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Follitropin-α versus human menopausal gonadotropin in an in vitro fertilization program

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Objective: To compare the efficacy of recombinant FSH and urinary-derived hMG for ovarian stimulation during IVF.

Design: Retrospective analysis of data from IVF cycles conducted over 15 months.

Setting: University hospital IVF unit.

Patient(s): Three hundred twenty-four women undergoing their first to sixth IVF cycle.

Intervention(s): After pituitary down-regulation, patients received recombinant FSH or hMG, according to personal choice. After hCG administration, patients underwent oocyte retrieval, oocyte fertilization, and embryo transfer.

Main Outcome Measure(s): Implantation rate and clinical ongoing pregnancy rate per oocyte retrieval.

Result(s): Patients who chose recombinant FSH were slightly younger than those who chose hMG (34.1 vs. 35.1 years, respectively). Although more embryos were transferred in the hMG group (3.6 vs. 3.2), the ongoing pregnancy and implantation rates were significantly higher in the recombinant FSH group (ongoing pregnancy rate, 50.0% vs. 36.2%).

Conclusion(s): Recombinant FSH is more effective than hMG for ovarian stimulation in IVF cycles. This increased efficacy, which is achieved with fewer ampoules, is likely to offset the higher acquisition costs of recombinant FSH. (Fertil Steril® 2003;80:1094–9. ©2003 by American Society for Reproductive Medicine.)

Key Words: Human menopausal gonadotropin, in vitro fertilization, ovarian stimulation, recombinant follicle-stimulating hormone, follitropin-α

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The role of the pituitary gland in regulating the gonads was first postulated in 1909 (1). In the 1930s, attempts were made to stimulate ovarian response in women using extracts from animal sources. These efforts were unsuccessful, however, probably because of an immunologic response to the extracts (2, 3). During the early 1960s, gonadotropins extracted from human pituitary glands (human pituitary gonadotropins) were used for inducing ovulation in women with hypothalamic amenorrhea (4). Although these preparations were used in Australia, the United Kingdom, and France, these extracts were never used on a large scale because of their limited supply. In the late 1980s, human pituitary gonadotropin was withdrawn from the market because several cases of Creutzfeldt–Jakob disease were thought to be linked to the use of this product (5).

In 1960, Lunenfeld et al. reported on use of hMG, a product extracted from the urine of postmenopausal women, to treat hypothalamic amenorrhea (6). Subsequently, this product became the mainstay of gonadotropin therapy. In the 1980s, use of hMG increased greatly because it began to be used in IVF and IUI protocols to treat various types of infertility. Recombinant human FSH was developed in the early 1990s through transfer of the human FSH gene into a genetically stable immortalized mammalian cell line (7).

Recombinant FSH has many potential advantages over hMG. Production of recombinant FSH is independent of urine collection, which guarantees constant availability of a biochemically pure FSH preparation with minimal variation in composition (8). The high purity of recombinant FSH (it lacks urinary protein contaminants) also means that this product can be administered by subcutaneous injection with good local tolerance. Greater consistency between batches means that the dose of FSH

delivered is more consistent with recombinant FSH than with urinary-derived hMG. Finally, in contrast to hMG, recombinant FSH is associated with markedly fewer immunologic reactions (9).

Despite all of these potential advantages of recombinant FSH, it is a newer product that lacks the long safety record of urinary products. In addition, urinary products have rarely been in short supply, have induced immunologic reactions only rarely (10), and have been associated with reasonable pregnancy rates. Although patients seem to prefer subcutaneous injections, intramuscular injection of urinary gonadotropins is generally well tolerated. In addition, many urinary gonadotropins are now routinely administered subcutaneously, although this tends to elicit local injection-site reactions (11).

In the United States, recombinant products can be up to 50% more expensive than their urinary counterparts. The generally trouble-free use of hMG may make it difficult to justify the increased price of recombinant FSH, unless it can be shown that the recombinant product leads to higher pregnancy rates. Few clinical studies have compared the efficacy of recombinant FSH and urinary-derived hMG in women undergoing IVF and other ART procedures. Most studies have compared hMG with "pure" urine-derived FSH preparations (which contain no or negligible LH activity but do contain some urinary proteins).

