Testosterone Undecanoate As An Effective Treatment In Men With Idiopathic Oligoasthenozoospermia

Usman Mehmood,[1*] Sohail Mahmood Ch [1]

ABSTRACT

Objective — *To assess the effect of treatment with the androgen testosterone undecanoate on seminal variables and frequency of pregnancy in subfertile men with idiopathic oligoasthenozoospermia.*

Study design — *Descriptive Case Series.*

Place & Duration of study — *Department of Obstetrics & Gynaecology, Bahawal Victoria Hospital & Civil Hospital Bahawalpur, from December 2015 to December 2018.*

Methodology — *Men, aged 18-50 years, who visited the outpatient department with the complaint of infertility were enrolled in this study. They were given testosterone undecanoate 40mg t.i.d for 3 months and followed up for another 3 months without treatment. Seminal analysis was done after 3 days of abstinence, before and after treatment as well as at the end of a 3-month treatment-free follow up period.*

Results — *A total of 1800 patients were included. Asthenozoospermia was the most common abnormality, found in 76.1% (n=1370) of the sample. The baseline mean sperm concentration was 16.65 +7.14x10^6/ml and the mean percentage of progressively motile sperm was 17.21+ 13.52%. These parameters increased to 54.28 + 20.11x10^6/ml and 35.07+ 16.39% at the end of 3-month follow up period, respectively. Pregnancies were achieved in 469 (26.05%) female partners of male patients during the study period.*

Conclusion — *Testosterone undecanoate has tangible positive effects on seminal parameters leading to conceptions among subfertile couples.*

Key words — *Male Infertility, Oligozoospermia, Asthenozoospermia, Testosterone undecanoate*.

INTRODUCTION:

The essence of man's existence is based upon his ability to reproduce. Inability to do so is a source of agony for many couples worldwide. Infertility, which is defined as one year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycle. It occurs in about 10-15% of the couples. Male factor contributes to 50-60% of overall infertility but is solely accountable in only 20% of couples.[1] Although an anomalous seminal analysis is predominantly responsible for labelling male infertility, other factors can be instrumental especially if the seminal analysis returns normal. Infertility in the male population can be due to discernable hormonal, anatomical or infectious etiologies that may or may not be reversible. However, despite technological advances, a concrete cause cannot always be isolated, as is the case with 40-50% of men evaluated for infertility.[2] Undetermined male infertility is known as idiopathic oligo/astheno/teratozoospermia which indicates that men have an unexplained reduction in either sperm count, motility or an increase in abnormal morphological forms, respectively.

[1] Department of Obstetrics & Gynaecology Quaid-e-Azam Medical College Bahawal Victoria Hospital Bahawalpur

Correspondence:
Dr. Sohail Mahmood Ch [1*]
Department of Obstetrics & Gynaecology
Quaid-e-Azam Medical College
Bahawal Victoria Hospital
Bahawalpur
E mail: drsohailch@hotmail.com

The therapeutic approaches to infertility can be broadly classified into specific and non-specific. The specific modus operandi is used for certain etiologies such as hypogonadotropic hypogonadism, retrograde ejaculation and antisperm antibodies (ASA).[3] On the other hand, the non-specific empirical therapy, includes hormonal therapy that is widely used because it is minimally invasive and has few or no side effects. Top of the list of hormonal agents to be used was the androgen testosterone because of its classical association with masculinity. Testosterone is a pleiotropic hormone that plays various physiological roles in the development of male reproductive tract in utero and during puberty. With the contemporary advances obtained from the use of hypophysectomised and transgenic mice and non-human primates, the previously elusive effects of testosterone depletion and over-expression have been identified and thoroughly studied which has reinvigorated the debate of whether to use exogenous testosterone for the treatment of idiopathic male infertility. In a survey of the members of American Urological Association, 25% urologists reported using testosterone to treat male factor infertility.[3]

