ORIGINAL ARTICLE

A Retrospective Review Comparing the Use of Gonal-F and Metrodin-HP for In-Vitro Fertilisation (IVF)

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Summary

All cycles of IVF with pituitary down-regulation (n=57) done at the Damansara Fertility Centre in the year 2000 were studied. All the 57 patients had controlled ovarian hyperstimulation, either using Metrodin HP (n=27) or Gonal-F (n=30). Of these, 53 patients reached oocyte pick-up, 26 patients in Metrodin HP group and 27 patients in Gonal-F group. Gonal-F resulted in a higher clinical pregnancy rate of 66.6% compared to Metrodin HP 38.5% ($p<0.05$). The live birth rate tends to be higher in Gonal-F group (40.7%) compared to Metrodin HP (30.8%), ($p>0.05$).

Key Words: In-Vitro fertilization, Metrodin HP (uFSH-HP), Gonal-F (rFSH), Clinical pregnancy rate, Live birth rate

Introduction

In subfertile women undergoing therapy with assisted reproductive techniques (ART), such as in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), the use of gonadotrophins to achieve multifollicular development is now well established.

Until recently, the main source of exogenous follicle stimulating hormone (FSH) for therapeutic use had been the urine of postmenopausal women. Over the past four decades, FSH products have evolved from menotropin, also known as human menopausal gonadotrophin (which consists of FSH, luteinizing hormone (LH), human chorionic gonadotrophin (hCG) and urinary proteins), to urofollitropin (a purified FSH preparation of menotropin from which LH, but not the urinary proteins, has been removed), to urofollitropin highly purified (HP) (i.e. urofollitropin from which most of the urinary proteins have been removed), to the recently developed follitropin produced in vitro by recombinant DNA technology using Chinese hamster ovary cells, transfected by both alpha and beta subunit genes. When compared with commercially available urinary gonadotrophin preparations, recombinant FSH (rFSH) is very pure (99.9%), has no intrinsic LH activity and has very high specific bioactivity for FSH (>10,000 IU/mg protein). This purity and its batch-to-batch consistency make rFSH an attractive alternative to urinary FSH (uFSH)[1].

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The biological characteristics of rFSH are indistinguishable from those of natural FSH preparations, including commercial and international reference preparations. There are two licensed preparations of rFSH with proven clinical effectiveness now available for ovarian stimulation: follitropin alpha (known commercially as Gonal F from Ares-Serono, Geneva, Switzerland) and follitropin beta (known commercially as Puregon or Follistim from NV Organon, Oss, The Netherlands).

The purpose of this study is to compare the efficacy of Gonal-F and Metrodin HP, when used for controlled ovarian hyperstimulation in IVF.

Materials and Methods

This is a retrospective review, which compares Gonal-F (recombinant FSH) and Metrodin HP (highly purified urinary FSH), used for controlled ovarian hyperstimulation in patients undergoing in-vitro fertilization (IVF) treatment for the year 2000, at the Damansara Fertility Centre, Damansara Utama, Petaling Jaya.

The main outcome measures were number of days of stimulation to oocyte retrieval, number of oocytes retrieved, number of transferable embryos, total number of ampoules of FSH used, clinical pregnancy and take-home baby rates.

Clinical pregnancy was identified by the presence of a gestational sac on ultrasonography or pathologic confirmation of trophoblast tissue in the event of a spontaneous miscarriage or ectopic pregnancy. Biochemical pregnancies (i.e. those with only serologic confirmation) were not included in the analysis.

All women received gonadotrophin releasing hormone agonist (Buserelin), in the long luteal protocol (flare down). Twenty-seven women received Metrodin HP and 30 women received Gonal-F. Human chorionic gonadotropin (hCG, 10,000 IU) was administered when appropriate. The numbers of embryos transferred were in accordance to the American Society for Reproductive Medicine 1999[2]. Luteal phase support was provided as appropriate.

One ampoule of Metrodin HP and one ampoule of Gonal-F contain 75 IU (uFSH) and 75 IU (rFSH) respectively.

Variables were recorded in the EPI INFO Version 604-program and univariate analyses were performed where appropriate.

Results

During the study period a total of 57 down-regulated IVF cycles were carried out, 53-reached oocyte pick-up (OPU) and embryo transfer. There were 4 cases cancelled due to poor response (one in Metrodin HP group and 3 in Gonal-F group). Of the 53 patients, 26 received Metrodin HP and 27 received Gonal-F for controlled ovarian hyperstimulation.

Table I

Gonadotrophins	Number of Cycles Started	Number of Cycles Reached OPU	Number of Cycles Reached Embryo Transfer
Metrodin HP	27	26	26
Gonal-F	30	27	27

*Patients who had 2 cycles or more are considered as 2 patients or so respectively.

