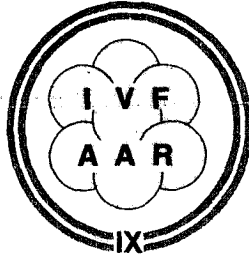


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IX

Luteinizing hormone (LH) in follicle stimulating drugs not needed despite long suppression with gonadotropin releasing hormone agonists (1)

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SUMMARY

The advent of recombinant DNA technology will soon produce for the market a product that has pure follicle stimulating hormone (pFSH) but no luteinizing hormone (LH). A prospective randomized study was performed to see if pFSH (Metrodin^R) was able to stimulate the same in vitro fertilization (IVF) parameters as human menopausal gonadotropin (hMG) when preceded by gonadotropin suppression by leuprolide acetate (LA). The results showed similar parameters between the two drugs, i.e., no. oocytes, no. embryos, endometrial thickness at time of human chorionic gonadotropin (hCG), fertilization rates and pregnancy rates (PRs) in a protocol purposely designed to stimulate as many follicles as safely possible because of a shared oocyte and successful cryopreservation program.

INTRODUCTION

Initial studies comparing pure follicle stimulating hormone (pFSH) for purposes of controlled ovarian hyperstimulation (COH) for in vitro

fertilization (IVF) failed to find any significant differences in various parameters including number of oocytes retrieved, peak serum estradiol (E_2) level, number of cleaved embryos, or pregnancy rates (PRs) (2,3). One study did suggest significantly less immature oocytes with pFSH vs human menopausal gonadotropin (hMG) and even a trend toward more oocytes retrieved and more embryos for transfer (4).

Many IVF centers now use gonadotropin releasing hormone agonists (GnRHa) prior to the use of gonadotropins to prevent premature luteinization. One method uses the GnRHa in the early follicular phase for three days prior to starting gonadotropin therapy, taking advantage of the agonistic properties of GnRH to try to recruit more follicles; this COH method is referred to as the short flare (5). A recent study suggested a trend toward a higher fertilization rate and a higher PR with pFSH vs hMG (6).

Another COH regimen uses the GnRHa for at least ten days (usually in the luteal phase) prior to gonadotropin stimulation (7). Since this technique establishes more prolonged LH suppression, theoretically, this method creates the greatest challenge to a gonadotropin preparation mostly devoid of LH activity. The study presented herein prospectively and randomly compared the efficacy of pFSH vs hMG in patients pre-treated with leuprolide acetate (LA) for a minimum of ten days in the luteal phase.

MATERIALS AND METHODS

The study prospectively and randomly (by last digit of year of birth) assigned patients at the Cooper Center for IVF, from October 1, 1992 to January 15, 1993 to either receiving hMG (even ending digit for year of birth) vs pFSH (odd ending digit). In all cases LA had been started subcutaneously (s.c.) at 1 mg for at least ten days before starting gonadotropin therapy (300 IU daily); the LA was continued at 0.5 mg during gonadotropin stimulation. Human chorionic gonadotropin (hCG) (10,000 IU) was given intramuscularly (IM) when at least two lead follicles were 20 mm by transvaginal sonography and a minimum serum estradiol (E_2) of 800 pg/mL was attained.

Statistical comparison of various IVF parameters were made using the t-test. Pregnancy rates (PRs) were compared by chi-square analysis.

RESULTS AND CONCLUSIONS

The randomization process lead to 31 patients assigned to hMG and 22 patients to pFSH. There were three cancelled cycles in the pFSH group because of premature luteinization in two patients, i.e., serum progesterone (P) >2.0 ng/mL prior to hCG and poor response in another; there was one cancellation in the hMG group for over stimulation.

Thus, the final analysis involved retrievals on 19 patients receiving pFSH and 30 stimulated with hMG. First time retrievals were found in 15 (78.9%) pFSH and 25 (83.3%) hMG cycles. There were two (6.7%) hMG-treated patients having their third retrieval. The reasons for IVF were as follows: pFSH - 2 unexplained, 13 tubal factor, 3 male factor and

1 endometriosis; hMG - 3 unexplained, 17 tubal factor, 4 male factor, and 6 endometriosis.

The two groups (pFSH vs hMG) were comparable on age (33.5 vs 32.6) and early follicular phase sera LH (5.0 vs 4.3) and FSH (8.4 vs 6.9) levels. There were no differences in any of the other parameters measured including no. follicles (20.6 vs 20.0), no. oocytes retrieved (16.6 vs 15.5), no. mature oocytes (14.4 vs 11.8), no. immature oocytes (1.9 vs 2.6), fertilization rate (68.2 vs 57.8), sera E_2 (1701.0 vs 1990.0pg/mL), P (.7 vs .5ng/mL), or LH (2.9 vs 2.9mIU/mL) levels on day of hCG, or endometrial thickness (12.5 vs 12.6mm) on day of hCG.

There were two pFSH and three hMG cycles where all embryos were cryopreserved as zygotes because the sera P levels exceeded 1.5 ng/mL (but were <2 ng/mL). Thus, there were 17 pFSH and 27 hMG transfers. The clinical viable PRs per transfer were 17.6% (3/17) and 22.2% (6/27) for pFSH and hMG therapy, respectively.

The data showed no difference between the use of pFSH or hMG in any of the important parameters for monitoring IVF response, despite the use of prolonged LA suppression prior to starting gonadotropin therapy and thus reached similar conclusions as previous studies using the same COH regimen (8-10).

