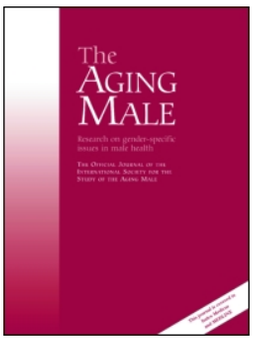

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ORIGINAL ARTICLE

FSH therapy for idiopathic male infertility: four schemes are better than one

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ABSTRACT

Objective: The aim of this article is to propose an algorithm that aids the clinician to choose the best therapeutic scheme of follicle-stimulating hormone (FSH) in the treatment of men with idiopathic infertility, based on testicular volume (TV) and serum total testosterone concentrations; highlighting the potential role of additional therapy with hCG in a sequential temporal scheme.

Materials and methods: We subdivided patients in four clinical groups: patients with normal TV and serum testosterone concentrations (A); patients with normal TV and reduced serum testosterone concentrations (B); patients with reduced TV and serum testosterone concentration (C); patient with low TV e normal serum testosterone concentrations (D). Then, we administered to each group a specific therapeutic scheme. Group A: treated with FSH alone for at least 3 months; group B: treated with hCG alone twice a week for 3 months and addition of FSH for poor responders (unmodified sperm parameters); group C: treated ab initio with FSH and hCG until the pregnancy was reached; group D: treated with FSH alone for 3 months and addition of hCG for moderate poor responders (increased TV but unmodified sperm parameters) or second cycle of FSH for 3 months for severe poor responders (unmodified TV and sperm parameters). After 6 months we evaluated the therapeutic response in term of sperm parameters normalization rate, spontaneous pregnancy rate, and sperm DNA fragmentation normalization rate.

Results: 40% of patients became normozoospermic after treatment, while 30% achieved spontaneous pregnancy. B was the group that best responded to treatment in terms of normalization of seminal parameters; while the highest spontaneous pregnancy rate was obtained from the D group. B group also obtained the highest sperm DNA fragmentation normalization rate.

Conclusions: To date, no reliable predictors of response to treatment with FSH exist, but TV and serum testosterone concentrations can help the clinician to choose the best therapeutic scheme for men with idiopathic infertility. The groups treated with a sequential temporal scheme (B and D groups) showed better clinical results compared with two groups treated with conventional schemes (A and C groups).

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Introduction

Idiopathic male infertility is a medical condition characterized by an alteration of conventional and/or biofunctional sperm parameters [oligoasthenoteratozoospermia] without a known cause and in presence of normal gonadotropins levels. This alteration is responsible for the failure to establish a clinical pregnancy in couples where there are no female factors of infertility [1].

In the clinical practice, follicle-stimulating hormone (FSH) could be an important therapeutic option for idiopathic male infertility [2]. In fact, several studies have shown the positive effects of FSH on conventional (density, motility and morphology) and biofunctional sperm parameters [3]. In particular, numerous evidences have accumulated on the beneficial effects of FSH on sperm DNA fragmentation [4], a parameter closely associated not only with spontaneous pregnancy rates but also with assisted reproductive technology (ART) outcomes [5].

However, not all patients respond to FSH therapy and this heterogeneous response underlies the contrasting results obtained by clinical trials [6]. To date, there are no reliable predictors of response to treatment: the FSH receptor and FSHβ subunit polymorphisms could represent the most useful tool to predict the clinical response [4], but their use actually remains prerogative of clinical research; some studies have highlighted the importance of testicular cytology and of the presence of spermatids in the ejaculate [7]; while no differences in efficacy between recombinant

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Table 1. The four groups of patients with idiopathic male infertility and normal gonadotropins concentration, and the respective recommended therapeutic regimen.

