

# Ovarian stimulation using a new highly purified urinary FSH: a prospective randomized clinical study

S. Gerli<sup>1</sup>, M. Perino<sup>2</sup>, A. Abate<sup>2</sup>, L. Costabile<sup>3</sup>, H. Gholami<sup>3</sup>, L. Vitiello<sup>3</sup>

<sup>1</sup>Gynecological and Obstetric Institute, University of Perugia; <sup>2</sup>Physiopathology of Human Reproduction Dept., "Papardo" Hospital, Messina;

<sup>3</sup>Association for Infertility Studies, Rome (Italy)

## Summary

The aim of this study was to determine the effectiveness of a new highly purified urinary FSH.

A total of 60 in vitro-fertilization (IVF) patients, undergoing embryo transfer (ET) for the first time, were randomly allocated into two groups:

**Group A (n=30).** Subcutaneous administration of urinary follicle-stimulating hormone (FSH, Fostimon 75, A.M.S.A., Italy).

**Group B (n=30).** Subcutaneous administration of urinary follicle-stimulating hormone (FSH, Metrodin 75 HP, Serono, Italy).

Statistical analysis was performed using the chi-square test,  $p < 0.05$  was assumed as significant. This prospective randomized clinical study in an IVF-ET program showed that both drugs were equally safe and effective. Except for the number of the high quality embryos (3.16 vs 2.9;  $p = 0.03$ ) the two groups did not differ in stimulation parameters or clinical pregnancy rates per attempt and per transfer. On the other hand, a mean number of 3.56 vs 2.18 embryos were cryopreserved in group A and in group B, respectively, as a result of the high number of mature oocytes and high quality embryos. When frozen embryo cycles were included, the difference in pregnancy rate became significant.

**Key words:** FSH; Effectiveness; Fostimon; Metrodin HP.

## Introduction

Ovarian induction is one of the most important phases of assisted reproductive techniques: in fact, it is through ovarian stimulation that we can induce multiple follicular growth in order to recover many mature oocytes [1]. A high number of oocytes corresponds to a high number of embryos allowing the transfer and the cryopreservation of the supernumerary. By obtaining a high number of transferable embryos we have a great opportunity to choose the best embryos, which is, without doubt, associated with a higher pregnancy rate [1].

Since 1980 gonadotrophins have been used in assisted reproduction programs to induce multifollicular growth [2].

Urinary FSH is the most known and used gonadotrophin by medical class to induce ovulation [3-4].

A new urinary FSH, highly purified, is characterized by a very low content of urinary protein contaminants and by a high specific activity that has been recently obtained through a chromatographic procedure.

The aim of this study was to determine the effectiveness of this new form of urinary FSH.

The indication for an assisted reproductive technique was the tubal factor.

## Controlled ovarian hyperstimulation

Before follicular stimulation each female patient was given a gonadotrophin-release hormone agonist Triptorelina (Decalel-tal: 3.75 mg ampoules, IPSEN, Italy) on the 21<sup>st</sup> day of the previous cycle.

The start of menses was designated as day 1 of the treatment cycle: stimulation began on day 3 with the administration of 3 ampoules,

**Group A (n=30),** s.c. administration of urinary follicle-stimulating hormone (FSH, Fostimon 75, A.M.S.A., Italy).

**Group B (n=30),** s.c. administration of urinary follicle-stimulating hormone (FSH, Metrodin 75 HP, Serono, Italy) and continued on subsequent days until the leading follicle reached a diameter of 17-19 mm (the mean number of FSH ampoules used was 28 in Group A and 30 in Group B).

Cycle monitoring was performed by vaginal ultrasound and beginning on day 7 of the treatment, oestradiol and progesterone blood concentration were determined.

Ovulation was induced with 10,000 I.U. of human chorionic gonadotrophin (HCG, Gonasi HP, A.M.S.A., Italy), and oocytes were aspirated 34-36 h after HCG administration by a transvaginal ultrasound procedure.

## In vitro procedures

Oocytes were retrieved 34-36 h after HCG administration under vaginal ultrasound control (day 0). IVF medium (Medi-Cult a/s, Innogenetics, Denmark) was used for culturing. Spermatozoa for insemination were prepared using the swim-up technique.

The embryo transfer was performed at the 2-to-4-cell stage, 40-44 h after insemination (day +2). A maximum of four embryos was placed.

## Materials and Methods

### Patients

A total of 60 in vitro-fertilization (IVF) patients (duration of infertility  $\geq 4$  years) undergoing ET for the first time, regular menstrual pattern, normal day-3 FSH levels, no sonographic signs of polycystic ovary disease and no male factor were randomly allocated to either treatment in this study.