Meta-analyses have shown that "pure FSH" is superior to hMG (12) and that recombinant FSH is superior to urinary FSH (13). A combined analysis of data from three multicenter randomized trials (14) found a significant advantage of recombinant FSH over urinary gonadotropins (urinary FSH and hMG combined) in terms of pregnancy rate per started cycle.

On the basis of these data, it is reasonable to expect that recombinant FSH would yield higher pregnancy rates in IVF cycles than would hMG, but this has not been shown directly. A recent randomized trial comparing recombinant FSH and hMG in women undergoing ICSI (15) found no difference in percentage of metaphase II oocytes retrieved (86.9% with hMG vs. 87.4% with recombinant FSH) or in measures of oocyte and embryo quality. Similarly, a larger study (16) found no differences in pregnancy rates between women treated with recombinant FSH (n = 296; 30.1%) and those treated with hMG (n = 282; 32.3%). Further comparative studies are required to increase the evidence base on the relative efficacy of hMG and recombinant FSH.

MATERIALS AND METHODS

In this analysis, we included 324 IVF procedures initiated at our clinic during the 15 months between January 1998 and April 1999. Surrogate and oocyte donor cycles were excluded. Patients were offered recombinant FSH or urinary-derived hMG and they were told that recombinant FSH could be administered by subcutaneous injection, but that it was a substantially more expensive product than hMG. Patients were also told that the investigators believed there was no evidence from similar programs to show that one product was more successful than the other in terms of pregnancy rate. The meta-analysis of Daya (13) showing a significant benefit of recombinant FSH over urinary FSH was not available when the study began. Patients were, however, made aware of the report from Out et al. demonstrating a marginal benefit of recombinant FSH over urinary-derived gonadotropins (14). After being given the above information, patients were permitted to choose whether they received hMG or recombinant FSH for ovarian stimulation in their IVF cycle.

All patients underwent pituitary down-regulation with leuprolide acetate, 0.5 mg once daily, starting on approximately day 21 of the menstrual cycle before the IVF procedure. After menses, a baseline ultrasonogram was obtained and baseline E_2 level was measured. Gonadotropin treatment was initiated if no follicles were larger than 10 mm in diameter and the E_2 level was less than 50 pg/mL. Gonadotropin therapy was generally initiated at a dose of 225 IU/day but this could be modified according to patients' previous response. Urinary gonadotropin was administered as hMG (Humegon; Organon, West Orange, NJ) in 212 cycles. The recombinant FSH used was Gonal-F (Serono Laboratories, Norwell, MA) and was administered in 112 cycles.

For dosing purposes, the two types of FSH (urinary or recombinant) were considered equipotent, because evidence indicating otherwise was yet to be conclusively presented. Follow-up ultrasonography and E_2 levels were performed after 5 days and the gonadotropin dose was modified depending on the results. A 10,000 IU dose of hCG (Profasi; Serono Laboratories) was administered when at least two follicles with a mean diameter of 18 mm were present. Cycles were canceled if this criterion was not met.

Transvaginal ultrasonography–directed oocyte retrieval was performed 36 hours after hCG administration. Insemination in microdrops or by ICSI was performed approximately 6 hours after oocyte retrieval. GenX (GenX International, Madison, CT) culture medium with serum supplementation was used for embryo culture. Embryo replacement was performed using a Wallace catheter (Marlow Technologies, Inc., Willoughby, OH) on the third day after oocyte retrieval in all but six cases. These six transfers (three in the hMG group and three in the recombinant FSH group) were made on the fifth day after oocyte retrieval.

Patients received counseling relative to the number of embryos to transfer. In general, patients who were younger than 35 years of age were advised to have two or three embryos transferred, those 35 to 40 years of age were advised to have three or four embryos transferred, and those older than 40 years of age were counseled to have four or possibly more embryos transferred. (Only one patient in this

TABLE 1

Cause of infertility.

