



IBSA

ESHRE 2007

23rd Annual Meeting of the European Society
of Human Reproduction and Embryology

Lyon, France, July 1-4, 2007

IBSA Satellite Symposium

**Recent clinical evidences
for selecting human FSH
or recombinant FSH in ART**

Tuesday, July 3, 2007

Lyon Convention Centre, Amphitheatre

ABSTRACTS

Recent clinical evidences for selecting human FSH or recombinant FSH in ART

Chairmen:

P.G. Crosignani (Italy) / J. Cohen (France)

1

**An abundance of gonadotrophins:
an overview of human and recombinant gonadotrophins**

J. Collins (Canada)

2

**Effectiveness and tolerability of hFSH compared to rFSH in ICSI:
the European study**

J.G. Grudzinskas (UK)

3

**Clinical efficacy of hFSH versus rFSH for IVF:
confirmatory results from the USA randomised trial**

V. Baker (USA)

An abundance of gonadotrophins: an overview of human and recombinant gonadotrophins

Prof John Collins, MD^{1,2}

¹*Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, and*

²*Department of Obstetrics and Gynecology, Dalhousie University, Halifax, Nova Scotia, Canada*

Although research on gonadotrophins began in the 1930s, applications in humans came later. By 1966, the G Club was discussing the mechanisms, benefits and risks of gonadotrophins extracted either from human pituitary tissues or from menopausal urine. In 2007, both human and recombinant products are available for use in ovulation induction and ovarian stimulation. In all areas of gonadotrophin research a key element has been the focus on improving quality and ease of use without compromising effectiveness. An overview of the effectiveness and safety of gonadotrophins is relevant to the clinical practice of reproductive medicine.

Human gonadotrophin products are extracted from menopausal urine and generally contain 75 IU of follicle stimulating hormone (FSH). For each 75 IU of FSH the luteinizing hormone (LH) content varies from <1 IU (urofollitrophin) to 75 IU (hMG). Highly purified formerly referred to a reduction in the LH content, but now refers to a manufacturing process that excludes extraneous proteins and potential risks while maximising the concentration of FSH. In a correspondingly extensive extraction and purifying process, recombinant gonadotrophins (follitrophins alpha and beta) are extracted from Chinese hamster ovarian cells.

Numerous trials have compared the effectiveness of human and recombinant gonadotrophins in ovarian stimulation for IVF/ICSI cycles. The most inclusive meta-analysis of twenty trials reported no significant difference in pregnancy rate per started cycle human and recombinant gonadotrophins (Al-Inany, Aboulghar *et al.*, 2003) in long agonist cycles. Other systematic reviews agree or report small differences in either direction but the nuances would not be important in clinical practice. Adding three studies published since the 20-study meta-analysis (Andersen, Devroey *et al.*, 2006; Balasch, Penarrubia *et al.*, 2003; Kilani, Dakkak *et al.*, 2003) makes the overall rate difference: 0.3% (95% CI 2.6 - 3.2). The difference is so small that the direction hardly matters. In a categorical analysis there was a significant difference among human gonadotrophin types compared with recombinant FSH, but none of the differences between human and recombinant gonadotrophins were significant. It is worth noting that the majority of the large studies were efficacy trials which may not be as relevant to clinical practice as effectiveness or pragmatic trials.

The most important safety issue with use of gonadotrophins stems not from the products themselves but from their clinical application, and that is the generation of multiple follicles, and multiple births. The only practical means of addressing multiple birth is to reduce the number of embryos transferred. In the shadow of this dominating adverse effect which is common to all gonadotrophins, and given the industry-wide focus on safe manufacturing processes, any other hypothesized differences in safety among the products are of little importance.

The availability of many effective and safe gonadotrophin products means that there is room for flexibility in prescribing according to a given patient's needs and preferences.

References

1.

Al-Inany H., Aboulghar M., Mansour R., and Serour G. Meta-analysis of recombinant versus urinary-derived FSH: an update. *Hum Reprod* 2003; 18: 305-313.

