Evidence that exclusive use of Follistim® may produce better pregnancy results than the use of Gonal-F® following in vitro fertilization (IVF) - embryo transfer (ET)

M. Check, C. Wilson, J. H. Check, D. Kiefer, J. K. Choe

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)

Summary

Purpose: To evaluate whether the equal mixture of human menopausal gonadotropin (hMG) to recombinant (r) follicle stimulating hormone (FSH) for controlled ovarian hyperstimulation (COH) adversely affects outcome following in vitro fertilization (IVF). Furthermore, to determine if the specific rFSH preparation used has any differing effects on outcome.

Methods: Retrospective study of women using the luteal phase leuprolide acetate-gonadotropin COH regimen. Outcome measures included clinical and viable pregnancy rates (PRs) and implantation rates.

Results: The clinical and viable PRs and implantation rates were significantly lower in the group receiving exclusively Gonal-F. Addition of hMG to the treatment protocol not only did not lower the PRs further, but in fact seemed to obviate the adverse effect of Gonal-F.

Conclusion: Since exclusive use of Gonal-F did not adversely affect fertilization rates or quality of embryos we suspect its exclusive use in some way makes the uterine environment less receptive.

Key words: Recombinant FSH; Human menopausal gonadotropin; In vitro fertilization.

Introduction

By transfecting Chinese hamster cell lines with the human genes for follicle stimulating hormone (FSH) alpha and beta subunits, a highly pure (> 99%) FSH preparation with bioactivity identical to that of native pituitary FSH without luteinizing hormone (LH) bioactivity has been developed [1, 2]. There have been several studies suggesting that recombinant (r) FSH is more effective than urinary derived gonadotropins [3-5].

A meta-analysis by Daya *et al.* [6] of randomized trials of FSH vs human menopausal gonadotropin (hMG) used for controlled ovarian hyperstimulation (COH) with or without gonadotropin releasing hormone agonists (GnRHa) [7-10] concluded that in IVF cycles, the exclusive use of FSH is associated with a significantly higher clinical pregnancy rate (PR) than hMG [6]. A randomized controlled trial by Daya *et al.* [11] found a significantly higher fertilization rate with FSH vs hMG; however, though there was a trend for higher PRs with FSH, there was not a significant difference. Another study by Jansen *et al.*, also found higher PRs and implantation rates with rFSH vs hMG [12]. Thus, whether the adjunct of LH is necessary, somewhat beneficial, or detrimental has been an ongoing matter of debate [13].

Studies evaluating comparisons of FSH stimulation versus mixtures of FSH and preparations with some LH content have been hard to find. One study by Mercan *et al.* [14] found that the use of FSH alone produced better quality oocytes than FSH/hMG combined. Another study comparing rFSH to rFSH and 75 IU or rLH found a trend for higher clinical PR per transfer with rFSH alone (68.8% vs 45.5%) [15]. Recently another study, in contrast to previous ones favoring all FSH stimulation, found no difference in PRs with IVF whether stimulation was with rFSH or hMG [16].

A study by Check *et al.* did not find any difference in PRs with 300 IU rFSH vs 150 rFSH mixed with 150 hMG [17]. Interestingly unexpectedly, the PRs were even higher with mixed gonadotropins in women whose mean serum LH during the early follicular phase was greater than the median of 4mIU/ml [17].

The study presented here re-evaluated another series of patients stimulated with rFSH vs rFSH and hMg but in this study evaluation of the brand of rFSH was also made.

Materials and Methods

A retrospective study was conducted where the luteal phase leuprolide-gonadotropin regimen was used. The results were evaluated separately for women age ≤ 39. The data was evaluated according to whether the female partner used hMG with Follistim (group 1, 138 transfers) hMG with Gonal-F (group 2, 113 transfers), Follistim only (group 3, 25 transfers) or Gonal-F only (group 4, 60 transfers). The choice of medication was usually based on economics; if insurance covered the cost, all rFSH was given, and if not, a mixture of hMG/FSH was given to save money. In all instances a total of 300 IU daily of gonadotropin was initiated in two divided doses (ISO IU per injection).

