

Pure FSH (Metrodin) for ovarian stimulation in the IVF-ET programme

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Summary: Purpose: a comparative analysis of the clinical effectiveness of pure FSH (Metrodin) and conventional gonadotropin (Pergonal) for ovarian stimulation was performed.

Methods: each group consisted of 30 selected patients with tubal infertility, practically identical by average age, duration of infertility, age at menarche, weight and height and husband's semen analysis. The average number of vials of drug used for stimulation, number of oocytes retrieved and embryos transferred was the same for both groups of patients. The failure of oocyte retrieval and fertilization was higher in the Pergonal (16.8%) than in the Metrodin group (6.8%).

Results: in both groups there were 8 pregnancies - 4 in the Pergonal and 4 in Metrodin group. All pregnancies in the pure FSH group resulted in the delivery of a healthy baby, while in the Pergonal group there were two deliveries and two spontaneous abortions.

Author's conclusions: evaluating the data we can conclude that pure FSH stimulation provides respectively lower failure and spontaneous abortion rates than Pergonal stimulation, leading to a higher take home baby rate.

Key words: Ovarian stimulation; Pure FSH, IVF-ET programme.

INTRODUCTION

One of the main determining factors involved in the successful outcome of the assisted reproduction methods concerns ovulation induction. The different protocols and drugs have been used to determine the respective number of follicles and oocytes retrieved, the quality of fertilization and embryos. There have been times characterized by enthusiastic application of special treatment schedules, followed by other times of new combinations and new drugs used in various protocols.

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The initial use of clomiphene-citrate was later followed by combined gonadotropin treatment, applied at the same time or at different time intervals in various doses. The comparison of the results obtained from different ovulation induction protocols was unable to (or did not) reveal any significant differences in the number of live-born babies (^{1, 2, 3, 4}).

The introduction of GnRH analogues was characterized in initial studies as very successful (^{5, 6, 7, 8}), but later clinical experiences was unable to or (did not) confirm higher pregnancy rate: the only advantage was a lower spontaneous abortion rate (⁹).

Recently the tendency towards simplification was evident, introducing spontaneous cycles and pure FSH stimulating physiological growth and development of ovarian follicles (^{11, 12, 13}).

MATERIALS AND METHODS

In the comparative analysis we aimed at finding out the effects of the drugs Metrodin (Serono) and Pergonal (Serono) on the number of stimulated follicles, oocytes retrieved, embryos transferred, number of the vials used and number of pregnancies.

The inclusion criteria were the age between 18 and 37 years, regular menstrual period; tubal infertility and normal sperm count of the husband. Patients with elevated body weight, clinically evident disease and those having had more than one IVF procedure in the past were not included in the study.

Thirty patients conforming to the inclusion criteria were stimulated by Metrodin (1 amp contains 75 IU of pure FSH), 30 other patients chosen by the same criteria were treated with Pergonal (1 amp contains 75 IU of FSH and 75 IU of LH). The patients treated with Metrodin

represented the study group, those with Pergonal were in the reference group.

Ovarian stimulation was started on the second day of the menstrual cycle with a daily dose of 3 ampules of Metrodin or Pergonal for the following 3 or 4 days when the dose was reduced to 2 ampules until the criteria for human chorionic gonadotropin (HCG - Profasi 5,000 IU) application were fulfilled: the leading follicle of 17 mm or more in diameter and E2 concentration equal to or higher than 0.67 nmol/l. Normal values for mature follicle in preovulatory phase in our laboratory range from 0.67 to 1.01 nmol/l.

Vaginal ultrasound probe was used (Bruel & Kjaer) for folliculometry and oocyte retrieval. Oocytes were incubated for 2 to 4 hours and then inseminated with fresh, previously prepared husband's semen. Fertilization was checked after 48 hours, and at the same time embryo-transfer (ET) was performed on outpatient basis. Pregnancy was determined by blood testing for beta HCG 14 days after HCG administration.

Both groups of treated patients were included in the IVF-ET programme for tubal factor infertility. Clinical data are presented in Table 1.

