (1/51)	2.0 (1/50)	$P = 1.0$, RR = 0.98, CI: −5.47 to 5.40
Delivered or ongoing pregnancy rate (%)	31.3 (16/51)	4.0 (2/50)	$P = 0.0005$, RR = 7.82, CI: 13.53–41.22

CI = 95% confidence interval.

Friedler S., Schachter M., Strassburger D., Kasterstein E., Ron – El R., Raziel A. (2007): A randomized clinical trial comparing Recombinant hyaluron / recombinant albumin versus human tubal fluid for cleavage stage embryo transfer in patients with Multiple IVF – embryo transfer failure. Hum Reprod.; 22:2444 - 2448

LH - supplementation

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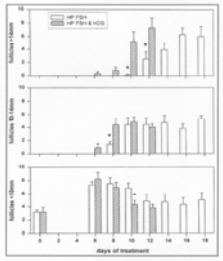


50 IU HCG per day

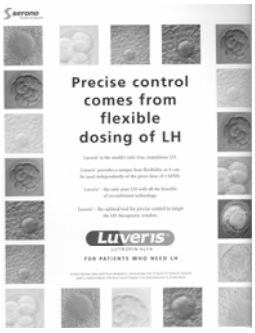
Figure 2. Number (mean ± SE) of small (<10 mm diameter), medium (10–14 mm), and large ovarian follicles (>14 mm) measured during HP FSH treatment. On treatment day 0, only small follicles were detected, whereas pelvic ultrasound was not performed on days 1–5. *, $P < 0.05$ or less (see *Results*).

Filicori M., Cognigni G.E., Taraborrelli S., Spettoli D., Ciampaglia W., Tabarelli de Fatis C., Pocognoli P. (1999): Luteinizing Hormone Activity Supplementation Enhances Follicle - Stimulating Hormone Efficacy and Improves Ovulation Induction Outcome. J Clin Endo Metab; 84:2659 - 2663

Table 2. Clinical and endocrine response parameters in the two groups of patients

	Group A	Group B	P
Days of gonadotropin administration (range in *parentheses*)	17.3 ± 0.7 (9–19)	12.5 ± 0.6 (8–14)	<0.0001
HP FSH dose (IU)	2,670 ± 149	1,725 ± 84	<0.0001
Preovulatory E_2 (pg/mL)	977 ± 27	1,171 ± 151	NS
Preovulatory follicles			
<10 mm	3.2 ± 0.6	3.2 ± 0.4	NS
10–14 mm	3.8 ± 0.5	3.8 ± 0.4	NS
>14 mm	7.9 ± 0.8	8.7 ± 0.7	NS
Follicular phase hormone levels			
LH (IU/L · day)	13 ± 1	14 ± 1	NS
FSH (IU/L · day)	146 ± 11	112 ± 8	<0.03
E_2 (pg/mL · day)	3,529 ± 276	3,163 ± 240	NS
P (ng/mL · day)	6.4 ± 1.0	5.6 ± 0.7	NS
T (ng/mL · day)	4.3 ± 0.5	4.0 ± 0.4	NS
hCG (IU/L · day)	<0.1	16.2 ± 3.2	<0.0001

Follicular phase hormone levels were calculated as the area under the curve.



Luveris

A compound in search of its own indication

The crucial questions:

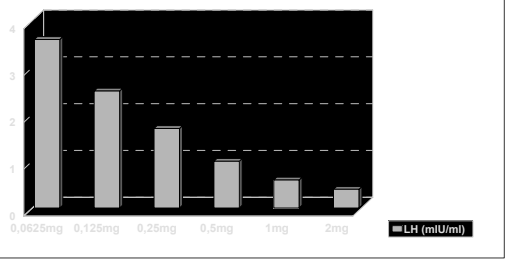
- **Who needs LH?**
- **When do we need LH?**
- **How much LH do we need?**

Oversuppression of LH ?

COH with rec.FSH and Ganirelix in six different dosages

Prospective, randomised, multi centre, double blind dose finding study

LH at the day of HCG



The ganirelix dose-finding study group. (1998) A double-blind, randomized, dose-finding study to assess the efficacy of the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462) to prevent premature luteinizing hormone surges in women undergoing ovarian stimulation with recombinant follicle stimulating hormone (Puregon). Hum Reprod, *13*:3023-3031.