Diagnosis	hMG group	Recombinant FSH group
All patients undergoing ovarian stimulation (hMG, n = 212; FSH, n = 112)		
Endometriosis	14	4
Tubal	64	34
Immunologic	1	0
Idiopathic	54	25
Male factor	68	44
Ovulatory dysfunction	5	3
Other	2	1
Uterine	4	1
Patients undergoing oocyte retrieval (hMG, n = 174; FSH, n = 98)		
Endometriosis	10	4
Tubal	54	30
Immunologic	1	0
Idiopathic	46	22
Male factor	57	38
Ovulatory dysfunction	3	2
Other	0	1
Uterine	3	2

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latter age group transferred five embryos, and none transferred more.) The final decision on the number of embryos transferred, however, remained with the couple.

Embryos in excess of those transferred were observed for progression to the blastula stage, and those that developed appropriately to blastocysts were frozen. A blood sample was taken from the participants approximately 16 days after oocyte retrieval for determination of hCG concentration. If the initial hCG reading was positive for pregnancy, a second hCG measurement was made 1 week later. Ultrasonography to confirm intrauterine pregnancy was performed 7 to 10 days after the second positive hCG measurement. Patients returned to their referring obstetrician after the pregnancy-confirming ultrasonogram.

Data from 324 IVF cycles were retrospectively analyzed to compare the results according to the cause of infertility (Table 1), cycle number (Table 2), and outcome (Table 3) in the two self-selected groups of patients. The data were also analyzed by patient age (<35 and ≥ 35) and number of cycles (first cycle vs. second and later cycles). Clinical pregnancy was defined as the presence on ultrasonography of an intrauterine pregnancy with fetal heart activity.

The Fisher exact test was used to analyze data expressed in rates; *t*-tests were used to analyze continuous data. A Cochran–Mantel–Haenszel χ^2 test was used to analyze the stratified data. A cost analysis of the data was also performed to determine the cost per pregnancy achieved with hMG and recombinant FSH.

TABLE 2

Number of IVF cycles.

No. of cycles	No. of oocyte retrievals (%)	Clinical pregnancy rate (%)
hMG group		
1	98 (56.3)	35.7
2	41 (23.6)	36.6
3	21 (12.1)	28.6
4, 5, or 6	14 (8.0)	50.0
Recombinant FSH group		
1	65 (66.3)	49.2
2	24 (24.2)	50.0
3	9 (9.2)	55.6

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Because the study was a retrospective chart review no institutional review board approval was needed.

RESULTS

Data from 324 IVF cycles were analyzed for the 15 months of the study. Urinary-derived hMG was used in 212 cycles (65%) and recombinant FSH in 112 cycles (35%). There was no significant difference in the causes of infertility between the two groups (Table 1). Although 14 patients in the hMG group were undergoing at least their fourth IVF cycle, the pregnancy rate in this subgroup was higher than in

TABLE 3

Clinical variable.

Variable	hMG group (n = 212)	Recombinant FSH group (n = 112)	*P* value
Patient age (y)	35.1 ± 4.2	34.1 ± 4.0	.04
No. of ampoules of medication used	38.2 ± 20.6	33.0 ± 13.5	.02
Days of medication used	9.7 ± 2.0	9.9 ± 2.0	.35
Baseline E_2 level (pg/mL)	20.7 ± 15.1	21.7 ± 16.1	.56
E_2 level after 5 days of stimulation (pg/mL)	324.1 ± 267.5	297.3 ± 275.4	.4
Peak E_2 level (pg/mL)	1691 ± 959	1653 ± 919	.74
Cancellation rate (%)	17.9	12.5	.27
No. of oocytes retrieved	12.3 ± 6.9	13.1 ± 7.0	.35
Fertilization rate (%)	63 ± 21	59 ± 24	.18
No. of embryos transferred	3.6 ± 0.9	3.2 ± 1.1	.01
Clinical pregnancy rate per initiated cycle (%)	29.7	43.8	.01
Clinical pregnancy rate per oocyte retrieval (%)	36.2	50.0	.03
Implantation rate (%)	14	25	.001

Note: Values are mean (±SD) or percentages.

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hMG subgroups where the women had undergone fewer previous cycles (Table 2).

All women in the recombinant FSH group were undergoing their first to third IVF cycle. There was a 1-year difference in the age of patients in the two groups (35.1 in the hMG group vs. 34.1 in the recombinant FSH group; $P=.04$) (Table 3). The cycle cancellation rate was nonsignificantly higher in the hMG group than the FSH group (17.9% vs. 12.5%; $P=.27$). The groups were not significantly different in baseline, day 6, or peak E_2 levels.

