# Evaluation of two doses of recombinant luteinizing hormone supplementation in an unselected group of women undergoing follicular stimulation for in vitro fertilization

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**Objective:** To evaluate the efficacy of two doses of recombinant (r)LH, 75 IU (recommended) or 37.5 IU, for follicular stimulation and outcomes in a randomized cohort of IVF patients.
**Design:** Randomized, prospective analysis.
**Setting:** Private hospital incorporating an established IVF center.
**Patient(s):** Women undergoing IVF who had a body mass index >18 or <35 and no abnormal karyotype, anovulation, oligomenorrhea, or any known endocrinopathy/illness.
**Intervention(s):** Pituitary desensitization was achieved with triptorelin (0.1 mg SC), and gonadotropin stimulation was performed with either rFSH alone (group A) or in combination with rLH in one of two doses: 37.5 IU (group B) or 75 IU (group C), daily.
**Main Outcome Measure(s):** A range of endocrinologic, embryologic, clinical, and outcome parameters were evaluated.
**Result(s):** With rLH supplementation there was a significant increase in the incidence of implantation (9% for rFSH only [group A] vs. 11% and 16% with 37.5 IU rLH and 75.0 IU rLH [groups B and C], respectively) and clinical pregnancy (19% vs. 23% and 31%) ($P<.01$ and $P<.04$, respectively), whereas there was no difference in the multiple pregnancy rates. There was a significant ($P<.001$) increase in the total units of rFSH used in proportion to the amount of rLH supplementation (2,645 U vs. 3,475 U and 3,681 U) and in the level of peripheral $E_2$ on the day of hCG administration (1,049 pg/mL vs. 1,640 pg/mL and 1,226 pg/mL) ($P<.001$). There was no significant between difference in mean age, numbers of oocytes recovered, basal and downregulation hormone levels, or the incidence of fertilization in the absence or presence of rLH supplementation, but a higher incidence of grade 1 to 2 embryos was observed when rLH was supplemented.
**Conclusion(s):** After pituitary desensitization, there was an increase in the incidence of implantation, clinical pregnancy, and delivery rates in patients stimulated with rFSH supplemented with rLH. (Fertil Steril® 2005;83: 309–15. ©2005 by American Society for Reproductive Medicine.)

**Key Words:** IVF, recombinant gonadotropins, recombinant LH, follicular stimulation

In the natural menstrual cycle and during follicular stimulation with antiestrogens or gonadotropins (without pituitary desensitization), women are exposed to both FSH and LH during the follicular phase, and normal follicular responsiveness is regulated by these gonadotropins. Formation of a preovulatory follicle necessitates development through a gonadotropin-independent phase, FSH dependency, and a terminal maturation phase requiring LH. The prospect of testing the role of these hormones in a clinical setting has depended on the pathophysiologic condition of the hypogonadotropic hypogonadal woman. However, in recent years the introduction of recombinant technology, first with recombinant (r)FSH, upon a pituitary-desensitized cycle, uniquely subject normo-ovulatory women to follicular stimulation with predominantly FSH only; and even in those patients who were profoundly downregulated, it seemed that peripheral LH was insignificant. More recent studies have demonstrated that both FSH and LH are essential from the midfollicular phase for optimal physiologic function (1–6), although this has been disputed (7). Lisi et al. (8), in a pilot study, examined the use of recombinant rLH supplementation in downregulated patients undergoing IVF and demonstrated a potential benefit in terms of IVF outcomes.

Apart from obvious patient variation and the difficulties of understanding the complex roles of gonadotropins in patients undergoing IVF, it has been postulated that in addition to a requirement for minimal "threshold" levels, there exists an LH "ceiling effect," above which normal follicular maturation and possibly outcomes are affected (9). This was also indicated in women with hypogonadotropic hypogonadism (2, 10). Furthermore, the addition of rLH to a patient's IVF stimulation regimen is of significant cost. We therefore un-

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dertook a clinical study to examine the effects of halving the recommended daily dose of rLH from 75 IU to 37.5 IU.