Results

The mean age (34.1, 34.3, 34.4, and 34.3) fertilization rate (65.1%, 66.5%, 63.4%, and 64.0%) and mean number of embryos transferred (3.1, 3.2, 3.1, and 3.2) were similar. The clinical PRs per transfer were similar in

Revised manuscript accepted for publication May 6, 2002

groups 1-3 (47.8%, 43.4%, 44.0%) but lower in group 4 with all Gonal-F (36.7%). The viable PR per transfer (live fetus at end of first trimester) was similar in groups 1 and 3 (44.2%, 44.0%), showed a trend to be lower in group 2 with use of Gonal-F and hMG (38.1%), and was significantly lower in group 4 (31.7%) which received all Gonal-F ($p < .05$). Implantation rates were similar in groups 1-3 (23.7%, 23.4%, 21.8%) but lower in group 4 (18.2%) ($p < .05$). Embryo morphology of transferred embryos was similar in all four groups.

Discussion

A study by Horsman *et al.* compared biological, immunological and physico-chemical clinical batches of the rFSH preparations Gonal-F and Puregon (Follistim) [18]. The study found that Gonal-F and Follistim were similar in terms of immunopotency, in vitro biopotency and internal carbohydrate complexity. However they differed slightly in charge heterogeneity with Gonal-F having slightly more acidic glycoforms [18]. The authors concluded that these two recombinant hormone preparations are intrinsically very similar, and they would not expect any difference in clinical efficacy on the basis of their respective structures [18].

However, despite the prediction of equal efficacy, the results of the present study suggested that the exclusive use of Gonal-F resulted in lower PRs and implantation rates than Follistim. Addition of hMG to the Gonal-F COH protocol seemed to obviate the disadvantage of using Gonal-F alone.

These results also showed that mixing the COH regimen with 50% hMG does not decrease PRs or implantation rates. This is important to know since hMG is less expensive than rFSH and thus the patient could at least reduce the cost somewhat by using a mixed protocol.

The conclusions of the current study – that use of Gonal-F for COH results in lower PRs and implantation rates – are not consistent with the study by Harlin *et al.* who found similar PRs with the two preparations [19]. Similar to our study, Harlin *et al.* found no differences in fertilization rates nor did they find any differences in serum estradiol, endometrial thickness, follicle number, or number of retrieved oocytes [19].

The data presented here suggest that the exclusive use of Gonal-F vs Follistim for COH using a luteal phase leuprolide acetate protocol lowers rather than increases the PRs and implantation rates. This effect seems to be on the uterine environment since fertilization rates were comparable as was morphology.

References

[1] Olive W., De Boer W., Mulders J. W. M. *et al.*: "Molecular biology and biochemistry of human recombinant follicle stimulating hormone (Puregon)". *Mol. Hum. Reprod.*, 1996, *5*, 371.

[2] Shoham Z., Insler V.: "Recombinant technique and gonadotropin production: new era in reproductive medicine". *Fertil. Steril.*, 1996, *66*, 187.

[3] Out H. J., Mannaerts B. M. J. L., Driessen S. G. A. J., *et al.*: "A prospective, randomised, assessor-blind, multicenter study comparing recombinant and urinary follicle-stimulating hormone (Puregon vs Metrodin) in in-vitro fertilization". *Hum. Reprod.*, 1995, *10*, 2534.

[4] Aboulghar M. A., Mansour R. T., Serour G. I. *et al.*: "Recombinant follicle stimulating hormone in the treatment of patients with history of severe ovarian hyperstimulation syndrome". *Fertil. Steril.*, 1996, *66*, 757.

[5] Bergh C., Howles C. M., Borg K. et al.: "Recombinant human follicle stimulating hormone (r-h FSH; Gonal-F) versus highly purified urinary FSH (Metrodin HP): results of a randomized comparative study in women undergong assisted reproductive techniques". Hum. Reprod., 1997, *12*, 2133.