2.

Andersen A.N., Devroey P., and Arce J.C. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. *Hum Reprod* 2006; 21: 3217-3227.

3.

Balasz J., Penarrubia J., Fabregues F., Vidal E., Casamitjana R., Manau D., Carmona F., Creus M., and Vanrell J.A. Ovarian responses to recombinant FSH or hMG in normogonadotrophic women following pituitary desensitization by a depot GnRH agonist for assisted reproduction. *Reprod Biomed Online* 2003; 7: 35-42.

4.

Kilani Z., Dakkak A., Ghunaim S., Cognigni G.E., Tabarelli C., Parmegiani L., and Filicori M. A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing ICSI: ovarian response and clinical outcomes. *Hum Reprod* 2003; 18: 1194-1199.

Effectiveness and tolerability of hFSH compared to rFSH in ICSI: the European study

Antoine J.M.¹, De Mouzon J.², Nicollet B.³, Salle B.⁴, Urbancsek J.⁵, Grudzinskas J.G.⁶

¹*Service Gynécologie Obstétrique, Hôpital Tenon (AP-HP), Paris, France,* ²*INSERM U569 – Le Kremlin-Bicêtre, France,* ³*Clinique du Val de l'Ouest, Ecully-Lyon, France,* ⁴*Service Gynécologie-Obstétrique, Hôpital Edouard Herriot, Lyon, France,* ⁵*Semmelweis Medical School, First Department of Obstetrics and Gynaecology, Budapest, Hungary,* ⁶*London Bridge Fertility, Gynaecology and Genetics Centre, One St Thomas' Street, London, UK.*

Objective

Since 1980 gonadotrophins have been used in assisted reproduction programs to induce multifollicular growth and in the past decade highly purified human follicle-stimulating hormones (hFSH) have been successfully adopted.

Since 1997, a new highly purified hFSH (Fostimon[®], IBSA) has been made available in some European countries. Since 2006, Fostimon has been approved in the European Union by means of a Mutual Recognition Procedure. In spite of their efficacy and clinically proven safety, recently recombinant FSH (rFSH) has been proposed as being safer and clinically more effective than hFSH. Our purpose here was the comparative evaluation of the clinical efficacy and the general tolerability of two different subcutaneous FSH preparations (hFSH vs rFSH) when administered to women undergoing ICSI.

Design

Multicentre (6 centres), investigator blind, prospective, randomised, controlled clinical trial. Two parallel groups, one receiving the test drug hFSH (Fostimon[®], IBSA) and the other the reference drug rFSH (follitrophin alpha).

Materials and Methods

One-hundred and fifty women aged 18-39 years with normal basal FSH (<10 IU) and Body Mass Index <30 kg/m² were selected for the study. After a standard, long down-regulation protocol using GnRH analogues, patients were randomised to receive either Fostimon or rFSH at the initial dosage of 225 IU for 5 days. The dose was subsequently adjusted according to the ovarian response. Both drugs were administered by the subcutaneous route. The primary endpoint was the total number of oocytes retrieved. The secondary endpoints included the total dose of FSH (IU), the number of days

of FSH stimulation and the duration of stimulation, the cancellation rate, the serum oestradiol concentration on the day of hCG injection, the number of follicles >14 mm on the day of hCG trigger injection. In addition, the oocyte quality was assessed in relation to the number of mature oocytes (grade III-metaphase II), oocytes injected, fertilisation rate (Day 1), cleavage rate and blastocyst rate.

Safety was evaluated with respect to adverse events occurring during the study (time of onset, severity, duration and action/treatment required), the assessment of the local tolerability at the injection site and the incidence of OHSS risk.