The literature recommendations regarding empirical treatment of male infertility remain inconclusive, which until now have largely reflected the flaws and deficiencies in our understanding of the physiology and pathology of male infertility. Simultaneous advancement in assisted reproductive Techniques (ART) had shifted the focus of research away from empirical to specific treatments such as IVF/ICSI. Nonetheless, the cost of this man-made technology is substantial, and intolerable for a major part of the society in the developing social landscape of our country. In addition, there is a slight but recognized risk of testicular damage from sperm extraction and ovarian hyperstimulation as well as the feto-maternal consequences of multiple gestation and the distress of failed IVF cycles on the psychological and financial situation of the patients. Hence, in our opinion, further research and enhancement of hormonal therapy should take preference. In light of these factors, we conducted our research with testosterone undecanoate (TU), as it had shown promise in previous studies and was suggested as first line treatment for idiopathic oligospermia.[4-6]

METHODOLOGY:

This study was conducted in the Outpatient Department (OPD) of Obstetrics & Gynaecology, Bahawal Victoria Hospital and Civil Hospital Bahawalpur, from December 2015 to December 2018. All patients, aged 18-50 years, who presented with complaint of inability to conceive for at least one year with no history of contraceptive use, underwent a standardized baseline seminal analysis at a designated laboratory as laid out by the 'WHO laboratory manual for the Examination and processing of human semen 5th Edition' and were included in this study after a detailed interaction which included a history taking session and general physical examination. Couple counselling was part of the intervention for all patients and informed consent was taken. Eligible patients were included in a continuous manner to avoid selection bias and obtain a more representative sample.

All male patients aged between 18-50 years whose seminal parameters were below the lower reference limits as set out by WHO on baseline seminal analysis without any identifiable cause, were included in this study. Patients with known medical disorders such as diabetes, hypertension, cardiac disease and tuberculosis, cryptorchidism, varicocele, previous Chlamydia trachomatis or Herpes/Mumps virus infection and previous history of testicular trauma or users of drugs such as marijuana, alcohol and chain smokers or those with exposure to environmental pollutants/toxins or with family history of genetic abnormalities, were excluded.

Patients were prescribed TU 40mg t.i.d for 3 months, after which a post-treatment seminal analysis was done. All patients were followed up after 3 months without any medication and a final seminal analysis was done at the end of follow up period. All semen samples were obtained after 3 days of abstinence. Sperm concentration and progressive motility were the main seminal parameters examined by the pathologist who was blind to this study.

Data was collected prospectively and put into Microsoft Excel 2018 (v16.19). Descriptive statistical analysis was done using Excel Data Analysis ToolPak. Frequency and percentages were calculated for variables like abnormalities of semen. Arithmetic mean and standard deviation were calculated using the same software for sperm concentration and progressive motility.

RESULTS:

A total of 1800 male patients were included over the three-year period. The ages of the patients were between 18 and 50 years. The mean age of the patients was 34.64 + 6.36 year. Asthenozoospermia was the most common abnormality on baseline seminal analysis being found in 76.1% (n=1370) of the sample. The frequency of oligozoospermia was 70.2% (n=1264). Percentage of the different abnormalities of semen as seen on baseline seminal

Table I: Frequency of Different Abnormalities Of Semen				
	Asthenozoospermia	Oligozoospermia		
		Mild (10-15x10^6/mL)	Moderate (5-10x10^6/mL)	Severe (<5x10^6/mL)
Percentage	76.1%	34.5%	17.1%	18.6%
Number of Patients	1370	621	308	335

Table II: Frequency of Changes In Seminal Parameters On 2nd Semen Analysis				
	Increase		Decrease	
Sperm Concentration	36.3%	n=653	63.7%	n=1147
Progressive Motility	75.2%	n=1354	24.8%	n=446

Table III: Frequency of Changes In Seminal Parameters After 3 Treatment Free Months						
	Increase		No change		Decrease	
Sperm Concentration	84.4%	n=1519	11.9%	n=214	3.7%	n=66
Progressive Motility	82.1%	n=1478	12%	n=216	5.9%	n=106

analysis is presented in table I & II. Patients with seminal parameters in the sub-fertile range were 536 (29.8%). The mean sperm concentration was 16.65 7.14x10^6/mL and the mean percentage of progressively motile sperm was 17.21 13.52%.