Group	TV	Total testosterone	Recommended regimen
A	≥12 mL (≥15 if hypoechoic)	≥350 ng/dL	*Monotherapy with FSH* for at least 3 months
B	≥12 mL (≥15 if hypoechoic)	<350 ng/dL	At first hCG for 3 months; then therapy with FSH for another 3 months, continuing (*combined sequential therapy*) or not (*not combined sequential therapy*) the administration of hCG.
C	<12 mL (<15 if hypoechoic)	<350 ng/dL	*Combined treatment* with FSH and hCG ab initio until pregnancy achievement or permanently.
D	<12 mL (<15 if hypoechoic)	≥350 ng/dL	*Cyclic or prolonged monotherapy with FSH* if TV remains low after 3 months (*severe poor responders*). Addition of hCG for *moderate poor responders* (increase of TV without increase of sperm parameters after FSH treatment).

human FSH and high purified FSH have been demonstrated [8].

Until now, little interest has been attributed to the testicular volume (TV) as a possible predictor of response to therapy. However, an adequate TV is fundamental for a physiological spermatogenesis [9]. Most of the TV is made up of germinal cells. If at the end of pubertal development a correct testicular maturation is not reached, the physiological sequence of maturation of the spermatozoa is disturbed [10].

Based on TV and total serum testosterone (TT) concentrations, it is possible to identify four groups of men with idiopathic infertility and normal gonadotropins concentrations that could benefit from FSH treatment (Table 1):

- *A:* Patients with normal TV (≥12 mL) and normal serum TT concentration (≥350 ng/dL);
- *B:* Patient with normal TV (≥12 mL) and serum TT concentration <350 ng/dL;
- *C:* Patient with low TV (<12 mL) and serum TT concentration <350 ng/dL;
- *D:* Patient with low TV (<12 mL) and normal serum TT concentration (≥350 ng/dL).

Aim of this study is to propose a specific scheme of gonadotropins administration for each of these four groups, in order to personalize the treatment and to optimize the therapeutic response.

Patients and methods

We retrospectively evaluated sperm parameters and spontaneous pregnancy rate of patients referring to Catania Andrology Center for idiopathic male infertility who had been treated with FSH. Different regimens were administered to patients, based on their TV and total serum testosterone values:

- 60 patients with normal TV and TT were treated with FSH for at least 3 months (group A);
- 40 patients with normal TV and low TT (group B) were at first treated with human chorionic gonadotropin (hCG), 2000 IU twice a week for 3 months, in order to improve testosterone serum levels. Then, sperm parameters were reevaluated: in patients with no improvement in sperm parameters, FSH therapy was prescribed for other 3 months (sequential therapy). Discontinuation of hCG treatment depended on TT serum levels reached after 3 months of hCG administration: if serum TT levels had remained low, patients continued hCG administration, together with FSH, for another 3 months (combined sequential therapy) (B1 group, no. 10 patients); if TT serum levels had normalized, patients suspended the treatment with hCG and continued only with FSH (not combined sequential therapy) (B2 group, no. 30 patients);
- 65 patients with low TV and serum TT (group C) were treated *ab initio* with combined therapy with FSH and hCG. The therapy was continued until the pregnancy was reached, if the periodic seminal revaluation showed a progressive improvement in sperm parameters;
- 45 patients with low TV and normal TT (group D) were treated with FSH for 3 months. At the end of the therapy, a reevaluation of TV and sperm parameters was carried out. If an increase in TV has been obtained but sperm parameters have not improved, we added low-doses of hCG (2000 IU/week) for 3 months (D1 group or moderate poor responders, no 25 patients). If both TV and sperm parameters were unchanged, patients underwent a second cycle of FSH (cyclic monotherapy with FSH) (D2 group or severe poor responders, no 20 patients) (Figure 1).

The evaluation of sperm DNA fragmentation, before and 6 months after therapy, was also carried out on 85 patients (25 patients of A group, 8 patients of B1 group, 12 patients of B2 group, 20 patients of C group, 6 patients of D1 group and 14 patients of D2 group).

Weight and height measurement for the calculation of body mass index (BMI) and a detailed medical history were collected.