Results

The total number of oocytes retrieved (10.9 ± 4.9 oocytes after hFSH vs 11.9 ± 5.7 oocytes after rFSH, $p=0.25$) was not statistically significantly different. The total dose of FSH (2526 ± 802 IU [hFSH] vs 2349 ± 779 IU [rFSH], $p=0.18$), the number of embryos transferred (2.60 ± 0.81 vs 2.69 ± 0.93 , $p=0.54$) and frozen embryos derived (2.5 ± 3.4 vs 1.7 ± 2.6 , $p=0.11$), the implantation rate (14.8% vs 18.3%, $p=0.38$) and the clinical pregnancy rate per initiated cycle (30.1% vs 30.6%, $p=0.96$), as well as all after hFSH and three women after rFSH and only one patient had a moderate OHSS in the rFSH group. However this difference was not statistically significant. There were no differences seen in relation to clinical safety.

Conclusions

We have shown that there are no apparent differences seen in the primary (no. of oocytes) and secondary end points between women who received hFSH in comparison to rFSH whilst undergoing ICSI. We conclude that other considerations, in particular cost, should be made when choosing between the two FSH preparations.

Clinical efficacy of hFSH versus rFSH for IVF: confirmatory results from the USA randomised trial

Baker V.L., MD^{1,2}, Fujimoto V.Y., MD³, Kettel L.M., MD⁴, Adamson G.D.², Jones C.E., PhD⁵ and Soules M.R., MD⁶.

¹*Obstetrics and Gynecology, Stanford University Medical Center, Stanford, CA, 94305*, ²*Fertility Physicians of Northern California, San José, CA, 95124*, ³*Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, 94115*, ⁴*San Diego Fertility Center, San Diego, CA 92130*, ⁵*Consultant, Huntington Beach, CA, 92646* and ⁶*Seattle Reproductive Medicine, Seattle, WA, 98109*.

Objective

To compare the clinical efficacy of two subcutaneous FSH preparations - human FSH (Fostimon[®], IBSA) versus recombinant FSH (follitrophin alpha) - in volunteers undergoing controlled ovarian stimulation for in vitro fertilisation.

Design

Prospective, investigator-blinded, randomised, controlled clinical trial conducted concurrently at four IVF centres in the United States.

Materials and Methods

Inclusion criteria were: female age 18-39, BMI 18-30 kg/m², basal FSH <10 IU/L and oestradiol <80, >10 antral follicles (2-10 mm), normal uterine cavity and fewer than 3 prior oocyte retrievals. Volunteers were randomised to human FSH (n=76) or to recombinant FSH (n=76) at a starting dose of 300 IU in down-regulated cycles. The gonadotrophin dose could be increased or decreased after a minimum of two days of stimulation. Inferential statistics included intergroup comparisons of all study variables.