## MATERIALS AND METHODS

### Patients

All patients began treatment during a set period ("treatment run") when patients were allocated rFSH only or rFSH and either 37.5 IU or 75 IU rLH. Although patients were initially selected on the basis of randomization by allocation of treatment at consultation (approximately half for rLH and half for rFSH with rLH), the final division for those receiving treatment during the study period was 56%, 25%, and 18% for rFSH only, 37.5 IU rLH, and 75 IU rLH, respectively (groups A, B, and C, respectively). The reason for this was that 34 patients did not receive 75 IU rLH because of lack of availability or withdrawal due to cost; therefore, 13 were given the lower dose of 37.5 IU, and 21 received rFSH only (Fig. 1). The trial was initiated with a computer-generated random number program, which covered 600 patients being assessed at either initial or review consultation for treatment by IVF ("enrollment"). No preselection of patients was undertaken. The eventual allocation and distribution of the patients, according to the CONSORT approach (11), is outlined in Figure 1. Exclusion criteria were a body mass index $<18$ or $>35$, an abnormal karyotype, anovulation, oligomenorrhea, or any known endocrinopathy/illness.

Pituitary desensitization (downregulation) was induced with triptorelin (0.1 mg SC; Ipsen, France) from the midluteal phase of the previous cycle (day 21) for 3 weeks before starting gonadotropin stimulation (12). All patients were started on a daily dose of 150 IU rFSH; those in group A had no further supplementation. Group B patients were supplemented daily with 37.5 IU rLH (Luveris; Serono, Geneva, Switzerland) from the 7th day of stimulation, and group C patients were supplemented with 75 IU rLH from day 7. The decision to start rLH on day 7 was based on the two-cell, two-gonadotropin model involving a transition from FSH-mediated acquisition of granulosa cell LH receptors at a follicular size of approximately 10 mm (13) to LH stimulation of folliculogenesis independent of FSH activity after this stage (3, 5, 14). This is a particularly significant feature in the spontaneous cycle, whereby rising levels of serum LH and falling levels of FSH occur at the time of dominant follicle selection, as demonstrated in sheep (15).

If additional or a reduction in stimulation was required, this occurred by modulating the amount of rFSH only; for group B and C patients, rLH was maintained at a constant dose. The decision to increase FSH stimulation was based on the rate of growth of leading follicles, as observed by daily ultrasound measurements, and/or the rate of rise of $E_2$ levels; in some patients a clinical decision was made on the basis of previous response profiles and concerns to not compromise the leading follicles. Ovulation induction occurred by administration of hCG injection (10,000 IU Profasi; Serono). Follicle growth and endometrial thickness were tracked by ultrasound scanning from day 7 of stimulation to hCG administration. Oocytes were recovered 36 hours after hCG administration. Patients had either IVF or intracytoplasmic sperm injection (ICSI), but there was no difference in the data between these insemination procedures (data not presented). For luteal support, all patients received P (50 mg IM Prontogest daily; Amsa, Rome, Italy).

### Embryology and Outcome

Oocyte retrieval and IVF-ET were carried out in accordance with our usual clinical practice, which has been published previously (16). The term "clinical pregnancies" is used to denote patients who are in their third trimester and in whom a fetal heartbeat had been monitored, or who have already delivered.

### Statistics

Continuous random variables, such as hormone levels, were analyzed by one-way analysis of variance. Proportions, such as the incidence of pregnancy, were analyzed by logistic regression, but all summaries are presented on the original scale of proportions, whereby the dependent variable was the logistic transform of the proportion of interest. The growth of follicles was summarized by average values of the linear regression coefficients, which had been calculated for each patient. The approach to statistical analysis was acceptable because there was no cyclical bias among the subjects, and the "treatment run" approach provided the required spread of patients over an extensive period to minimize other potential effects, such as laboratory conditions.