The duration of gonadotropin stimulation did not differ between hMG recipients and FSH recipients (9.7 days vs. 9.9 days). However, significantly fewer ampoules of gonadotropin were required in the recombinant FSH group than in the hMG group (33.0 vs. 38.2; $P=.02$). The difference in the number of ampoules used was not due to the fact that 14 patients in the hMG group were undergoing at least their fourth IVF cycle; the significant difference persisted when these patients were eliminated.

The number of oocytes retrieved and fertilization rates with conventional fertilization and ICSI were similar between the two groups. The mean number of embryos transferred was significantly higher in the hMG group than in the recombinant FSH group (3.6 vs. 3.2; $P=.01$). There were 63 clinical pregnancies in the hMG group (36.2% per oocyte retrieval and 29.7% per cycle initiated) compared with 49 in the recombinant FSH group (50.0% per oocyte retrieval and 43.8% per cycle initiated). These differences were statistically significant in favor of recombinant FSH ($P=.03$ for pregnancies per oocyte retrieval and .01 for pregnancies per initiated cycle). Differences in implantation rates (14% in the hMG group vs. 25% in the recombinant FSH group) were also statistically significant in favor of recombinant FSH ($P=.001$) (Table 3).

Subanalyses revealed some differences when patients were stratified by age and by number of previous cycles. Among younger patients, the implantation rate differed significantly between the hMG and recombinant FSH groups, in favor of recombinant FSH (0.19 vs. 0.33; $P=.006$). When patients ≥35 years of age alone were considered, patients in the recombinant FSH group were younger (37.3 vs. 38.3 years; $P=.004$) and had a higher clinical pregnancy rate per initiated cycle (36.4% vs. 20.7%; $P=.04$) compared with those in the hMG group.

Among patients undergoing their first treatment cycle, the only significant difference between the treatment groups was for implantation rate (0.16 with hMG and 0.26 with recombinant FSH; $P=.02$). For patients undergoing their second or subsequent cycle, the groups differed significantly in mean age (35.8 years in the hMG group vs. 34.2 years in the recombinant FSH group; $P=.03$), implantation rate (0.12 and 0.23; $P=.02$), and total number of embryos transferred (3.86 vs. 3.27; $P=.008$).

TABLE 4

Cost analysis.

Variable	hMG	r-hFSH
Cycles	212	112
No. of canceled cycles (%)	38 (17.9)	14 (12.5)
Cost per canceled cycle ($)	2,540	3,000
Total cost of canceled cycles ($)	96,250	42,000
No. of completed cycles	174	98
Cost per completed cycle ($)	8,540	9,000
Total cost of completed cycles ($)	1,485,960	882,000
Total cost (all cycles) ($)	1,582,480	924,000
Clinical pregnancies (%)	63 (36.2)	49 (50.0)
Cost per clinical pregnancy ($)	23,591	18,000

Note: Clinical pregnancy rates are per oocyte retrieval.

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The cost of completed cycles was found to be approximately $9,000 when recombinant FSH was used and $8,540 when hMG was used; the costs of canceled cycles were approximately $3,000 and $2,540, respectively. Cost analysis (Table 4) indicated that recombinant FSH recipients had fewer canceled cycles and a higher pregnancy rate than did hMG recipients. As a result, the cost per pregnancy was lower in the recombinant FSH group than in the hMG group.

DISCUSSION

As conditions for embryo culture have improved, use of natural or clomiphene-induced cycles for IVF has been reevaluated. However, ovarian stimulation with gonadotropins remains the mainstay of treatment. The availability of recombinant FSH has elicited debate about its potential benefits over urinary gonadotropins.

In our retrospective study, use of recombinant FSH yielded superior implantation and pregnancy rates. However, there is a large price differential (ranging from 20% to 50% in the United States, reflecting differences in pharmacy pricing policies) between recombinant FSH and hMG. Thus, when recombinant FSH became available, patients were informed that although recombinant FSH could be administered subcutaneously and might have a slight benefit in terms of pregnancy rate, it was more expensive than hMG.

