

LH Supplementation in ART

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Ovarian stimulation is a key element of all ART procedures. In the past, urinary gonadotropins such as u-hMG were used for ovarian stimulation. HMG is an impure urine derived gonadotropin with a fixed ratio of 1:1 in terms of FSH:LH activity.

When Gonal-f as the first recombinant FSH preparation (r-hFSH) was available, it was shown that for most women successful ovarian stimulation can be achieved with r-hFSH alone. However there is an ongoing debate as to whether or not some patients might need additional LH. Since recombinant LH (r-hLH) is nowadays available, several authors have addressed this question and the following lecture will highlight the most recent findings on the use of r-hLH in ART.

R. Marrs et al. (2003) published a randomized controlled study comparing two groups of patients in the long agonist protocol, either receiving r-hFSH alone or a combination of r-hFSH + rhLH at a ratio of 2:1 from stimulation day six onwards. The authors showed that women <35 years could successfully be stimulated with r-hFSH alone however the supplementation of LH was beneficial for women ≥ 35 years, resulting in similar implantation as well as clinical pregnancy rates compared to those women <35 years treated with r-hFSH + r-hLH.

Humaidan et al. (2004) were able to confirm these results. They showed that for women >35 years treated with the classic long protocol, the supplementation of LH at a ratio of 2:1 (FSH:LH) in the late phase of ovarian stimulation results in significantly better implantation and pregnancy rates. Furthermore the supplementation of LH led to a significantly reduced total amount of r-hFSH required.

Placido et al. (2004) studied the effects of LH supplementation on slow responders. They showed that for women with inadequate response to FSH alone, the addition of LH results in higher number of oocytes and higher implantation and pregnancy rates.

Concluding from the above mentioned studies, there are two groups of patients who could benefit from Luveris supplementation:

- Patients ≥ 35 years
- Slow responders

A ratio of 2:1 for Gonal-f :Luveris seems to be the most favorable. Administration of Luveris in the late phase of the stimulation cycle is recommended as at this time the follicles express adequate levels of LH receptors.

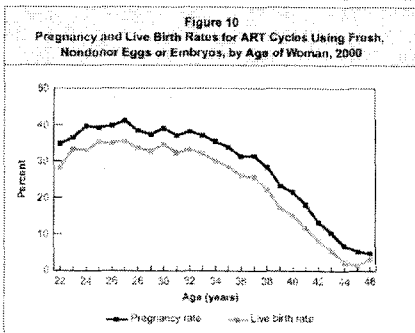
LH Supplementation in ART

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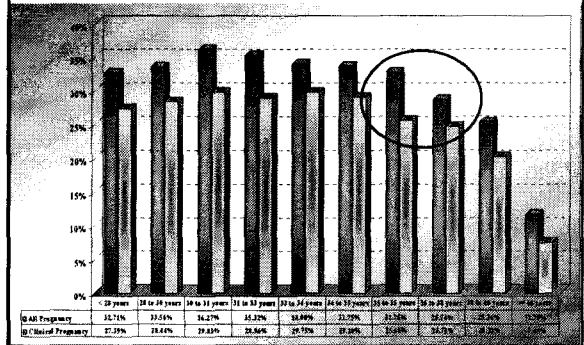
LH Supplementation in ART: Questions to be answered

- Is the requirement for LH supplementation different between patient populations?
 - Age
 - Type of GnRH agonist?
- How much LH should be administered?
 - In same ratio as FSH or less?
- When should LH supplementation be administered?
 - Beginning, middle, or end of FSH stimulation?
- Does LH supplementation increase the chance for pregnancy/live birth in slow responders ?

ART Success Rates in USA 2000: CDC report

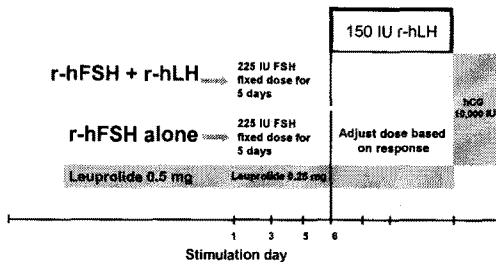


Clinical Pregnancy Rate according to age: Data from Serono database



Randomized trial to compare the effect of recombinant human FSH (follitropin alfa) with or without recombinant human LH in women undergoing assisted reproduction treatment