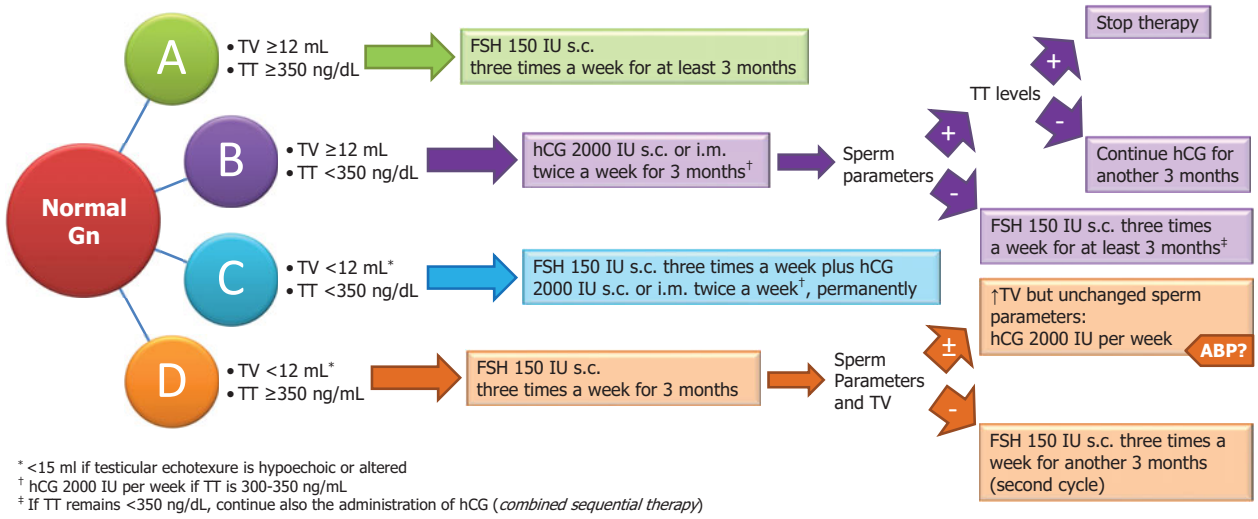

Figure 1. The four possible drug treatment strategies in patients with idiopathic male infertility. TV: testicular volume; TT: total testosterone; Gn: Gonadotropins.

TV was measured by scrotal ultrasound. Semen analysis before and 6 months after pharmacological treatment was performed in accordance with the 2010 World Health Organization manual (5th edition). The sperm DNA fragmentation was evaluated by TUNEL (terminal deoxyuridine nick end labeling) assay.

FSH formulations used was Fostimon® (IBSA, Lodi, Italy). hCG administered was Gonasi HP® (IBSA, Lodi, Italy).

The number of patients who normalized conventional sperm parameter and sperm DNA fragmentation, and who reached spontaneous pregnancy was recorded. Statistical analysis was performed calculating the rate of patients who achieved these goals, overall and for each clinical phenotype. The success rates of each individual phenotype were compared with the overall rates by chi-square test and Fisher exact test. Mean age and BMI, and mean age of the female partner were also calculated.

Results

Data from 210 patients were analyzed. Mean age was 30.75 years; mean BMI was 24.5 kg/m^2; mean age of the female partner was 29.5 years. Age and BMI were not statistically different among the four clinical groups.

Overall, 83/210 patients (39.5%) normalized sperm parameters after therapy, and 62/210 patients (29.5%) reached a pregnancy spontaneously.

Among patients of A group who received FSH for at least 3 months, 20/60 (33%) showed normalization of sperm parameters, and 15/60 (25%) achieved spontaneous pregnancy.

Among patients of B group, 18/40 (45%) normalized sperm parameters, and 12/40 (30%) reached a spontaneous pregnancy. B2 group (not combined sequential therapy) showed a better response in term of sperm parameters normalization compared with B1 group (combined sequential therapy) (47% *vs.* 40%), although the spontaneous pregnancy rate of the two groups was the same (30%).

Among patients of C group, 25/65 (38%) normalized sperm parameters, while 20/65 (31%) achieved spontaneous pregnancy.

