Treatment of idiopathic infertility with Testosterone Undecanoate

A double blind study

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Summary: This study refert to 50 couples treated for subfertility. Twenty five of these patients were treated with TU (Testosterone Ur econoate), the remaining 25 received placebo.

Sperm characteristics, including ejaculate volume, pH, sperm density, morphology, motility, total testosterone, FSH, LH, DHT and E_2 were evaluated both before and after treatment. A statistically significant increase of DHT levels was noticed after TU administration, whereas a marginally significant improvement of sperm morphology was present.

Serum FSH concentrations, decreased significantly in the TU group whereas serum LH presented a slight but not statistically significant decrease; 4 pregnancies were achieved by the TU group whereas none were achieved by the patients belonging to the placebo group.

The administration of TU per os to patients with idiopathic oligospermia presents a demonstrably positive effect.

INTRODUCTION

At least one quarter of the cases being evaluated for infertility are considered as being idiopathic in nature ([2]). The majority of patients with idiopathic oligospermia have gonadodropin and androgen levels which are considered as being within normal ranges.

Although many different medical treatment plans are available for idiopathic oligoasthenospermia and/or teratozoospermia controversy surrounds the sucess of these treatments ([9]).

Most of the studies lack placebo controls or data on achieved pregnancies ([1, 3, 5, 7, 8, 10]).

In order to evaluate better the effect of oral testosterone undecanoate (TU) for the treatment of idiopathic oligoasthenospermia we performed this double blind study.

MATERIALS AND METHODS

Our material consisted of 50 couples admitted to the 2nd Dept. of Obstetrics and Gynecology, at the University of Athens for either primary or secondary subfertility. (Time of infertility ranged from 3-14 years).

The female partner had no demonstrable cause of infertility as assessed by routine gynecologic investigation, evaluation of follicular and luteal function and of tubal patency by hysterosalpingography as well as diagnostic laparoscopy.

The diagnosis of idiopathic infertility in all males studied, aged 24 to 38 years (mean age SD = 28.4 ± 1.1 years) was ascertained after

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exclusion of any iatrogenic, systemic, congenital, infectious, autoimmune or endocrinologic cause. Varicocele was excluded after clinical palpation and contact thermography.

Investigation before and during the study of at least three semen samples were performed in agreement with WHO recommendations [11] before initiation of treatment.

The spermiograms were categorized as abnormal if at least two of the following criteria were fulfilled:

a) concentration $<20\times10^6$/ml; b) total progressive motility $<50\%$; c) and sperm morphology $<25\%$ of ideal forms.

All spermiograms were negative for antisperm antibodies (Biorad, Richmond, CA). The procedure of the immunobead test was performed as described [11]. All semen analysis was performed by the same investigator and showed a sterile bacteriologic culture.

Before initiation of treatment, blood samples were taken for measurement of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), dihydrotestosterone (DHT), and estradiol (E_2) using standard commercially available RIA kits (Diagnostic Products Corp. Los Angeles, CA).

After 3 months of therapy an additional spermiogram was performed and the same hormones were measured.

Twenty-five randomly selected patients received 120 mg TU, (Restandol, Organon Greece) daily for 3 months (i.e. 3 capsules of 40 mg of testosterone undecanoate after each meal one capsule).

Another 25 randomly selected patients received treatment with placebo capsules. Placebo and T-undecanoate were identically packed.

Statistical analysis

The statistical analysis method used to compare and evaluate the effect of T-undecanoate on sperm characteristics, the paired t-test, (Fischer exact test) was also used to compare conception incidence between placebo and T-undecanoate treated groups.

RESULTS

The evaluation of semen data did not present significant differences as to the volume and pH between the TU and placebo treated groups.

Furthermore, the administration of TU did not influence sperm motility or density, but a marginally significant improvement of sperm morphology was however noticed ($p=0.06$).

From an endocrinological point of view, an increase of total serum testosterone concentrations was evident in the TU treated group without achieving statistical significance in contrast to DHT concentrations which were statistically significant for the TU treated group $p<0.001$.

Serum FSH concentrations were significantly decreased in the TU treated group when compared to the placebo group ($p<0.01$).

A slight decrease of serum LH was noticed after TU treatment, although it was not statistically significant.

Pregnancies

The group treated with TU, resulted in four pregnancies. Of these one aborted, one at this time is 28 weeks in gestation, whereas the remaining 2 have produced 2 healthy children.

The placebo group did not present any pregnancies. The statistical significance of this difference using Fischer's Exact test was $p=0.056$.