Marrs et al 2003 RBMOnline § 175-182



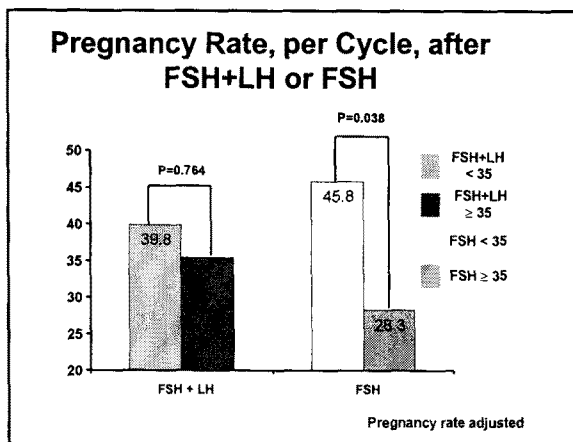
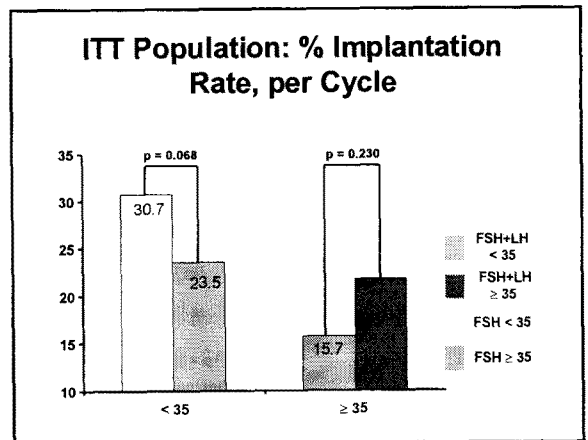
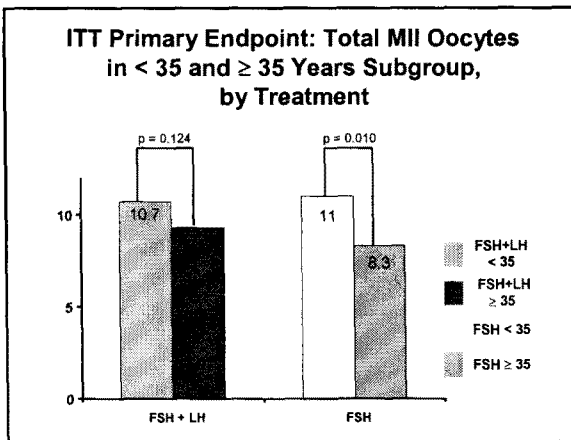
Randomized trial to compare the effect of recombinant human FSH (follitropin alfa) with or without recombinant human LH in women undergoing assisted reproduction treatment

Marrs et al 2003 RBMOnline § 175-182

Table 3. Oocyte retrieval and outcome of CGS. Values are mean ± SD unless otherwise stated

Characteristic	Desam group (n=212)	r-hFSH alone (n=219)	Total patients (n=431)	P-value
Number of MII oocytes	10.3 ± 8.9	10.4 ± 6.3	10.3 ± 6.1	NS
Number of 2PN oocytes	7.6 ± 4.7	7.2 ± 4.6	7.3 ± 4.6	NS
Fertilization rate	55.4 ± 21.8	52.7 ± 22.1	54.1 ± 22.0	NS
Embryos cryopreserved	2.4 ± 3.6	2.2 ± 3.5	2.2 ± 3.5	NS
Patients with embryos transferred (%)	198 (93.4)	197 (90.0)	395 (91.6)	NS
Number of embryos transferred	2.9 ± 6.6	2.8 ± 6.7	2.8 ± 6.7	0.037
Patients with clinical pregnancy (%)	90 (42.5)	91 (41.6)	181 (42.0)	NS

Overall except for no. embryos transferred there was no significant Difference in outcome parameters



Randomized trial to compare the effect of recombinant human FSH (follitropin alfa) with or without recombinant human LH in women undergoing assisted reproduction treatment

Marrs et al 2003 RBMOnline 8 175-182


Table 4. Clinical pregnancy rates per started cycle in the intention to treat (ITT) primary and multiple treated population for women aged <35 and ≥35 years after ovarian stimulation with r-hFSH + r-hLH or r-hFSH alone

Maternal age (years)		Treatment group		P-value*
		r-hFSH + r-hLH	r-hFSH	
All <35	ITT (%)	53/147 (36.0)	74/163 (45.4)	0.231
	Adjusted† (%)	39.8	45.8	0.038
All ≥35	ITT (%)	27/80 (33.8)	17/56 (30.4)	0.756
	Adjusted† (%)	35.5	28.3	0.231
Aged ≥35 and undergoing first assisted reproduction cycle	ITT (%)	23/48 (47.9)	9/29 (31.0)	0.027
	Adjusted† (%)	39.3	19.6	0.009