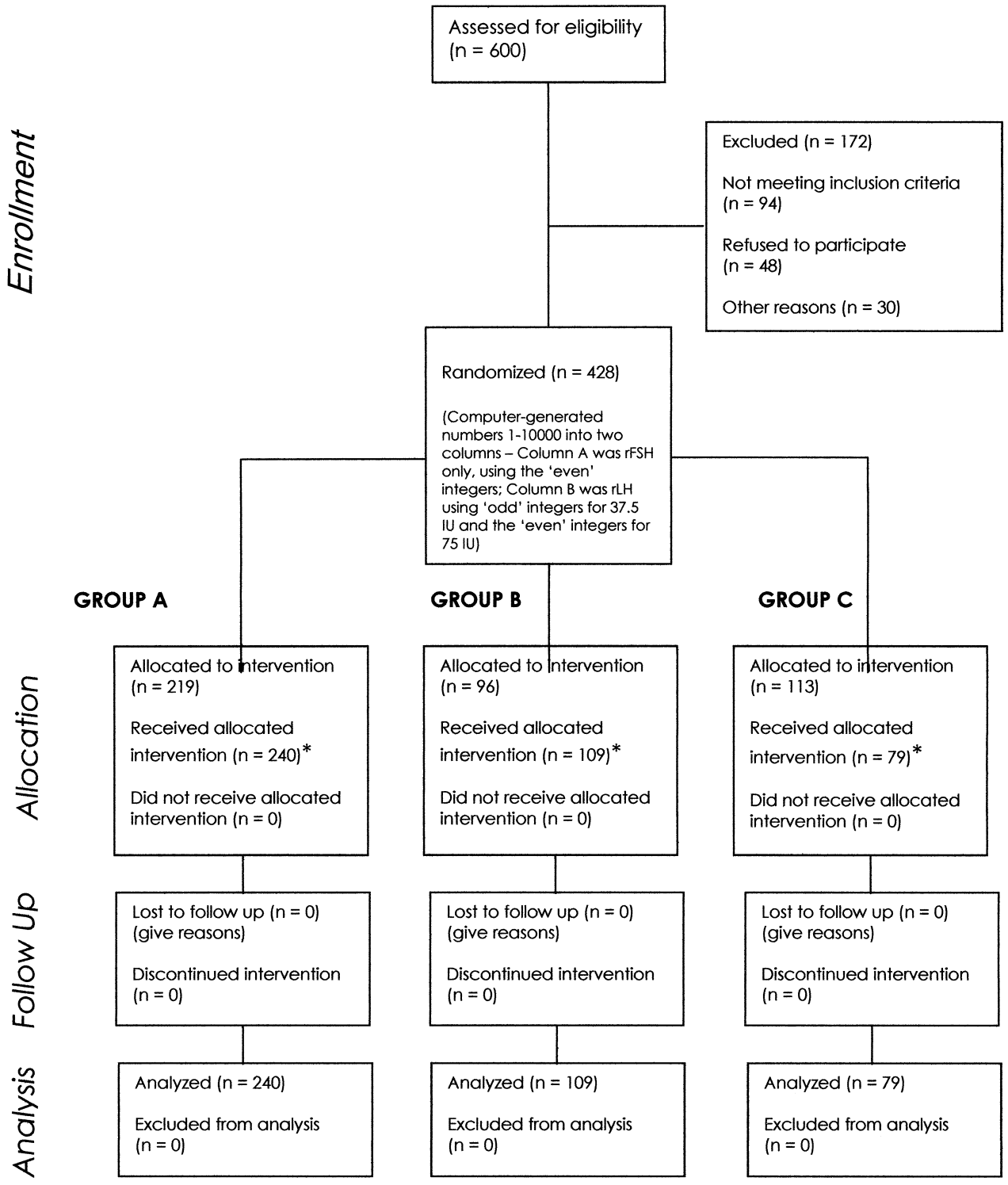
## RESULTS

A total of 428 patients were stimulated for oocyte recovery after pituitary desensitization (Fig. 1), and the numbers reaching egg recovery, ET, and clinical pregnancy (delivery) are shown in Table 1. There was no difference in the percentage of patients reaching egg recovery or ET, but there was a significant ($P<.05$) increase in the incidence of pregnancy in group C (75 IU rLH) compared with group A (FSH only). There was no significant difference in the mean age of patients (Table 1), the cause of infertility, or previous IVF history (data not shown). Basal hormone levels (FSH, LH, $E_2$, and prolactin) were measured on day 3 of the natural menstrual cycle, and peripheral FSH, LH, and $E_2$ were measured at downregulation; no significant differences between the groups were observed. A mean of 6.9–7.2 oocytes were recovered per cycle; approximately 80% were metaphase 2, of which approximately 52%–55% were fertilized with two pronuclei, and no significant difference in the presence or absence of exogenous LH was observed. The rates of fertilization with conventional IVF and with ICSI were similar (data not shown).

There was a significant ($P<.001$) increase in the mean number of units of FSH required for optimal stimulation

## FIGURE 1

Flow diagram of patients. *Thirty-four patients did not receive 75 IU rLH because of lack of availability or withdrawal due to cost; therefore, 13 were given the lower dose of 37.5 IU, and 21 received rFSH only.




*Lisi. rLH for follicular stimulation. Fertil Steril 2005.*

**TABLE 1**

**Overall egg recovery, ET, and clinical pregnancy rates in patients stimulated with rFSH alone or with rFSH and either 37.5 IU or 75 IU rLH.**

| Group | n | Mean (± SEM) age (y) | No. of patients with eggs recovered | No. of patients with embryos transferred | No. of clinical pregnancies/ deliveries |
|---|---|---|---|---|---|
| A (FSH only) | 240 | 36.1 ± 0.6 | 238 (99.2%)[a] | 206 (86.6%)[b] | 39 (18.9)[c,d] |
| B (37.5 IU rLH) | 109 | 35.2 ± 0.4 | 105 (96.3%) | 95 (90.5%) | 22 (23.2%) |
| C (75 IU rLH) | 79 | 35.8 ± 0.3 | 76 (96.2%) | 70 (92.1%) | 22 (31.4%)[d] |

[a]Percentage of total n.
[b]Percentage of patients with eggs recovered.
[c]Percentage of patients with embryos transferred.
[d]Group C > group A: $P<.05$.