Side effects were not noticed in those patients receiving TU treatment or were so minimal that therapy was continued.

DISCUSSION

The use of many medications for treating idiopathic oligoasthenospermia emphasizes that none of them are consistently effective or predictable.

Testosterone undecanoate (TU) continues to elicit high expectations among many clinicians. Testosterone undecanoate is an oral testosterone preparation which provides complete androgenic replacement after oral administration. Studies have repeatedly shown that administration of TU is an effective method for the treatment of hypogonadal male patients [12].

The efficacy of TU as treatment for male infertility has not yet been intensively studied.

Table 1. — *All cases before treatment (Mean±SD).*

	Placebo	TU
Ejaculate volume	3.80± 1.86 ml	3.55± 2.11 ml
pH	7.56± 0.22 pH	7.50± 0.21 ml
Sperm density	13.35± 9.51 mln/ml	15.86± 8.81 mln/ml
Morphology		
% Normal	55.65±12.20 mln/ml	52.48±16.10 mln/ml
% Abnormal	44.35±15.25 mln/ml	47.52±15.90 mln/ml
Motility		
% Progress	15.50±11.30 mln/ml	17.10± 9.85 mln/ml
% Weak	18.86± 6.18 mln/ml	16.50± 5.95 mln/ml
% Immotile	59.25±18.80 mln/ml	61.25±20.35 mln/ml
Testosterone total	6.18± 5.85 ng/ml	6.10± 6.05 ng/ml
FSH	4.75± 1.98 mlE/ml	4.60± 2.09 mlE/nl
LH	3.86± 1.85 mlE/ml	4.45± 1.16 mlE/ml
DHT	62.85±12.6 ng/ml	66.35± 8.7 ng/ml
E_2	28.30± 8.58 ng/ml	29.30±10.51 pg/ml

Della Casa *et al* ([4]) studied the efficacy of testosterone undecanoate (TU) on spermatogenesis. Nine normogonadic men with primary infertility whose sperm counts were less than 20 million/ml and with ejaculate volumes of less than 3 ml, received TU in doses of 160 mg/day for 3 months. After the end of treatment, the ejaculate volume and the motility of spermatozoa both increased significantly. The fertility rate in this group was 25% (2 out of 9). Pusch in 1989 ([6]) in a double blind trial treated 60 patients with 120 mg TU daily per os for 100 days and re-

Table 2. — *All cases after treatment (Mean ± SD).*

	Placebo	TU
Ejaculate volume	3.61± 1.85 ml	3.26± 1.95 ml
pH	7.36± 0.22 pH	7.41± 0.21 pH
Sperm density	15.45±10.15 mln/ml	17.95± 8.81 mln/ml
Morphology		
% Normal	54.56±11.10 mln/ml	56.86±10.65 mln/ml
% Abnormal	48.52±15.64 mln/ml	44.54±16.38 mln/ml
Motility		
% Progress	16.84±10.95 mln/ml	20.35±10.56 mln/ml
% Weak	18.50± 6.95 mln/ml	18.57± 6.15 mln/ml
% Immotile	58.50±20.35 mln/ml	60.54±22.30 mln/ml
Testosterone total	5.95± 4.53 ng/ml	7.95± 2.86 ng/ml
FSH	4.64± 1.45 mlE/ml	3.58± 1.28 mlE/ml
LH	3.51± 1.60 mlE/ml	3.10± 1.25 mlE/ml
DHT	66.12±12.1 ng/ml	145.48±17.9 ng/ml
E_2	29.10± 7.15 pg/ml	28.15± 9.55 ng/ml

corded 6 pregnancies which were considered to be result from improvement of sperm morphological quality. The same study presented 4 pregnancies in the placebo group.

Our material presented 4 pregnancies. These pregnancies may be accounted for by the improved sperm morphology observed. This hypothesis would be in agreement with Pusch (6).

It is accepted that 20 - 25% of those males with idiopathic oligospermia may present at some time, indifferently to any particular therapy, an incidental improvement of sperm quality. This may result in the achievement of a spontaneous pregnancy. As to this, we find ourselves in agreement with Dalla Casa (4) who pointed out that the results achieved after TU treatment occurred within a definite time period and not randomly after an indefinite time period.

In addition, although sperm morphology improved, the overall pregnancy rate presented only a marginally significant difference when compared to the placebo group.

In conclusion the administration of 120 mgr of TU per os to patients with idiopathic oligospermia presented a demonstrably positive effect. Further study is needed in order to properly select patients who will respond to this particular treatment.

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