Older patients (≥35) undergoing 1st ART cycle and treated with r-hFSH + r-hLH had a significantly higher pregnancy rate than those receiving r-hFSH alone


- ### Study Summary
- Patients < 35 years treated with r-hFSH alone had higher implantation and pregnancy rates than those patients < 35 years treated with r-hFSH and r-hLH
 - implantation (30.7% vs 23.5%)
 - pregnancy rates (45.8% vs 39.8%)
 - Patients ≥ 35 years old benefited from r-hLH supplementation which resulted in similar implantation and pregnancy rates to those of patients < 35 years treated with r-hFSH and r-hLH
 - implantation rates (23.5% vs 21.7%)
 - pregnancy rates (39.8% vs 35.4%)

- ### Conclusion
- In a routine GnRH agonist protocol
- younger patients (< 35 years old) respond well and have a better chance of pregnancy with r-hFSH alone
 - r-hLH supplementation limited to the last few days of r-hFSH stimulation may be important only in older patients (≥ 35 years old)


 Humaidan et al., 2004, ISSN 1472-6533 (print) ISSN 1473-0765 (online) DOI: 10.1093/humrep/dch012 © 2004 Oxford University Press

Article

Effects of recombinant LH supplementation in women undergoing assisted reproduction with GnRH agonist down-regulation and stimulation with recombinant FSH: an opening study

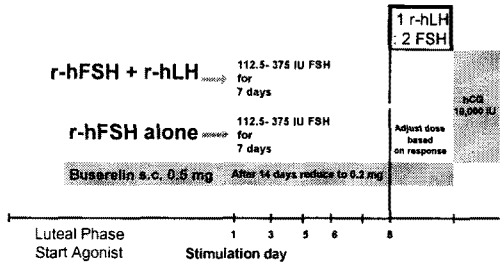


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Design/Methods

- Prospective, randomized study
- Women aged < 40 undergoing IVF or ICSI
- Down-regulation with GnRH agonist
- Stimulation with Gonadotropin-releasing hormone (Gonadotropin) (individual doses)
- Randomized at day 8 to supplementary Luveris or Gonadotropin alone

Humaidan Stimulation Protocol



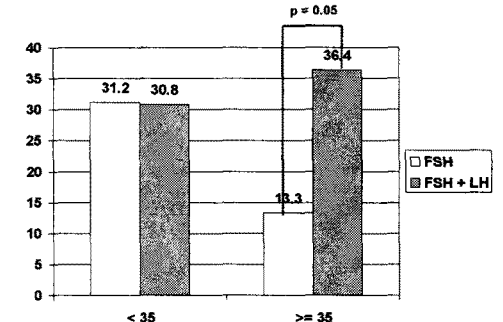
Humaidan et al., 2004

To examine the impact of r-hLH supplementation on age, patients were subdivided into 4 groups

< 35 years + LH	≥ 35 years + LH
< 35 years - LH	≥ 35 years - LH

Humaidan et al., 2004

% Implantation Rate, per Cycle



Humaidan et al., 2004

Women aged 35 or older

	r-hFSH + r-hLH	r-hFSH alone
Total FSH dose (IU)	2225*	2797
Implantation rate (%)	12/33 (36.4%)*	4/30 (13.3%)
Clinical pregnancy rate (%/started cycle)	7/21 (33.3%)	4/18 (22.2%)

*p < 0.05

Humaidan Conclusion

- Exogenous LH supplementation in a ratio of 2 FSH:1 LH from stimulation day 8 in patients ≥ 35 years of age:
 - significantly increased implantation rates,
 - significantly reduced total FSH consumption
 - in the non-supplemented group there was a significant lower pregnancy rate compared to the young patient. This difference was not seen in the supplemented group.
- Similar to findings of Marrs et al. (RBM Online 2004; 8(2): 175–82).