*Lisi. rLH for follicular stimulation. Fertil Steril 2005.*

when rLH was supplemented: 2,645 U for group A vs. 3,475 U and 3,681 U for groups B and C, respectively. A significant ($P<.001$) increase in the mean peripheral level of $E_2$ was also observed: 1,049 pg/mL for group A vs. 1,640 pg/mL and 1,226 pg/mL for groups B and C, respectively. There was no significant difference in the number of days of stimulation between the groups. When grading embryo morphology from 1 (regular blastomeres with no fragmentation) to 4 (heavy fragmentation with blastomeres difficult to discern), a combination of scores 1 and 2 showed a higher incidence in the presence of rLH (Table 2). The biochemical and clinical pregnancy implantation rates displayed a significant progressive trend of mean proportions with increasing dose of LH supplementation (0.09, 0.11, and 0.16 in groups A, B, and C, respectively), but there was no significant difference in the multiple pregnancy rate.

Two subgroups of patients were further examined: those who had profound downregulation, as determined by a peripheral LH level of <1.0 IU/L, and those patients who had a basal FSH level of <10 IU/L or ≥10/L; these data are shown in Table 3. In the group of patients who had profound downregulation, there was no significant difference in the clinical pregnancy rate with rLH supplementation (38%) compared with group A patients (17%). However, there was a significant ($P<.01$) increase in the incidence of pregnancy when rLH was supplemented in patients who had a basal FSH level of ≥10 IU/L, compared with group A patients (Table 3).

## DISCUSSION

The European Recombinant Human LH Study Group (3) reported on the efficacy of rLH for supporting rFSH-induced follicular recruitment and development, demonstrating that a range of doses from 25–225 IU rLH per day was well tolerated and not immunogenic. The European Study (3) investigated World Health Organization (WHO) type I anovulatory women and demonstrated that a daily dose of 75 IU rLH was adequate for inducing follicular development and, after hCG administration, appropriate luteinization. In the majority of patients, even those classified with WHO

**TABLE 2**

**Proportions of embryos, by grade.**

| | No. of embryos | Grade of embryo | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 and 2 |
| No LH (A) | 1,109 | 0.49 | 0.39 | 0.10 | 0.02 | 0.88 |
| LH (37.5 IU) (B) | 384 | 0.46 | 0.47 | 0.06 | 0.01 | 0.93 |
| LH (75.0 IU) (C) | 270 | 0.48 | 0.40<br>B > A[a] | 0.12<br>B < C[b] | 0.00<br>C < A[b]<br>B < A[b] | 0.88<br>B > A[b]<br>B > C[b] |

[a]$P<.01$.
[b]$P<.05$.

*Lisi. rLH for follicular stimulation. Fertil Steril 2005.*

**TABLE 3**

**Clinical pregnancies in patients with downregulation LH <1.0 IU/L or patients with basal FSH > 10 IU/L.**

| | LH | | | | FSH | | | |
|---|---|---|---|---|---|---|---|---|
| | <1.0 IU/L | | ≥1.0 IU/L | | <10 IU/L | | ≥10 IU/L | |
| | No ET | No CP | No ET | No CP | No ET | No CP | No ET | No CP |
| FSH only | 35 | 6 (17%) | 171 | 33 (19%) | 180 | 39 (22%)[a] | 26 | 0 |
| 37.5 rLH | 10 | 4 (40%) | 85 | 18 (21%) | 69 | 14 (20%) | 26 | 8 (31%) |
| 75 rLH | 11 | 4 (36%) | 59 | 18 (31%) | 47 | 16 (34%)[a] | 23 | 6 (26%) |

*Note:* CP = clinical pregnancy.

[a]$P<.01$ (No CP significantly higher in 75 IU rLH group than in FSH-only group).