In our study, patients chose to receive hMG for 65% of cycles. They were not asked the specific reasons for their choice, but the main criterion appeared to be whether their insurance covered medication costs. In the absence of any clear advantage over hMG on pregnancy rates, most patients did not appear to consider that the benefits of recombinant FSH justify its higher prices.

Although our report is retrospective, no obvious selection bias could be identified that would have resulted in the recombinant FSH group having a significantly higher clinical pregnancy rate (50.0% vs. 36.2%) or, more important, a

significantly higher implantation rate (25% vs. 14%). The 1-year age difference between groups is unlikely to have caused these differences. Furthermore, any small influence that this difference may have had would probably have been more than offset by the larger number of embryos transferred in the hMG group.

Although meta-analysis of recombinant FSH versus urinary FSH suggests that recombinant FSH is more potent, in our experience, hMG and recombinant FSH were viewed as equipotent. Therefore, doses were determined independently of the type of preparation and were decided on even before the patient had selected which preparation to receive. In contrast, use of lower recombinant FSH doses in other studies suggests that not all investigators consider the two types of preparation to be equipotent. Out et al. (14) used lower doses of recombinant FSH than of urinary gonadotropin for ovarian stimulation and found no increase in pregnancy rates with recombinant FSH unless frozen embryo cycles were included in the analysis. In another comparative study with hMG, Jacob et al. (17) also used a lower dose of recombinant FSH and reported a lower pregnancy rate in the recombinant FSH group. The experiences of Out et al. and Jacob et al. suggest that the discrepancies in their results between the two types of product may have been related to the differential dosing of recombinant FSH and hMG.

Bergh et al. (18) reported a randomized study of 200 IVF patients who were treated with equivalent doses of urinary gonadotropin and recombinant FSH. The primary end point of this study was the number of oocytes retrieved. Although more oocytes were retrieved in the recombinant FSH group, the ongoing pregnancy rates in the two groups were similar. In reviewing our retrospective data, we found no factor other than the type of gonadotropin to explain our findings.

In the Cleveland, Ohio, market, one ampoule of urinary-derived hMG costs approximately two-thirds as much as one ampoule of recombinant FSH (approximately $40 vs. approximately $60). Taking the mean total amount of gonadotropin used into account, the mean price for medication for recombinant FSH cycles is approximately 30% higher than that of hMG cycles. However, drug selection based on price alone is an inadequate means of determining cost-effectiveness, which evaluates both costs and outcomes. In this study, the significantly higher clinical pregnancy and implantation rates with recombinant FSH seem to justify the higher price of recombinant FSH. With the increase in pregnancy rates and decrease in the number of dropped cycles in the recombinant FSH group (Table 4), the cost per clinical pregnancy is approximately 31% higher in the hMG group than in the recombinant FSH group ($23,591 vs. $18,000 per clinical pregnancy).

Several studies have examined the relative cost-effectiveness of recombinant FSH and u-FSH in ovarian stimulation for ART by using Markov modeling (19) combined with Monte Carlo simulation (20). The most comprehensive studies were perfomed by Daya et al. (21) for the healthcare system of the United Kingdom and Silverberg et al. (22) for that of the United States. Both studies found that because of the superior clinical efficacy of recombinant FSH (13), the cost per pregnancy was significantly lower with recombinant FSH than with urinary FSH, and significantly fewer cycles on average were required to achieve a pregnancy when the recombinant preparation was used. A recent modeling study in the United States (23) examined the effect of varying the price of urinary FSH relative to that of recombinant FSH. When urinary FSH prices ranging from 68% to 83% of the price of recombinant FSH were assumed, the cost per pregnancy was significantly lower with recombinant FSH in all cases. These modeling studies thus strongly suggest that recombinant FSH is more cost-effective than urinary gonadotropins in terms of cost per pregnancy achieved.

Our results support the superior efficacy of recombinant FSH over urinary-derived hMG. Significantly higher ongoing pregnancy and implantation rates were obtained with recombinant FSH, and fewer ampoules were required. However, our results are not entirely in accordance with those of other studies. A well-controlled, randomized prospective study is needed to confirm the improved efficacy of recombinant FSH over hMG.

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