Humaidan et al., 2004

Humaidan et al., 2004

Humaidan et al., 2004

Effects of recombinant LH (rLH) supplementation during controlled ovarian hyperstimulation (COH) in normogonadotrophic women with an initial inadequate response to recombinant FSH (rFSH) after pituitary downregulation

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when compared with the group A (n=29; 13.2, 45.7%). The mean number of ampoules of rLH was significantly higher in the group B (n=4; 3.0 vs. 4.0), whereas those patients receiving a significantly lower total number of rFSH ampoules (448.0 ± 7.4 vs. 502.0 ± 23.0) (p=0.01), 3 (75.0%) and 2 (50.0%) ampoules were achieved in the groups A, B and C, respectively, respectively. These results suggest that patients with initial moderate responses to rFSH after pituitary downregulation benefit from the addition of a small dose of rLH starting from the eighth day of stimulation.

Summary

Background: This study was aimed to evaluate the effect of different recombinant LH (rLH) doses on the ovarian response of normogonadotrophic women with an initial inadequate response to recombinant FSH (rFSH) after pituitary downregulation.

Methods: Only women undergoing a long protocol with a GnRH agonist followed by rFSH administration were included. On the eighth day of stimulation, all patients with serum E2 levels < 100 pg/ml and with no follicles > 10 mm were randomized to the control to receive a supplementation with a daily rLH dose of 75 IU (group A) or 150 IU (group B) from day 8 to day 10.

Results: In the study, 100 normogonadotrophic women were included. The mean number of ampoules of rFSH was significantly higher in the group B (n=4; 3.0 vs. 4.0), whereas those patients receiving a significantly lower total number of rFSH ampoules (448.0 ± 7.4 vs. 502.0 ± 23.0) (p=0.01), 3 (75.0%) and 2 (50.0%) ampoules were achieved in the groups A, B and C, respectively, respectively. These results suggest that patients with initial moderate responses to rFSH after pituitary downregulation benefit from the addition of a small dose of rLH starting from the eighth day of stimulation.

Objective

- To study the effect of different doses of r-hLH (Luvetris®) administered during COH in normogonadotrophic downregulated women undergoing IVF or ICSI, who showed an initial inadequate ovarian response to r-hFSH (Gonal®) stimulation

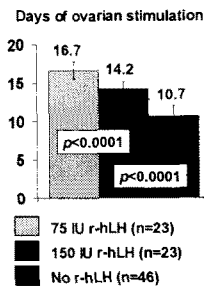
Design/Methods

- Prospective, randomized study
- Infertile women undergoing IVF or ICSI
- Long protocol GnRH-a suppression
- r-hFSH stimulation (150–300 IU/day, reduced to 75 IU on day 5 in women with E₂ > 160 pg/ml)

Design/Methods (cont.)

- Randomization on day 8 of COH
- Slow responders to stimulation (E₂<180 pg/ml and no follicle >10 mm) randomized to:
 - 75 IU/day r-hLH (n=23)
 - 150 IU/day r-hLH (n=23)
- Good responders assigned to control group (n=46)

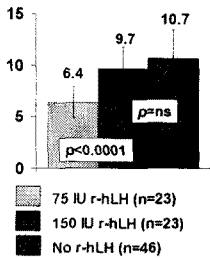
Results: ovarian stimulation



- Shortest stimulation required in the control group
- Significant difference between all three groups
- This trend was also reflected in the total IU r-hFSH used

Results: oocyte retrieval

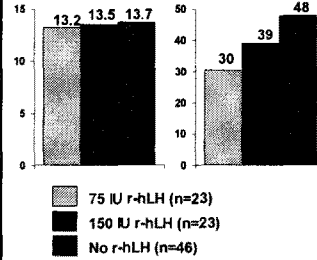
Number of oocytes retrieved



- Significantly more oocytes retrieved with 150 IU r-hLH than 75 IU r-hLH
- 150 IU r-hLH group comparable to control group

Results: IVF/ICSI outcome

Implantation rate (%) Pregnancy rate (%)



- Higher implantation and pregnancy rates with 150 IU r-hLH than 75 IU r-hLH
- No statistics reported

Conclusion

- Women with a poor response to COH may benefit from exogenous r-hLH:
 - significantly improves oocyte development and maturation
 - may also increase implantation and pregnancy rates
- 150 IU/day r-hLH is more efficacious than 75 IU/day r-hLH
- Most women do not require additional LH

Overall Conclusion LH supplementation in ART

- There are two groups of patients that could benefit from Luveris supplementation in ART:
 - Patients \geq 35 years
 - Slow responders
- Other variables in the stimulation regimen may also be important (type of agonist stimulation used)- more data required.
- A ratio of Gonad-f : Luveris of 2:1 seems to be the most favorable
- Administering at the end of stimulation makes physiological sense as it is at this time the follicle also expresses receptors for LH