COH with rec.FSH and Ganirelix in six different dosages

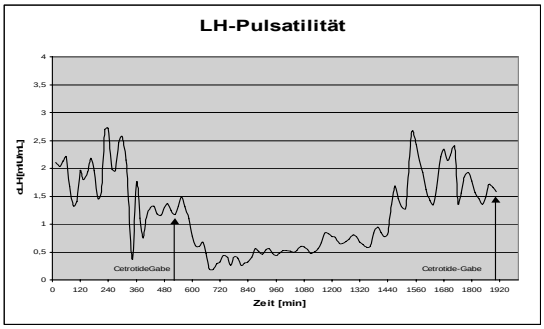
Multiple dose protocol

daily dose of Ganirelix (mg/day)	0,625	0,125	0,25	0,5	1	2
Patients (n)	31	65	69	69	65	30
COC*	9	9,5	10	8,8	9,3	8,6
Embryos*						
total*	5,4	5,9	5,4	4,6	5,3	4,9
good quality*	3,8	3,3	3,3	2,5	3,3	3,5
Implantation rate	14,2%	16,6%	21,9%	9%	8,8%	1,5%
Clin. pregnancies	7	17	25	8	9	1
Clin. pregnancy/ET	25,9%	28,3%	40,3%	14,8%	15,3%	4,3%
Abortion rate	0%	12%	4%	25%	56%	

* mean

The ganirelix dose-finding study group. (1998) A double-blind, randomized, dose-finding study to assess the efficacy of the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462) to prevent premature luteinizing hormone surges in women undergoing ovarian stimulation with recombinant follicle stimulating hormone (Puregon). Hum Reprod, *13*:3023-3031.

Pulsatility pattern analysis



The Lübeck – LH - Study

Table I. Causes of infertility, primary or secondary infertility, previous abortuses, and sterilization

Cause of infertility	Number (%) in indicated treatment group[a]	
	recFSH (n = 65)	recFSH/recLH (n = 62)
Male factor only	32 (49.2)	34 (54.8)
Tubal factor only	7 (10.8)	9 (14.5)
Male and tubal factor	10 (15.4)	8 (12.9)
Idiopathic/endometriosis	9 (13.8)	5 (8.0)
Male factor and endometriosis	2 (3.0)	2 (3.2)
Azoospermia	3 (4.6)	3 (4.8)
Vasectomy	1 (1.5)	1 (1.6)
Tubal sterilization	1 (1.5)	0 (0.0)
Primary infertility[b]	51 (78.5)	42 (67.8)
Secondary infertility[c]	14 (21.5)	20 (32.2)
Abortuses[d]	6 (9.2)	8 (12.9)

recFSH: recombinant FSH; recLH: recombinant LH.
[a]Intention-to-treat group (n = 127).
[b]Pregnancy has never occurred or never been established (i.e. no previous early or late abortion and no ectopic pregnancy).
[c]All other cases not covered by primary infertility.
[d]Number of patients with history of early or late spontaneous abortion.

Human Reproduction (2005); 20: 1200 - 1206

Table II. Patient data by treatment group and stage of trial

Treatment stage and reason for discontinuation	Number (%) in indicated treatment group		
	recFSH	recFSH/recLH	Total
Randomized	65 (100)[b]	62 (100)[b]	127 (100)[a,b]
Treated with gonadotropin	65 (100)	61 (98.3)[c]	126 (99.2)
Insufficient ovarian response	*3 (4.6)*	*2 (3.2)*	*5 (3.9)*
Insufficient ovarian response + LH rise	*1 (1.5)*	*0 (0.0)*	*1 (0.8)*
Premature luteinization	*3 (4.6)*	*1 (1.6)*	*4 (3.1)*
Risk of hyperstimulation	*2 (3.0)*	*2 (3.2)*	*4 (3.1)*
E_2 drop	*2 (3.0)*	*1 (1.6)*	*3 (2.4)*
Total discontinued stimulation	*11 (16.9)*	*6 (9.6)*	*17 (13.4)*
Treated with HCG	54 (83.0)	55 (88.7)	109 (85.8)
With oocyte pick-up	54 (83.0)	54 (87.0)[d]	108 (85.0)
No oocyte retrieved	*0 (0.0)*	*1 (1.6)*	*1 (0.8)*
No MII oocyte retrieved	*0 (0.0)*	*1 (1.6)*	*1 (0.8)*
Total discontinued after oocyte pick-up	*0 (0.0)*	*2 (3.2)*	*2 (1.6)*
With sperm incubation/injection	54 (83.0)	52 (83.9)	106 (83.5)
Number of ICSI cases	41 (63.1)	46 (74.2)	87 (68.5)
Number of IVF cases	13 (20.0)	6 (9.7)	19 (15.0)
Fertilization failure	*2 (3.0)*	*2 (3.2)*	*4 (3.1)*
With embryo transfer	52 (80.0)	50 (80.6)	102 (80.3)
Total discontinued treatment	*13 (20.0)*	*12 (19.4)*	*25 (19.7)*