The patients in the Metrodin group were all nulliparous, while in the Pergonal group 5 patients (17.2%) had had a delivery, but lost the child at childbirth or soon after it.

The average age of male patients of the Metrodin treated group was 35.50 ± 4.81 years; in the reference group it was 34.07 ± 2.61 years. The difference was not significant. The data on semen analysis are presented in Table 2.

RESULTS

Statistical analysis of the data for testing the significance of the differences

Table 1. - *Clinical data on 30 patients treated with Metrodin and 30 patients stimulated by Pergonal.*

| | Metrodin | Pergonal | Difference |
|---------------------------------|-------------------|-------------------|------------|
| Age at menarche (years) | 13.40 ± 0.71 | 13.90 ± 1.34 | NS |
| Age (years) | 32.43 ± 3.74 | 33.06 ± 3.07 | NS |
| Duration of infertility (years) | 8.00 ± 3.92 | 7.83 ± 3.55 | NS |
| Weight (kg) | 62.50 ± 8.98 | 64.03 ± 8.63 | NS |
| Height (cm) | 163.16 ± 5.77 | 163.46 ± 4.69 | NS |

Legend: NS = Statistically non-significant difference.

Table 2. - *Spermiograms of male patients of Metrodin and Pergonal stimulated group.*

| | Metrodin | Pergonal | Difference |
|-----------------------|---------------------|--------------------|-----------------------------|
| Volume (ml) | 2.54 ± 1.80 | 2.56 ± 0.85 | NS |
| Motility (%) | 42.50 ± 9.89 | 50.10 ± 7.72 | $t = 3.32$ S $p = 0.002$ |
| Number (10) | 268.13 ± 149.36 | 196.20 ± 34.78 | $t = 2.53$ S $p = 0.014$ |
| Normal morphology (%) | 61.76 ± 8.72 | 58.96 ± 4.35 | NS |

Legend: NS = Statistically non-significant difference

S = Statistically significant difference.

Table 3. – Number and size of follicles.

| | Metrodin | Pergonal |
|----------------------|------------|------------|
| Number of follicles: | | |
| right ovary | 3.56±2.12 | 3.36±1.27 |
| left ovary | 3.28±2.10 | 2.63±1.21 |
| Size of follicles: | | |
| right ovary | 17.13±2.55 | 17.36±1.03 |
| left ovary | 15.35±4.52 | 15.93±3.34 |

Table 4. – Average number of oocytes retrieved and embryos transferred.

| | Metrodin | Pergonal |
|-------------------------------|-----------|-----------|
| Number of oocytes | 5.30±4.01 | 5.00±3.37 |
| Number of oocytes fertilized | 2.73±2.03 | 2.96±2.05 |
| Number of embryos transferred | 2.46±1.73 | 2.63±1.82 |

between the mean values were performed by the Student's *t* test.

The comparison of the parameters indicating the efficiency of ovulation induction was performed between the average values of the study and of the reference group. The average number of stimulated follicles, oocytes retrieved and fertilized, and embryos transferred did not differ in either group of patients. The results are presented in Tables 3 and 4.

The average number of vials used for ovarian stimulation did not differ in the Metrodin (15.30±2.49) and Pergonal (16.62±2.56) treated group.

Mean E2 concentration at the time of HCG administration was the same for both groups of patients (3.45±1.87 nmol/l for Metrodin and 3.65±2.38 nmol/l for Pergonal treated patients).

The fertilization rate in the Metrodin group was 51.5%, and in the Pergonal group 59.2%. The data of failed stimulation for both groups of patients are presented in Table 5.

The comparison of follicular sizes of the left and right ovaries showed a sta-

tistically significant difference at the time of HCG administration, the right ovary follicles being 2 mm larger.

In both groups there were 8 pregnancies, 4 in the Metrodin and 4 in the Pergonal group. The data are presented in Table 6.

DISCUSSION

Analyzing the results of the comparative study we can summarize; that basic clinical parameters of women included were totally comparable (Table 1). The only significant difference registered was higher sperm motility (50.10%) in the reference (Pergonal) group, and higher total sperm count in the study (Metrodin) group (42.50%).

