Published in final edited form as:

Fertil Steril. 2011 January ; 95(1): 372–373. doi:10.1016/j.fertnstert.2010.08.020.

Enough is enough! Patients who do not conceive on 600IU/day of gonadotropins show no improvement from an additional 150IU of LH activity

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Abstract

Studies have suggested that supplemental LH improves outcomes in ART cycles. In this retrospective review, an additional 150IU of LH activity did not improve ART outcomes in women undergoing a second round of IVF/ICSI following an initial failed cycle employing 600IU of gonadotropins.

Keywords

lutinizing hormone; gonadotropin dose; pregnancy rate; miscarriage rate; cancellation rate

Some studies suggest that FSH doses greater than 450 IU/day offer minimal, if any, improvement in pregnancy outcome (1,2). One study where anticipated low responders were randomized to receive, 300, 450, or 600 IU/ day rFSH found that gonadotropin dosages greater than 300 IU/day did not improve pregnancy or cancellation rates (3). However, it is possible that supplemental LH activity may improve ovarian response to stimulation compared to protocols comprised of FSH alone. Gordon et al. (4) studied normogonadotropic women entering an initial cycle of ART randomized to receive varying doses of LH per ampule in addition to a stable dose of 75 IU FSH per ampule. The authors (4) found increasing implantation rates with increasing LH dose. A subsequent meta-analysis found no improvement in live birth rates with supplemental LH in patients treated with FSH and GnRH analogs (5). However, a 2007 Cochrane Review reported a trend towards improved pregnancy rates with supplemental LH, particularly in poor responders (6). Doses of rLH in studies included in this Cochrane review ranged from 37.5IU/day to 150IU/day, with most studies employing 75–150 IU/day. Given the possible beneficial effect of LH, we sought to determine whether increasing the LH dosage from 150IU/day to 300IU/day in women already receiving 450IU/day of FSH would improve ART outcomes.

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IRB approval for the study was obtained through Walter Reed Army Medical Center's (WRAMC) Department of Clinical Investigation. Retrospective review of the WRAMC IVF electronic database identified a total of 562 patients undergoing an initial cycle of IVF between January 2001 and March 2009 who received the program's standard microdose lupron (20 units twice daily), high dose gonadotropin (600 IU/day) regimen. Patients undergoing a second IVF/ICSI cycle after failing to conceive during an initial cycle employing 600IU gonadotropins/day were included in the analysis (n=127). Patients whose first cycles were cancelled or ended in no embryos being transferred were excluded. For their second IVF/ICSI cycle, all patients underwent baseline evaluation, including a clomid challenge test, antral follicle count and saline sonogram. After pretreatment with oral contraceptives, the control group (n=83) received microdose lupron (20 units twice daily) and a total gonadotropin dose of 600 IU/day, including 450 IU of FSH activity and 150 IU of LH activity. The study group (n=44) received microdose lupron and a total gonadotropin dose of 750 IU/day, including 450 IU of FSH activity and 300 IU of LH activity. LH activity was provided through hMG injections. FSH activity was provided through both recombinant FSH and hMG injections. hMG injections consisted of 75IU LH activity and 75IU FSH activity. Ovarian stimulation, oocyte retrieval, and embryo transfer were performed as described previously (7). A serum hCG was drawn 11 days following embryo transfer and all clinical pregnancies were confirmed by transvaginal ultrasound at approximately 6 to 7 weeks gestation. Miscarriage rates and cancellation rates were also recorded.

A student's t-test was used to compare mean values of normally distributed data between the two treatment groups. A Wilcoxon rank sum test was used to compare mean values of data that were not normally distributed. Differences in outcome rates were analyzed using a Chi-square or two-tailed Fisher's exact test as appropriate. An alpha error of 0.05 was considered significant for all comparisons.