E_2 = estradiol; MII = metaphase II.
[a]Intention-to-treat group = all patients randomized group.
[b]All percentages relative to the number intended to treat.
[c]One patient never received treatment and was lost for follow-up.
[d]One patient received HCG but no oocyte retrieval was performed because of psychogenic anejaculation on the day of the scheduled oocyte aspiration.

Human Reproduction (2005); 20: 1200 - 1206

Results:

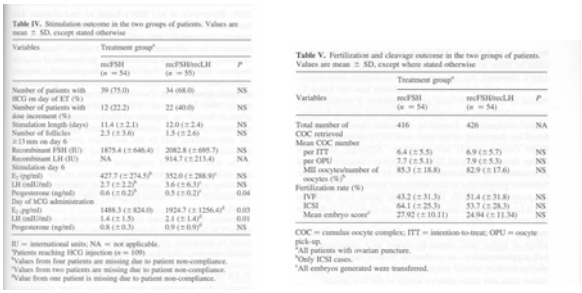


Table IV. Stimulation outcome in the two groups of patients. Values are mean ± SD, except stated otherwise

Variables	Treatment group[a]		
	recFSH (n = 54)	recFSH/recLH (n = 55)	P
Number of patients with HCG on day of ET (%)	39 (75.0)	34 (68.0)	NS
Number of patients with dose increment (%)	12 (22.2)	22 (40.0)	NS
Stimulation length (days)	11.4 (± 2.1)	12.0 (± 2.4)	NS
Number of follicles ≥ 13 mm on day 6	2.3 (± 3.6)	1.5 (± 2.6)	NS
Recombinant FSH (IU)	1875.4 (± 646.4)	2082.8 (± 695.7)	NS
Recombinant LH (IU)	NA	914.7 (± 213.4)	NA
Stimulation day 6			
E_2 (pg/ml)	427.7 (± 274.5)[b]	352.0 (± 288.9)[c]	NS
LH (mIU/ml)	2.7 (± 2.2)[b]	3.6 (± 6.3)[c]	NS
Progesterone (ng/ml)	0.6 (± 0.2)[b]	0.5 (± 0.2)[c]	0.04
Day of hCG administration			
E_2 (pg/ml)	1488.3 (± 824.0)	1924.7 (± 1256.4)[d]	0.03
LH (mIU/ml)	1.4 (± 1.5)	2.1 (± 1.4)[e]	0.01
Progesterone (ng/ml)	0.8 (± 0.3)	0.9 (± 0.9)[d]	NS

IU = international units; NA = not applicable.
[a]Patients reaching HCG injection (n = 109)
[b]Values from four patients are missing due to patient non-compliance.
[c]Values from two patients are missing due to patient non-compliance.
[d]Value from one patient is missing due to patient non-compliance.

Table V. Fertilization and cleavage outcome in the two groups of patients. Values are mean ± SD, except where stated otherwise

Variables	Treatment group[a]		
	recFSH (n = 54)	recFSH/recLH (n = 54)	P
Total number of COC retrieved	416	426	NA
Mean COC number			
per ITT	6.4 (± 5.5)	6.9 (± 5.7)	NS
per OPU	7.7 (± 5.1)	7.9 (± 5.3)	NS
MII oocytes/number of oocytes (%)[b]	85.3 (± 18.8)	82.9 (± 17.6)	NS
Fertilization rate (%)			
IVF	43.2 (± 31.3)	51.4 (± 31.8)	NS
ICSI	64.1 (± 25.3)	53.7 (± 28.3)	NS
Mean embryo score[c]	27.92 (± 10.11)	24.94 (± 11.34)	NS

COC = cumulus oocyte complex; ITT = intention-to-treat; OPU = oocyte pick-up.
[a]All patients with ovarian puncture.
[b]Only ICSI cases.
[c]All embryos generated were transferred.