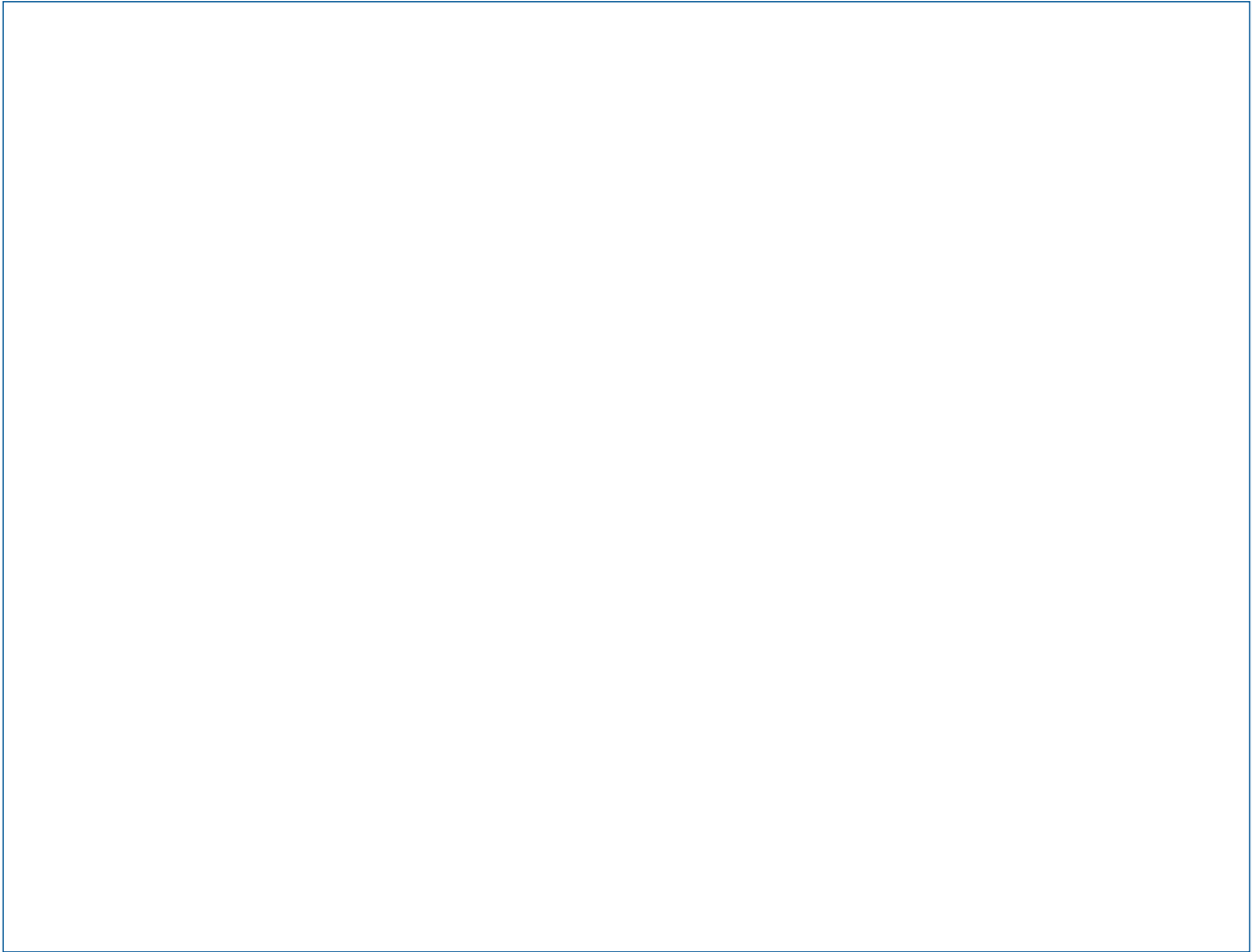
Results

There were no intergroup differences in any pre-treatment variables. The total IU of gonadotrophin used did not differ between the two groups (2641 ± 841 for hFSH versus 2715 ± 905 for rFSH). There was no difference in number of oocytes retrieved with hFSH (mean 16.3, range 0 – 47, CI 14.2 – 18.4) compared with rFSH (mean 17.1, range 0 - 54, CI 15.0 – 19.3), Confidence Interval of difference -3.79 to +2.18. Clinical pregnancy rate, as defined by the presence of a gestational sac, was 48.7% (CI 37.0% - 60.4%) with hFSH versus 44.7% (CI 33.3% - 56.6%) with rFSH (CI of difference -11.9% to +19.8%). Live birth rate was 38.2% (29/76) in both groups (CI 27.2% - 50.0%), for a difference between groups of 0.0% (Confidence Interval -15.4% to +15.4%). A higher percentage of volunteers randomised to human FSH complained of abdominal distension and/or discomfort in this single-blinded study, but there were no differences in any objective measures of hyperstimulation and no volunteers required medical intervention for hyperstimulation.

Conclusions

In this study of good prognosis patients at a fixed starting dose of gonadotrophin, there were no statistically significant differences in mean oocyte number, clinical pregnancy rate, or live birth rate between human versus recombinant FSH.

NOTES

A large, empty rectangular box with a thin blue border, intended for taking notes. It occupies the majority of the page below the 'NOTES' header.

IBSA Institut Biochimique SA
Via del Piano, P.O. Box 266, 6915 Lugano, Switzerland
Telephone +41 58 360 10 00, Fax +41 58 360 16 47
www.ibsa-international.com - info@ibsa.ch



Institut Biochimique SA