Revised manuscript accepted for publication April 9, 1999

Table 1. — Results of subcutaneous administration of a new form of urinary FSH (Fostimon) versus urinary FSH (Metrodin HP) in IVF-ET cycles

	Group A	Group B	Significance
Total FSH dose (I.U.)	2100	2250	NS
Duration of FSH administration (days)	9.6	9.9	NS
LH concentration* (I.U./l)	1.75	1.96	NS
E <sub>2</sub> concentration* (pmol/l)	2131	1873	NS
Total number of oocytes retrieved	11.7	9.6	0.001
Number of 2-PN oocytes	8.8	7.7	NS
Fertilization rate (%)	75.6	72.9	NS
Cleavage rate (%)	86.5	87.8	NS
Embryos/transfer	3.2±1.1	3.1±1.3	NS
Embryos cryopreserved	3.56	2.18	0.05
Pregnancy rate/cycle (%)	32.5	31.6	NS
Pregnancy rate/cycle fresh ± cryo cycles	27.2	25.4	0.03

Group A: Fostimon; Group B: Metrodin HP; \*the day of HCG administration; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E<sub>2</sub>: oestradiol; 2-PN: two pro-nuclear oocytes; NS: non-significant.

Table 2. — Patient characteristics in the two study groups.

Patient characteristics	Group A	Group B	Significance
No. of patients	30	30	NS
Age	26±5	25±4	NS
Days of GN treatment	11.5±1.9	12.2±1.5	NS
FSH ampoules	25.6±5.3	26.2±6.2	NS

### Luteal phase

Starting the day before embryo transfer all patients received intramuscular administration of 50 mg progesterone (Progesterone; Prontogest, A.M.S.A., Italy). Treatment was continued until  $\beta$  hCG evaluation (day +14).

### Assays

17- $\beta$ -oestradiol (pmol/l) and LH (IU/l) serum levels were determined by radioimmunoassay (RIA).

### Statistical comparison

Statistical analysis was performed using the chi-square test,  $p < 0.05$  was assumed as significant.

## Results

Patient characteristics were identical for the two groups. The indications for the treatment were similar. There were no significant differences in the mean dosage of FSH (28 and 30 ampoules per cycle), in the duration of treatment (11.5±1.9 vs 12.2±1.5 days) and in the number of preovulatory follicles on the day of HCG administration.

The number of oocytes retrieved per transfer cycles (11.7 vs 9.6) was statistically significant. The number of 2-PN oocytes (8.8 and 7.7), regular fertilization rate (75.6% vs 72.9%) and cleavage rates (86.5% vs 87.8%)

were not statistically different between the two groups. The number of transferred embryos was also similar (3.2±1.1 vs 3.1±1.3). The number of high quality embryos (3.16 vs 2.9;  $p=0.03$ ) in the two groups did not differ in stimulation parameters or clinical pregnancy rates per attempt and per transfer. On the other hand, a mean number of 3.56 vs 2.18 embryos were cryopreserved in group A and in group B respectively. The pregnancy rate became statistically significant when frozen embryo cycles were included (27.2 vs 33.4 [ $p=0.03$ ]).

There was not any statistical difference in 17- $\beta$ -oestradiol and LH serum levels between the two groups.

## Discussion

The introduction of gonadotrophins into the field of reproductive medicine has constituted a milestone in treating subfertility. Gonadotrophins have been used for ovulation induction in anovulatory women and are indispensable for controlled ovarian hyperstimulation prior to assisted-reproduction treatment.

The aim of this study was to determine the effectiveness of a new form of urinary FSH, highly purified, and characterized by a very low content of urinary protein contaminants and by a high specific activity that has been recently obtained through a chromatographic procedure.

This prospective randomized clinical study in an IVF-ET program showed that both drugs were equally safe and effective. Except for the number of high quality embryos (3.16 vs 2.9;  $p=0.03$ ) the two groups did not differ in stimulation rates or clinical pregnancy rates per attempt and per transfer. On the other hand, a mean number of (3.56 vs 2.18) embryos were cryopreserved in group A and in group B, respectively, as a result of the high number of the mature oocytes and high quality embryos. When frozen embryo cycles were included the difference in pregnancy rate became significant.

## References

- [1] Vandervost M., Devroey P.: "Recombinant FSH: results in assisted reproduction". 2<sup>nd</sup> World Conference on ovulation induction, Bologna, 12-13 September, 1997.
- [2] Flamigni C., Venturoli S., Paradisi R.: "Induction of ovulation with human urinary FSH". 10<sup>th</sup> Congresso Mundial de fertilidad e estemidad, Madrid, 1980, abstract 358.
- [3] Bentick B., Shaw R. W., Iffland C. A., Burford G., Bernard A.: "A randomized comparative study of purified FSH and hMG after pituitary desensitization with buserelin for superovulation and IVF". *Fertil. Steril.*, 1988, 50, 89.
- [4] Tanbo T., Dale P., Haug E., Abyolm T., Kjeskshus E.: "Stimulation with human menopausal gonadotrophin versus follicle stimulating hormone after pituitary suppression polycystic ovarian syndrome". *Fertil. Steril.*, 1990, 53, 798.

Address reprint requests to:  
Dr. LOREDANA COSTABILE  
Via Nomentana, 531  
00141 Rome (Italy)