Human Reproduction (2005); 20: 1200 - 1206

ART outcome

Table VI. Implantation, pregnancy and miscarriage in the two groups of patients. Values are mean ± SD, except where stated otherwise

Variables	Treatment group		
	recFSH	recFSH/recLH	P
Total number transferred embryos	109	99	NA
Mean number of transferred embryos			
per ITT	1.68 (± 0.9)	1.6 (± 0.9)	NS
per ET	2.1 (± 0.5)	1.98 (± 0.6)	NS
Positive pregnancy tests (n)	15	16	
% per ITT	23.1	25.8	NS
% per ET	28.8	32.0	NS
Early pregnancy losses[a] (n)	3	8[b]	NS
Clinical pregnancies (n)	12	8	NS
% per ITT	18.4	12.9	NS
% per ET	23.0	16.0	NS
Implantation rate (%)	13.8	8.1	NS

[a]Miscarriages before 12 weeks of gestation.
[b]Including one extrauterine gravidity (treated by laparoscopy).

Human Reproduction (2005); 20: 1200 - 1206

Conclusion:

- **There is no need for LH supplementation in COH using GnRH – antagonists!**

In the long protocol ?

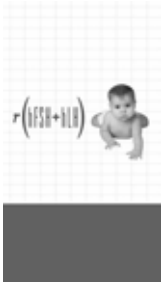
LH – supplementation in the long protocol?

- „Supplementing rec. FSH with daily doses of 75 – 150 IU of rec. LH during the second half of the follicular phase showed no evidence of increasing the ongoing pregnancy rates in the general population.“

Nyboe Andersen A., Humaidan P., Fried G., Hausken J., Antila L., Bangsboll S., Rasmussen PE, Lindenberg S., Bredkjaer HE, Meinertz H., Nordic LH study group. (2008): Recombinant LH supplementation to recombinant FSH during the final days of controlled ovarian stimulation for in vitro fertilization. A multicentre, prospective, randomized, controlled trial. Hum. Reprod.; 23:427 - 434

However…

Pergoveris



Die erste rekombinante Gleichung
Bezeichnung des Arzneimittels: Pergoveris 150 I.E. / 75 I.E. Pulver und Lösungsmittel zur Herstellung einer Injektionslösung, Wirkstoffe: Follitropin alfa, Lutropin alfa. Pharmazeutischer Unternehmer: Serono Europe Ltd., 56 Marsh Wall, London E14 9TP, Vereinigtes Königreich; Vertrieb in Deutschland: Serono GmbH, Freisinger Straße 5, 85716 Unterschleißheim.
Zusammensetzung:
Eine Durchstechflasche mit Pulver enthält 150 I.E. (11 µg) Follitropin alfa (r-hFSH) und 75 I.E. (3,0 µg) Lutropin alfa (r-hLH). Die rekonstituierte Lösung enthält 150 I.E. r-hFSH und 75 I.E. r-hLH in 1 ml. Sonstige Bestandteile sind Sucrose, Natriummonohydrogenphosphat-Dihydrat, Natriumdihydrogenphosphat-Monohydrat, Polysorbat 20, Methionin, Phosphorsäure, Natriumhydroxid und Wasser für Injektionszwecke. Anwendungsgebiete: Stimulation der Follikelreifung bei Frauen mit schwerem LH- und FSH-Mangel. Gegenanzeigen: Überempfindlichkeit gegen FSH oder LH oder einen der sonstigen Bestandteile des Arzneimittels, Tumoren des Hypothalamus oder der Hypophyse, Vergrößerung oder Zysten der Ovarien (ausgenommen polyzystisches Ovarialsyndrom), gynäkologische Blutungen unbekannter Ursache, Ovarial-, Uterus- oder Mammakarzinome. Pergoveris darf nicht angewendet werden, wenn Voraussetzungen vorliegen, die eine normale Schwangerschaft unmöglich machen, wie z. B. vorzeitige Menopause, Missbildungen der Geschlechtsorgane oder Tumoren des Uterus. Vorsicht und engmaschige
Überwachung sind angezeigt bei Patientinnen, die an Porphyrie leiden oder in deren Familie Porphyriefälle vorgekommen sind. Pergoveris ist in Schwangerschaft und Stillzeit nicht indiziert. Nebenwirkungen: sehr häufig (≥ 1/10): Ovarialzysten, Kopfschmerzen; häufig (≥ 1/100, < 1/10): Unterleibs-, Becken und Brustschmerzen, Übelkeit, Erbrechen, Unterleibskrämpfe, Völlegefühl, Somnolenz, lokale Reaktionen (Schmerz, Rötung, Bluterguss, Schwellung und/oder Reizung) an der Injektionsstelle, leichtes bis mittelschweres ovarielles Hyperstimulationssyndrom (OHSS); gelegentlich (≥ 1/1.000, < 1/100): schweres OHSS; selten (≥ 1/10.000, < 1/1.000): Torsion der Ovarien; sehr selten (< 1/10.000): Exazerbation oder Verschlechterung von Asthma, Thromboembolien, leichte systemische allergische Reaktionen (Erythem, Hautausschlag, Gesichtsschwellung, Urtikaria, Ödeme, Atembeschwerden), schwerwiegende allergische Reaktionen einschließlich anaphylaktischer Reaktionen. Warnhinweis: Arzneimittel für Kinder unzugänglich aufbewahren. Verschreibungspflichtig. Stand: Juni 2007
Rekombinante Innovation
• schließt die Lücke in den Therapieoptionen