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type II anovulation (17) or patients undergoing IVF, it seems that no addition of LH is required to achieve optimal follicular development (7, 18). Nevertheless, there emerges a subpopulation of patients who are profoundly downregulated after long-term GnRH pituitary desensitization for whom, in some studies, LH seems to be essential for improved outcomes (1, 6, 12, 19–23). In contrast, the existence of "true," effective LH deficiency has yet to be established with adequate steroidogenic responses to FSH alone (7, 24). Much of the controversy in the literature is related to the particular GnRH used for desensitization, with formulation and dosage being important in the disruption of the basal levels of LH (25–30).

Serum levels of ≥1.2 IU/L have been shown to be necessary to provide adequate LH support to FSH-induced follicular development (31, 32) in the total absence of endogenous LH secretion. To attain this, the European Recombinant LH Study Group (3) settled on a daily dose of 75 IU rLH as sufficient, but this was for the treatment of WHO type I anovulation. During routine IVF, the majority of women are normally ovulatory with tonic serum levels >1.0 IU/L, even after pituitary desensitization. It has been postulated that, in contrast to a minimum, "threshold" level of peripheral LH for optimum follicular development, there is an "LH ceiling effect"; and that secondary follicles are sensitive to high levels of peripheral LH, resulting in their atresia (3, 33), although the pharmacodynamics that explain this effect are not clear (34) and remain controversial. Loumaye et al. (35) indicated that, in both WHO type I and WHO type II anovulation, excessive peripheral LH can induce follicular growth arrest during the late follicular maturation phase. This supports the earlier study of Humaidan et al. (36), who examined normal women undergoing IVF and demonstrated that peripheral LH levels >1.5 IU/L on day 8 of stimulation can have a detrimental effect on subsequent ovarian response and pregnancy outcome. Excessive levels of LH might inhibit granulosa cell mitosis, which occurs during the LH surge and, similarly, might promote premature oocyte meiosis and functional morphologic changes within the cumulus oophorous cells (37). Whereas rFSH has a terminal half-life of approximately 35 hours (38), rLH has a terminal half-life of 10–12 hours (39), and excessive amounts might suppress intrafollicular regulation and mechanisms associated with follicle dominance.

The most steroidogenically active follicles during the midfollicular phase are at most risk to highest levels of LH (6, 40). This additional availability of androgen substrate is the likely cause of significantly elevated estrogens in patients with LH supplementation, which is consistent with previous observations (41). In contrast to other studies in which consumption of FSH had a significant inverse relationship with LH levels (12, 36), the present study showed increased units of FSH with LH supplementation. However, the present study examined FSH units up to administration of hCG, compared with the study of Humaidan et al. (36), which compared the consumption of FSH levels on stimulation day 8, which was as a result of endogenous stores of follicular stimulation after pituitary desensitization with rFSH only. Furthermore, patient populations will vary, effecting differing local ovarian and systemic interactions, as shown by the differing results between patients who had previously had suboptimal response (12) and an unselected population (23). Nevertheless, we need to understand whether the increased requirement for FSH observed in this study for the LH-supplemented group is physiologically consistent and whether it is observed across the spectrum of patients. More studies need to be undertaken to provide a mechanistic understanding of this observation. Difficult decisions are made in an attempt to avoid compromising treatment, but in future studies clearer parameters for providing or refraining from increasing FSH are required. Maintenance of the appropriate level of serum LH, between >0.5 and <1.5 IU/L, has been shown to improve the incidence of fertilization and pregnancy when compared with the "threshold" and "ceiling" effects (36); yet Fanchin et al. (41) demonstrated significantly higher numbers of fertilized oocytes

and embryos and higher pregnancy rates when LH was >2 IU/L.

This study evaluated for the first time two doses of rLH, 37.5 IU vs. 75 IU, in an unselected, normo-ovulatory population of patients undergoing IVF and demonstrated an apparent advantage of the addition of LH to pituitary-desensitized patients stimulated with rFSH, especially in relation to the incidence of implantation and clinical pregnancies and deliveries. There was no significant increase in the multiple pregnancy rates. It is unclear how the addition of LH confers an improved implantation rate—whether this is related to oocyte and subsequently embryo competence or to the maternal environment (e.g., optimized hormonal and endometrial milieu). Studies are under way to examine these possibilities. For patients whose basal FSH level was >10.0 IU/L, supplementation with LH was advantageous; in those patients who had profound suppression of LH, defined as <1.0 IU/L, further, extensive studies are needed to establish any benefit of LH supplementation (24). Results of this study suggest that for optimum outcomes the higher rLH dose of 75 IU might be beneficial, albeit with a consequential slight increase in the amount of rFSH for some patients. However, the cost of administering recombinant gonadotropins is considerable, and more studies are needed to enable us to tailor the appropriate medication to individual patients needs.

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