Finally, among patients of D group, 20/45 (44%) showed normalization of sperm parameters after therapy, and 15/45 (33%) reached pregnancy spontaneously. D1 group (moderate poor responders) showed a higher rate of sperm parameters normalization compared with D2 group (severe poor responders) (48% *vs.* 40%), but D2 group had a slightly better spontaneous pregnancy rate compared with D1 group (35% *vs.* 32%).

Normalization of sperm DNA fragmentation was obtained in 28/85 patients (33%): 5/25 patients (20%) of A group, 10/20 patients (50%) of B group (2/8 of B1 group and 8/12 of B2 group), 6/20 patients (30%) of C group, and 7/20 patients (35%) of D group (2/6 of D1 group and 5/14 of D2 group).

No statistically significant differences in sperm parameters normalization rate and spontaneous pregnancy rate have been demonstrated among the four groups and between the overall case study and each clinical groups. Regarding sperm DNA fragmentation, normalization rate was significantly higher in patients of B group compared with the overall case study ($p = .03$). Groups B and D (sequential therapy) showed

Table 2. Percentages of the main outcomes evaluated in the four groups after 6 months.

Group	Normalization of sperm parameters (%)	Spontaneus pregnancy (%)	Normalization of sperm DNA fragmentation (%)
A	33.0	25.0	20.0
B	45.0	30.0	50.0*
C	38.0	31.0	30.0
D	44.0	33.0	35.0
All groups	39.5	29.5	33.0
Conventional scheme (A + C)	38.5	28.0	25.0
Sequential scheme (B + D)	44.5	31.5	42.5*

*p Values = .03 compared with the overall case study.

a percentage of patients with significantly higher normalization of sperm DNA fragmentation compared with groups A and C (non-sequential therapy). Table 2 showed the percentages of the main outcomes evaluated in the four groups after 6 months.

Discussion

Spermatogenesis requires the coordinated action of FSH and endogenous testosterone. Notably, LH and FSH have a differential effect on the testes. LH stimulates maturation of the interstitial Leydig cells that secrete T. FSH acts on the seminiferous tubules to induce and maintain spermatogenesis. The seminiferous tubules account for approximately 90% of TV; hence, the size of the testes is a critical indicator of fertility potential. Importantly, both FSH and T are necessary for both quantitatively and qualitatively normal spermatogenesis [11].

Men with idiopathic infertility represent a heterogeneous group from the clinical point of view. The subdivision of these patients into four groups arises from the need to prescribe the most appropriate therapy to each patient.

The most used scheme in the treatment of infertile male with gonadotropins is the administration of FSH at a dose of 150 IU three times a week [8], but this scheme may not always be the most appropriate.

We applied to patients of A group (normal TV and TT) the classical FSH therapeutic regimen. If after 3 months of therapy sperm parameters (conventional parameters and sperm DNA fragmentation) do not improve, it would be advisable to carefully evaluate in these patients the presence of other predictors of poor clinical response (i.e. FSH receptor and FSHβ subunit polymorphisms) [4].

In patients of B group (normal TV and low TT), testosterone levels should be at first normalized through the administration of a drug with luteinizing hormone (LH)-like effects (hCG) in order to promote the progression of the spermatogenesis on the post meiotic phase [12]. In patients whose TT concentrations, after 3 months of therapy, do not reach the normal level but increase to the starting point of at least 50%, the prosecution of hCG therapy with a lower dose (2000 IU weekly) can be suggested. In patients with basal TT concentrations $<$350 ng/dL but $\geq$300 ng/dL, it may be advisable to start the therapy *ab initio* with low doses of hCG (Figure 1). In any case, a suppression of endogenous LH production must be avoided.

