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Comparison of Efficacy of High-Dose Pure Follicle-Stimulating Hormone versus Human Menopausal Gonadotropins for in vitro Fertilization

Key Words
Gonadotropin-releasing hormone agonist
Controlled ovarian hyperstimulation
Pure follicle-stimulating hormone
In vitro fertilization

Abstract
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. A prospective randomized study was performed to see if pFSH (Metrodin®) was able to stimulate the same in vitro fertilization parameters as human menopausal gonadotropin when preceded by gonadotropin suppression by leuprolide acetate. The results showed similar parameters between the two drugs, i.e., number of oocytes, number of embryos, endometrial thickness at time of human chorionic gonadotropin, fertilization rates and pregnancy rates in a protocol purposely designed to stimulate as many follicles as safely as 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 the number of oocytes retrieved, peak serum estradiol (E_2) level, number of cleaved embryos, or pregnancy rates (PRs) [1, 2]. 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 [3].

Many IVF centers now use gonadotropin-releasing hormone agonists (GnRHas) prior to the use of gonadotropins to prevent premature luteinization. One method uses the GnRHas in the early follicular phase for 3 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 [4]. A recent study suggested a trend toward a higher fertilization rate and a higher PR with pFSH vs. hMG [5].

Another COH regimen uses the GnRHa for at least 10 days (usually in the luteal phase) prior to gonadotropin stimulation [6]. Since this technique establishes more prolonged luteinizing hormone (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 pretreated with leuprolide acetate (LA) for a minimum of 10 days in the luteal phase.

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Table 1. Comparison of various IVF parameters and PRs following COH with pFSH vs. hMG when preceded by gonadotropin suppression with a GnRHa

	pFSH treatment	hMG treatment	p
Baseline LH, mIU/ml	5.0±2.4[1]	4.3±3.0	0.402
Baseline FSH, mIU/ml	8.4±3.4	6.9±2.7	0.146
Retrievals	19	30	
Follicles	20.6±11.4	20.0±14.6	0.884
Oocytes retrieved	16.6±8.8	15.5±10.6	0.722
Mature oocytes	14.4±7.4	11.8±7.8	0.252
Immature oocytes	1.9±2.5	2.6±3.9	0.514
Fertilization rate, %	68.2±19.5	57.8±27.1	0.154
Transfers	17	27	
Reasons for cancelled transfers	2 cancelled, all embryos frozen	3 cancelled, all embryos frozen	
Embryos transferred	3.3±1.3	3.2±1.6	0.793
Embryos frozen	7.4±8.0	4.7±7.0	0.219
E_2, pg/ml, day of hCG	1,701.0±745.9	1,990.0±1,328.3	0.351
LH, mIU/ml, day of hCG	2.9±2.7	2.9±0.9	0.925
Progesterone, ng/ml, day of hCG	0.7±0.4	0.5±0.4	0.339
Endometrial thickness, mm	12.5±2.1	12.6±2.7	0.896
Pregnancies (clinical)	4 (23.5%)	6 (22.7%)	
Pregnancies (viable)	3 (17.6%)	6 (22.7%)	
Age, years	33.5±2.7	32.6±3.6	0.342

[1] Mean ± 1 SD.

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 receive hMG (even-ending digit for year of birth) vs. pFSH (odd-ending digit). In all cases LH had been started subcutaneously at 1 mg for at least 10 days before starting gonadotropin therapy (300 IU daily); LA was continued at 0.5 mg during gonadotropin stimulation. Human chorionic gonadotropin (hCG; 10,000 IU) was given intramuscularly when at least two lead follicles were 20 mm by transvaginal sonography and a minimum serum E_2 of 800 pg/ml was attained.

Statistical comparison of various IVF parameters were made using the t test. PRs were compared by χ^2 analysis.

Results

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 2 patients, i.e., serum progesterone >2.0 ng/ml prior to hCG and poor response in another; there was one cancellation in the hMG group for overstimulation.

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 2 (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 2 groups were comparable for age and early follicular phase serum LH and FSH levels, as shown in table 1. There were no differences in any of the other parameters measured including number of follicles, number of oocytes retrieved, number of mature oocytes, number of immature oocytes, fertilization rate, serum E_2, progesterone, or LH levels on the day of hCG, or endometrial thickness on the day of hCG.

There were two pFSH and three hMG cycles where all embryos were cryopreserved as zygotes because the serum progesterone 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 of 17) and 22.2% (6 of 27) for pFSH and hMG therapy, respectively.

Discussion

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 [7–9].

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 the large number of patients interested in the shared oocyte program [10] and, also, to allow more cryopreserved embryos for future transfer.

The study by Edelstein et al. [9], 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 [9]. In fact, following pFSH, Edelstein et al. [9] retrieved an average of 11.5 oocyte/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. [11], in another study, found that one can reduce the number of follicles produced in high responders to GnRHa-hMG by substituting pFSH [11]. 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 2 patients had stimulated well. Thus, if one evaluates the PR per stimulation cycle, the level drops to 13.6% (3 of 22) for pFSH vs. 21.4% (6 of 28) for hMG. This is in contrast to the study by Hedon et al. [7] who used the short flare COH regimen and 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 of 22 (13.6%) failed to stimulate well with pFSH versus none of the 31 treated with hMG. The data presented herein do suggest, however, that the majority of patients will stimulate well with LA-pFSH.

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