Table II

Variables	Range	Metrodin HP (n=26)	Gonal-F (n=27)	Significance (p<0.05)
Age	28 to 46	35.2 ± 4.3	36.6 ± 3.5	NS
Years of Marriage	1 to 17	6.0 ± 3.2	7.1 ± 3.6	NS
Years of Trying to Conceive	1 to 16	4.2 ± 2.6	4.7 ± 3.4	NS
Day of Stimulation to OPU	10 to 17	13.3 ± 1.3	13.2 ± 1.5	NS
Interval of hCG to OPU (hours)	36.4 to 38.6	37.5 ± 0.3	37.4 ± 0.3	NS
Number of Oocytes Retrieved	4 to 35	14.2 ± 6.8	13.2 ± 6.9	NS
Number of Embryos Transferred	1 to 6	3.4 ± 1.1	3.7 ± 1.1	NS
Total ampoules of Gonadotrophin Used	22 to 82	40.1 ± 11.3	43.3 ± 18.2	NS

Table III

Drug	Clinical Pregnancy		Total (n=53)	Percentage	Significance (OR, 95% CI) p<0.05
	Yes	No			
Metrodin HP	10	16	26	38.5%	1.73 (1.0<OR<3.02)
Gonal-F	18	9	27	66.6%	Significant

Table IV

Drug	Live Birth		Total (n=53)	Percentage	Significance (OR, 95% CI) p<0.05
	Yes	No			
Metrodin HP	8	18	26	30.8%	1.55 (0.43<OR<5.61)
Gonal-F	11	16	27	40.7 %	NS

Table V shows the number of babies delivered

	Metrodin HP (n=26)	Gonal-F (n=27)
Singleton	6	6
Twins	1	5
Triplets	1	0
Total	11	16

As shown in Table II, there was no difference in the mean age of the two groups. The mean age for Metrodin HP and Gonal-F were 35.2 ± 4.3 years and 36.6 ± 3.5 years respectively.

There were also no differences in the other variables such as years of marriage, years of trying to conceive, days of stimulation to OPU, interval of hCG to OPU (hours), number of oocytes retrieved, number of embryos transferred and the total number of ampoules of Gonal-F or Metrodin HP used.

In Table III, there was a significant difference in clinical pregnancy rate between the two groups, with an OR of 1.73, 95% CI (1.0<OR<3.02).

Table IV shows a higher percentage of live birth in the Gonal-F group (40.7% vs 30.8%), but this did not reach statistical significance.

There were 4 cases of ovarian hyperstimulation syndrome, 3 in Metrodin HP group and 1 in Gonal-F group. There were 9 miscarriages, 2 in Metrodin HP and 7 in Gonal-F group. One ectopic pregnancy occurred in the Gonal-F group.

Discussion

Follicle stimulating hormone (FSH) has an essential role in follicular development, whereas luteinizing hormone (LH) plays a relatively minor role. In fact, too much LH during the periods of follicular development and peri-ovulation may have detrimental effects on reproductive outcome. Until recently, the main source of exogenous FSH was urine of postmenopausal women. Biotechnology has now provided recombinant FSH (rFSH).

The demographic variables such as the mean age, mean years of marriage and mean years of trying to conceive showed no significant difference, thus avoiding bias.

In this study, the number of oocytes retrieved was no different between the Metrodin HP and Gonal-F group (14.2 ± 6.8 vs 13.2 ± 6.9). In at least two other trials, the number of oocytes retrieved was significantly increased with rFSH, while the total dose of rFSH used was significantly lower than that of uFSH[3,4]. In the review of the Cochrane Database 2001[1], on the number of oocyctes retrieved, there are great deal of heterogeneity, in 3 trials the number of oocytes retrieved was significantly higher with rFSH, in 1 trial it was significantly higher with uFSH and in 9 trials there was no significant difference.

This study found no significant difference in number of oocytes retrieved or number of embryos transferred, but the higher clinical pregnancy could be due to improved oocyte quality (higher proportion of mature oocytes) with rFSH stimulation. The higher pregnancy rate with rFSH compared to uFSH, which was demonstrated in a recent meta-analysis[5], indicates that improved oocyte quality may result in not only a higher quantity, but also a higher quality, of embryos.

In the Cochrane Database 2001, the total dose of gonadotropin (uFSH vs rFSH), in 13 trials, the mean total dose of gonadotropin was 406 IU lower in the rFSH group. There was considerable heterogeneity in this variable, with 9 trials showing a significant reduction in total dose with rFSH and 4 trials showing no significant difference[1].

In this study, an average of 43.3 ampoules of Gonal-F was used compared to 40.1 ampoules of Metrodin HP, though the difference was not found to be statistically significant (p>0.05). Our study shows that there is a tendency to require more Gonal-F compared to Metrodin HP to achieve the same number of oocytes retrieved, though this tendency did not reach statistical significance (p>0.05)

In this study, there was a definite improvement in the clinical pregnancy rate in the Gonal-F (66.6%) compared to Metrodin HP (38.5%) with an OR 1.73, 95% CI (1.0<OR<3.02) and p<0.05. This

clinical pregnancy rate is comparable with the results of GIFT (42.5%) in our center presented in the Asian and Oceanic Congress Of Obstetrics and Gynaecology, 1998 [6]. Although the live birth rate was higher in the Gonal-F group compared to the Metrodin HP (40.7% vs 30.8%), it was not statistically significant.

The miscarriage rate is higher in the Gonal-F group (33.3%) as compared to the Metrodin-HP (20%). We cannot draw any conclusion, probably due to the limitations of this study, the small sample size and no randomisation and larger study is needed to evaluate this finding.

Conclusion

Gonal-F resulted in a higher clinical pregnancy rate of 66.6% compared to Metrodin HP 38.5% ($p<0.05$). The number of take-home babies per embryo transferred (number of babies take-home per OPU) tends to be higher in the Gonal-F group (59.3%) compared to Metrodin HP (42.3%), ($p>0.05$).

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