In patients of C group (low TV and TT) the action of the two gonadotropins must be balanced (FSH – stimulation of the spermatogonial mitosis; hCG – increase in intra-testicular testosterone levels and consequent stimulation of the post meiotic phase of spermatogenesis). For this purpose, these patients should be treated *ab initio* with combined therapy with FSH and hCG [11]. The hCG dose weekly administered (2000 or 4000 IU) should be choosen depending on the starting TT values (above or below 300 ng/dL) (Figure 1). A permanent treatment with gonadotropins should be considered for patients who return hypogonadic after the discontinuation of therapy.

Patients of D group (low TV and normal TT) who did not obtain an improve in TV nor in sperm parameters after 3 months (severe poor responders), should continue FSH therapy because the failure to increase the TV (by the stimulation of the sertolian compart) could explain the lack of effect on conventional and/or biofunctional sperm parameters. If an increase in TV has been obtained but sperm parameters have not improved (moderate poor responders), the addition of low-dose hCG (2000 IU/week) must be considered, because a discrepancy between serum TT levels and intra-testicular testosterone concentrations may occur. These patients may have a reduced expression of androgen-binding protein (Figure 1).

This study shows that gonadotropin therapy of male idiopathic infertility may have comparable or even better results than ART, if the therapeutic scheme is chosen correctly.

In Italy, every year, over 75,000 couples undergo assisted reproduction, and two-thirds of them perform second-level techniques (*in-vitro* fertilization – IVF, intracytoplasmic sperm injection – ICSI). In Italy the pregnancy rate per cycle of IVF or ICSI is about 20%

[13]. In our case series, the spontaneous pregnancy rate was 29.5%.

In support of our findings, a 2013 Cochrane review demonstrates that pregnancy rate and live birth rate are significantly higher in patients treated with FSH compared with those untreated or treated with placebo, with odds ratio (OR) of 4.9 and 9.3, respectively [14]. A more recent meta-analysis confirms these data, and shows, in addiction, a higher pregnancy rate after ART in patients treated with FSH compared with placebo or untreated group (OR 1.6) [3].

In this study, the evaluation of the increase in TV was used as a parameter for the evaluation of the efficacy of treatment with FSH, knowing the selective stimulation action of FSH on Sertoli cells; while total serum testosterone levels obtained after 3 months of hCG were used as a parameter to evaluate whether or not to continue treatment with hCG to avoid excessive increases in serum TT detrimental to spermatogenesis.

The main limitations of this study are the following: (1) the retrospective design; (2) the lack of data on FSH levels obtained after 3 and 6 months that would have allowed us to assess the achievement of serum FSH levels ideal for the correct spermatogenesis, usually between 4 and8 IU/L [11].

Conclusion

Gonadotropins therapy may represent a good alternative to ART in couples suffering from idiopathic male infertility. But, the scheme must be customized and, in the evaluation of the patients, it is necessary to keep in mind that:

a. TV must always be measured by testicular ultrasound, since the orchidometric evaluation may be inaccurate due to overestimation [15];
b. the echotexture as well as the volume is an important indicator of testicular health. For this reason, patients with TV between 12 and 15 mL can be treated with the scheme suggested for the C or D groups (according to serum testosterone levels) if testicular echotexture is hypoechoic or altered;
c. the evaluation of the clinical response to treatment with FSH should be always carried out considering, in addition to the conventional sperm parameters, also the biofunctional ones, in particular the sperm DNA fragmentation;
d. the sperm DNA fragmentation must be evaluated with one of the following methods: TUNEL, Comet assay (single cell gel electrophoresis), SCSA (sperm chromatin structure assay);
e. in patients with TT $<$ 350 ng/dL and gonadotropins in the low quartile of the range, secondary hypogonadism should be excluded. In these cases, the evaluation of the pituitary function and a magnetic resonance imaging of the hypothalamic-pituitary region could be indicated.

Ethical approval

All procedures performed in the study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

For this type of study formal consent is not required.

Disclosure statement

The authors declare that the content of the submitted manuscript (in part or in full) has not been previously published, and is not under consideration for publication elsewhere. Authors also declare they have no conflict of interest that could prejudge the interpretation of the results presented in the article, and that no financial support was received in conjunction with the generation of this submission.

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