[6] Daya S., Gunby J., Huges E. G., Collins J. A., Sagle M. S.: "Follicle-stimulating hormone versus human menopausal gonadotropin for in vitro fertilization cycles: a meta-analysis". *Fertil. Steril.*, 1995, *64*, 347.

[7] Check J. H., O'Shaughnessy A., Nazari A., Hoover L.: "Comparison of efficacy of high-dose pure follicle-stimulating hormone versus human menopausal gonadotropins for in vitro fertilization". *Gynecol. Obstet. Invest.*, 1995, *40*, 117.

[8] Edelstein M. C., Brzyski R. G., Jones G. S., Simonetti S., Muasher S. J.: "Equivalency of human menopausal gonadotropin and follicle-stimulating hormone stimulation after gonadotropin-releasing hormone agonist suppression". *Fertil. Steril.*, 1990, *53*, 103.

[9] Lavy G., Pellicer A., Diamond M. P., DeCherney A.: "Ovarian stimulation for in vitro fertilization and embryo transfer, human menopausal gonadotropin versus pure human follicle stimulating hormone: a randomized prospective study". *Fertil. Steril.*, 1988, *50*, 74.

[10] Scoccia B., Blumenthal P., Wagner C.: "Comparison of urinary human follicle-stimulating hormone and human menopausal gonadotropins for ovarian stimulation in an in vitro fertilization program". *Fertil. Steril.*, 1987, *48*, 446.

[11] Daya S., Gumby J., Hughes G., Collins J. A., Sagle M. A.: "Randomized controlled trial of follicle stimulating hormone versus human menopuasal gonadotrophin in in-vitro fertilization". *Hum. Reprod.*, 1995, *10*, 1392.

[12] Jansen C., Van Os H. C., Out H. J.: "A prospective randomised clinical trial comparing recombinant follicle stimulating hormone (Puregon) and human menopausal gonadotropins (Humegon) in non-down regulated in vitro fertilization patients". *Hum. Reprod.*, 1998, *13*, 2995.

[13] Filicori M.: "The role of luteinizing hormone in folliculogenesis and ovulation induction". *Fertil. Steril.*, 1999, *71*, 405.

[14] Mercan R., Mayer J. F., Walker D., Jones S., Oehninger S., Toner J. P. *et al.*: "Improved oocyte quality is obtained with follicle stimulating hormone alone than with follicle stimulating hormone/human menopausal gonadotropin combination". *Hum. Reprod.*, 1997, *12*, 1886.

[15] Sills E. S., Levy D. P., Moumjy M., McGee M., Rosenwaks Z.: "A prospective, randomized comparison of ovulation induction using highly purified follicle-stimulating hormone alone and with recombinant human luteinizing hormone in in-vitro fertilization". *Hum. Reprod.*, 1999, *14*, 2230.

[16] Strehler E., Abt M., El-Danasouri I., DeSanto M., Sterzik K.: "Impact of recombinant follicle-stimulating hormone and human menopausal gonadotropins on in vitro fertilization outcome". *Fertil. Steril.*, 2001, *75*, 332.

[17] Check J. H., Check M. L., Nazari P., Davies E., Choe J. K.: "Presence of LH in gonadotropins associated with higher IVF pregnancy rates when basal serum LH is increased". *Clin. Exp. Obst. Gyn.*, 2001, *28*, 102.

[18] Horsman G., Talbot J. A., McLughlin J. D., Lambert A., Robertson W. R.: "A biological, immunological and physico-chemical comparizon of the current clinical batches of the recombinant FSH preparations Gonal-F and Puregon". *Hum. Reprod.*, 2000, *15*, 1898.

[19] Harlin J., Csemiczky G., Wramsby H., Fried G.: "Recombinant follicle stimulating hormone in in-vitro fertilization treatment-clinical experience with follitropin alpha and follitropin beta". *Hum. Reprod.*, 2000, *15*, 239.

Address reprint requests to:
J. H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)