Though the study consisted of only 44 cycles and, unfortunately, the randomization lead to more hMG than pFSH cases, the number of cases was adequate to conclude that pFSH is sufficient to generate enough follicles, even when the objective is to provide a high number of oocytes. Some centers prefer not to induce a large number of oocytes thinking that there is a reduced PR per cycle with too many eggs. However, at the Cooper Center for IVF a purposeful attempt is made to stimulate multiple oocytes because of a large number of patients interested in the shared oocyte program (11) and, also, to allow more cryopreserved embryos for future transfer.

The study by Edelstein et al., similar to the present study, used 300 IU of gonadotropin initially but then decreased the dosage, in contrast to maintaining the 300 IU dosage as used at the Cooper Center for IVF (10). In fact, following pFSH, Edelstein et al. retrieved an average of 11.5 oocytes per cycle, transferred an average of 3.8 embryos and cryopreserved 2.3; in comparison there were 16.6 oocytes retrieved, 3.3 embryos transferred, and 7.4 embryos frozen in the study presented herein. Edelstein et al. in another study found that one can reduce the number of follicles produced in high responders to GnRHa-hMG by substituting pFSH (12). Thus we considered the possibility that with attempts to purposely develop a large number of oocytes, pFSH would be less efficient than hMG. However, the present study found pFSH to be equally as effective as hMG in the number of oocytes and embryos produced.

Two of the three pFSH cycles were cancelled for premature luteinization; however, neither of these two patients had stimulated well. Thus, if one evaluates the PR per stimulation cycle, the level drops to 13.6% (3/22) for pFSH vs 21.4% (6/28) for hMG. Thus, in contrast to the study by Hedon et al. (8) using the short flare COH regimen who found that, if anything there was a trend toward a lower PR with pFSH.

Only a much larger study could determine whether a significantly higher proportion of patients treated with pFSH will demonstrate poor response to pFSH. In this study 3/22 (13.6%) failed to stimulate well with pFSH versus none of 31 treated with hMG. The data presented herein do suggest, however, that the majority of patients will stimulate well with LA-pFSH.

REFERENCES

1. Check JH, O'Shaughnessy A, Nazari A, Hoover L. A randomized prospective study to determine the efficacy of pure follicle stimulating hormone stimulation vs human menopausal gonadotropin preceded by gonadotropin suppression on various in vitro fertilization parameters. *Gynecol Obstet Invest* In Press.
2. Lake Polan M, Daniele A, Russell JB, DeCherney AH. Ovulation induction with human menopausal gonadotropin compared to human urinary follicle-stimulating hormone results in a significant shift in follicular fluid androgen levels without discernible differences in granulosa-luteal cell function. *J Clin Endocrinol Metab* 63:1284-1291;1986.
3. Lavy G, Pellicer A, Diamond MP, DeCherney AH. Ovarian stimulation for in vitro fertilization and embryo transfer, human menopausal gonadotropin versus pure human follicle stimulating hormone: a randomized prospective study. *Fertil Steril* 50:74-78;1988.
4. Scoccia B, Blumenthal P, Wagner C, Prins G, Scommegna A, Marut EL. Comparison of urinary human follicle-stimulating hormone and human menopausal gonadotropins for ovarian stimulation in an in vitro fertilization program. *Fertil Steril* 48:446-449;1987.
5. Garcia JE, Padilla SL, Bayati J, Baramki TA. Follicular phase gonadotropin-releasing hormone agonist and human gonadotropins: a better alternative for ovulation induction in in vitro fertilization. *Fertil Steril* 53:302-305;1990.
6. Daya S, Gunby J, Hughes E, Collins J, Sagle M. Randomized controlled study of two different gonadotropin regimens in IVF: an interim analysis. 10th Annual Meeting of the European Society of Human Reproduction and Embryology, Abstract Book, 1994.
7. Meldrum DR, Wisot A, Hamilton F, Gutlay AL, Kempton W, Huynh D. Routine pituitary suppression with leuprolide before ovarian stimulation for oocyte retrieval. *Fertil Steril* 51:455-459;1989.
8. Hedon B, Eld J, Audibert F, Boulal P, Bachelard B, Benos P, Amal F, Humeau C, Laffargue F, Viala JL. Etude randomisee FSH pure/hMG dans les stimulations ovariennes sous agonistes (Protocole Long). *Contraception-fertilite-sexualite* 18:670;1990.
9. Tanbo T, Dale PO, Kjekshus E, Haug E, Abyholm T. Stimulation with human menopausal gonadotropin versus follicle-stimulating hormone after pituitary suppression in polycystic ovarian syndrome. *Fertil Steril* 53:798-803;1990.
10. Edelstein MC, Brzyski RG, Jones GS, Simonetti S, Muasher SJ. Equivalency of human menopausal gonadotropin and follicle-stimulating hormone stimulation after gonadotropin-releasing hormone agonist suppression. *Fertil Steril* 53:103-106;1990.

11. Check JH, Nowroozi K, Chase J, Nazari A, Braithwaite C. Comparison of pregnancy rates following in vitro fertilization-embryo transfer between the donors and the recipients in a donor oocyte program. *J Assist Reprod Genet* 9:248-250;1992.
12. Edelstein MC, Brzyski RG, Jones GS, Gehminger S, Sieg SM, Muescher S. Ovarian stimulation for in vitro fertilization using pure follicle stimulating hormone with and without gonadotropin releasing hormone agonist in high responder patients. *J In Vitro Fert Embryo Transf* 7:172-176;1990.

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