One hundred twenty seven (n=127) patients met criteria for analysis. There were 83 patients in the control group and 44 patients in the LH-supplemented group. Patients' ages were similar in both groups (36.6 in the control group vs. 36.8 in the study group). At baseline, the study group had significantly fewer antral follicles (8.6 versus 11.4) and higher basal FSH values (9.1 versus 7.6), although both were considered in the normal range (AFC >8, FSH <12) for our facility. The study group had a significantly fewer number of oocytes retrieved (10.2 versus 14.6) and total embryos (4.2 versus 6.6, respectively). There were no statistically significant differences in clinical pregnancy rates (38.64% versus 36.14%, p=0.85), miscarriage rates (17.7% versus 13.3%, p=0.69), or cancellation rates (0% versus 1.2%, p=1.0) between the two groups.

Based on these results, supplemental LH above 150IU in women undergoing controlled ovarian hyperstimulation with 450IU/day of FSH did not improve oocyte recovery, embryo development, or pregnancy rates in IVF/ICSI cycles. It is reasonable to speculate that, by stimulating synthesis of substrates for use in estrogen synthesis, LH may enhance ovarian response during controlled ovarian hyperstimulation. Indeed, LH is capable of sustaining the growth of follicles that have developed an adequate number of LH receptors, even in the face of declining FSH levels (8). However, as with FSH, there appears to be a maximal LH dose, above which additional medication does not improve ART outcome.

This study has a potential bias due to differences in baseline characteristics between patients in the control and study groups. Because of significantly fewer antral follicles and higher basal FSH values, cycle outcomes might be expected to be worse in the "LH-supplemented" study group. The fact that pregnancy rates were comparable between the groups may be viewed as evidence of a beneficial impact of added LH. However, the data for these patients were collected and recorded prospectively which minimized data collection bias. In addition,

all patients who had a prior cycle with maximum gonadotropins were considered eligible. The differences in baseline characteristics reflect the retrospective nature of the study and while significant, did not exceed threshold levels where outcomes have been shown to differ based on prior studies. With those considerations, the analysis did not support benefit of LH supplementation above 150IU.

Acknowledgments

The authors thank the ART Institute of Washington with special consideration to Aidita James, PhD, Jacques Cohen, PhD, Donna Hoover RN, and Darshana Naik RN. We would also like to thank Alan DeCherney, MD for his continuing support.

Financial Support

This research was supported, in part, by the intramural research program of the NICHD, NIH

References

1. Tarlatzis BC, Zepiridis L, Grimbixis G, Bontis J. Clinical management of low ovarian response to stimulation in IVF: a systematic review. *Hum Reprod Update* 2003;9(1):61–76. [PubMed: 12638782]
2. Siristatidis CS, Hamilton MP. What should be the maximum FSH dose in IVF/ICSI in poor responders? *Journal of Obstetrics and Gynaecology* 2007;27(4):401–405. [PubMed: 17654194]
3. Berkkanoglu M, Ozgur K. What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders? *Fertil Steril*. 2009 [Epub ahead of print].
4. Gordon UD, Harrison RF, Fawzy M, Hennelly B, Gordon AC. A randomized prospective assessor-blind evaluation of luteinizing hormone dosage and in vitro fertilization outcome. *Fertil Steril* 2001;75(2):324–331. [PubMed: 11172834]
5. Kolibianakis EM, Kalogeropoulou L, Griesinger G, Papanikolaou EG, Papadimas J, Bontis J, et al. Among patients treated with FSH and GnRH analogs for in vitro fertilization, is the addition of recombinant LH associated with the probability of live birth? A systematic review and meta-analysis. *Human Reproduction Update* 2007;13(5):445–452. [PubMed: 17586849]
6. Mochtar MH, Van der Veen, Ziech M, van Wely M. Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles. *Cochrane Database Syst Rev* 2007;18(2) CD005070.
7. James AN, Hennessey S, Reggio B, Wiemer K, Larsen F, Cohen J. The limited importance of pronuclear scoring of human zygotes. *Hum Reprod* 2006;21(6):1599–1604. [PubMed: 16488905]
8. Sullivan MW, Stewart-Akers A, Krasnow JS, Berga SL, Zeleznik AJ. Ovarian Responses in Women to Recombinant Follicle-Stimulating Hormone and Luteinizing Hormone (LH): A Role for LH in the Final Stages of Follicular Maturation. *JCEM* 1999;84(1):228–232. [PubMed: 9920089]