The average number of vials of the drug used, oocytes retrieved and fertilized, and embryos transferred was the same for both groups of patients. Also the size and number of follicles and E2 concentration at the time of HCG administration did not differ.

Analyzing the failure rate i.e. the number of cycles that did not result in an ET, it was higher in the Pergonal group, where ET was not performed in 5 pa-

Table 5. – Failed ovarian stimulation.

| | Metrodin | Pergonal |
|----------------------|----------|-----------|
| No oocytes retrieved | 1 (3.4%) | 1 (3.4%) |
| Unfertilized | 1 (3.4%) | 4 (13.4%) |
| | 2 (6.8%) | 5 (16.8%) |

Table 6. – Outcome of pregnancies in Metrodin and Pergonal treatment patients.

| | Metrodin | Pergonal |
|--------------------------|--------------|--------------|
| Number of pregnancies/ET | 4/28 (14.3%) | 4/25 (16.0%) |
| Number of deliveries/ET | 4/28 (14.3%) | 2/25 (8.0%) |
| Miscarriages | 0/28 | 2/25 (8.0%) |

tients (16.8%) while in the Metrodin group it was not performed in 2 patients (6.8%).

The outcome of pregnancies was superior in the study group, resulting in deliveries in all pregnant patients, while in the reference group there were two spontaneous abortions (8%) in the first trimester of pregnancy. Although the effectiveness of ovarian stimulation for both drugs evaluated with clinical and hormonal parameters was the same, the difference was obvious in end-effect of the IVF-ET procedure, that is in take home baby rate.

In the patients stimulated with Metrodin pregnancies ended in deliveries, while in the Pergonal group there were two spontaneous abortions (8% per stimulated cycle). The results of ovarian stimulation were similar in patients with polycystic ovaries (PCOD), showing significantly lower spontaneous abortion rate in the Metrodin stimulated patients (14.15%). The etiology of spontaneous abortions in PCOD patients might be premature luteinization of follicles, leading to the retrieval of oocytes capable of fertilization with impaired ability of implantation and development⁽¹⁶⁾. The administration of pure FSH in cases with endogenous elevated LH concentration may normalize ovarian response in PCOD patients⁽¹⁷⁾ as demonstrated by Raj *et al.*⁽¹⁸⁾. They registered lower incidence of ovarian hyperstimulation, lower multiple pregnancy rate and higher percentage of deliveries compared to the group of patients stimulated by conventional HMG. However, some authors could not confirm the difference in ovarian response comparing pure FSH and HMG^(19, 20).

Although our study included only the patients with tubal infertility, the clinical effect of ovarian stimulation follows the one registered in patients with PCOD. We did not register any differences either in quantity or in quality of ovarian re-

sponse, the only difference being the lower incidence of spontaneous abortions in FSH group.

The use of pure FSH for ovarian stimulation in the IVF-ET programme was based on the knowledge, that follicular growth depends on FSH and low concentrations of LH⁽²¹⁾. Using pure FSH, the possibility of premature LH elevation and premature follicular luteinization was diminished and consequently the conditions for better IVF-ET outcome were established.

In the patients with normal menstrual cycle and normal LH concentration it could be speculated that follicular growth would be normal, as well as oocytes retrieved and embryos transferred, followed by higher percentage of pregnancy rate and take home baby rate. One of the parameters supporting these statements was the result of the failed cycles. Ovarian stimulation in the HMG group was not successful in 16.8%, while in the pure FSH group only in 6.8% of patients the oocytes were not retrieved or fertilized. This bias would be of relevance in the case that the outcome of IVF procedure dependend only on the type of ovarian stimulation. Final result of the IVF-ET programme involves also the endometrial stage and respectively, laboratory conditions, semen quantity and quality, psychological factors, age and several other conditions.

CONCLUSION

The only direct conclusion resulting from the comparison of pure FSH and HMG ovarian stimulation was the lower spontaneous abortion rate, indirectly leading to a higher delivery rate.

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