LH – supplementation in poor responders

Short protocol:
600 IU rec. FSH / 600 IU rec. FSH + 75 IU rec. LH / 600 IU rec. FSH + 75 IU rec. HCG

	Group A (rFSH) (n = 51)	Group B (rFSH + rLH) (n = 46)	Group C (rFSH + r-hCG) (n = 48)	*P* value
	34.9 ± 0.5	36.3 ± 0.7	35.2 ± 0.9	.26
nts >37 years (%)	29.4	41	36.9	.37
ntral follicles	5.8 ± 0.4	6.6 ± 0.6	6.3 ± 0.5	.69
FSH (IU/L)	6.8 ± 1.7	7.9 ± 1.8	7.1 ± 1.9	.98
E_2 levels	1897.1 ± 427	2003.1 ± 468	2362.7 ± 292	.44
of stimulation	9.1 ± 0.3	8.5 ± 0.3	8.1 ± 0.2	.06
mbinant FSH dosage (IU)	5454.5 ± 177	5125.7 ± 165	4902.4 ± 148	.053
ocytes retrieved	5.6 ± 0.7	4.8 ± 0.6	3.8 ± 0.4	.19
bryos transferred	2.5 ± 0.2	2.4 ± 0.3	2.1 ± 0.2	.46

Note: Values are mean ± standard error of mean.
Fertil Steril 2007.

Berkkanoglu M., Isikoglu M., Aydin D., Ozgur K. (2007): Clinical effects of ovulation Induction with recombinant follicle – stimulating hormone supplemented with recombinant Luteinizing hormone or low – dose recombinant human chorionic gonadotropin in the Midfollicular phase in microdose cycles in poor responders. Fertil. Steril; 88:665 - 669

TABLE 3

Clinical outcomes.

Outcome	Group A	Group B	Group C	*P* value
Cancellation rate of COH (%)	13.7	10.2	10.8	.85
Cancellation rate of ET (%)	15.9	17.1	21.9	.75
Cancellation rate of COH + ET (%)	27.4	25.6	30.4	.88
Pregnancy rate (%) per transfer	35.1	27.6	31.2	.80
Clinical pregnancy rate (%) per transfer	27.1	27.5	21.8	.65

Note: COH, controlled ovarian hyperstimulation; ET, embryo transfer.

Isikoglu. Recombinant hCG in microdose cycles. Fertil Steril 2007.

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Berkkanoglu M., Isikoglu M., Aydin D., Ozgur K. (2007): Clinical effects of ovulation Induction with recombinant follicle – stimulating hormone supplemented with recombinant Luteinizing hormone or low – dose recombinant human chorionic gonadotropin in the Midfollicular phase in microdose cycles in poor responders. Fertil. Steril; 88:665 - 669

Results are yet not convincing:

- **Berkkanoglu M. et al. (2007): Additional exogenous LH activity in the form of either recombinant luteinizing hormone or low – dose rec. HCG is unnecessary in poor responders in microdose cycles to increase pregnancy rates.**
  Fertil. Steril.; 88: 665 - 669
- **Berrenetxea G. et al. (2007): The addition of LH produces no further benefit in poor responder women. Fertil. Steril.; 89:546 - 553**

Cochrane Database Syst. Rev. 2007:

- „There is insufficient evidence to support the routine use of any particular intervention either for pituitary downregulation, ovarian stimulation or adjuvant therapy in the management of poor responders to controlled ovarian stimulation.“