After treatment with TU, an increase in the sperm concentration was observed in 36.3% whereas 63.7% had a decreased sperm concentration. However, the percentage of progressively motile sperm increased in 75.2% of the population. The frequency of changes in seminal parameters observed on 2nd seminal analysis after three-month treatment with TU are outlined in table. The mean sperm concentration was 18.24 8.75x10^6/mL and the mean percentage of progressively motile sperm was 19.94 12.39%.

Sperm concentration after three treatment-free months showed an increase from baseline value in 84.4% of patients. However, there was a reduction in sperm concentration in 3.7% of patients and 11.9% showed no change from baseline. Whereas the percentage of progressively motile sperm showed an increase in 82.1% of patients, no change in 12% and a decrease in 5.9% of sample. Table shows the frequency of changes in seminal parameters from baseline after the treatment free period. The mean sperm concentration was 54.28 20.11x10^6/mL and the mean percentage of progressively motile sperm was 35.07 16.39%. Conception was achieved in 469 female partners of male patients (26.05%) during the study period.

DISCUSSION:

The fundamental finding of our study was that treatment with testosterone undecanoate resulted in a manifest improvement in seminal parameters which led to conception among sub-fertile couples. Our results reiterate the findings of various other studies that have shown beneficial effects of androgens, especially TU, on seminal parameters for the treatment of idiopathic male infertility.[4-9] Hence the reason why TU was recommended by the European Association of Urology (EAU) guidelines as the first-line practical curative option for male infertility.[10,11]

We are aware of the latest EAU guidelines restricting the use of Testosterone for the treatment of male infertility. Although sufficient number of well performed and controlled clinical trials that provide concrete evidence in favor of drug treatment are unavailable at the moment, the opportunity to prove that these drugs are effective should be considered, and rigorous follow up with the use of this drug should be encouraged and evidence based data reported.

Results of a double-blind placebo-controlled trial with the same 120mg TU dose showed statistically significant enhancement in sperm morphology, sperm density, pregnancy incidence and decline in head and tail deformities.[9] A substantial increase in dihydrotestosterone (DHT) levels, sperm morphology and pregnancy incidence was also noted in another double-blind study.[7] A pilot study with 120mg TU had also shown promising results with a 36.4% pregnancy rate, calling for larger RCT to be undertaken.[8]

A major part of the reason why TU was never given the acclaim it deserves was the ongoing concern that exogenous androgens would induce negative feedback on hypothalamic-pituitary-gonadal (HPG) axis, resulting in decreased gonadotropin secretion and intra-testicular testosterone (ITT). This skepticism is derived from the unilateral likeminded approach of andrologists and endocrinologists that contraception could be achieved by androgens. Reliable opinions have indicated that inhibition of spermatogenesis by androgens through negativefeedback requires substitution that far exceeds normal physiological levels and a long-time course.

Furthermore, recent studies have concluded that spermatogenesis is possible due to the constitutive ITT production that is independent of gonadotropin stimulation which contradicts the current doctrines of our knowledge.[12] A similar study with transgenic non-human primates concluded that under normal biological conditions, the negative feedback loop governing ITT synthesis plays no role in regulating sperm output, because the normal level of ITT is maintained far in excess of serum levels (25 to 125 fold higher).[13] Rather, the goal of this feedback loop is to sustain circulating serum testosterone levels at the optimal level for proper functioning of androgen-dependent non-gonadal tissues such as muscle, brain and male reproductive tract. These findings would explain the fact which numerous studies have concluded that exogenous testosterone is a poor contraceptive on its own.[14]

Testosterone is required for four indispensable physiological processes inside the seminiferous tubule, namely, maintenance of the Blood-Testes barrier (BTB) and promotion of the transit of preleptotene spermatocytes through it, development of the haploid spermatid stage during meiosis, promotion of Sertoli-spermatid adhesion and elongation and the release of mature sperm.[15] Another study, after a 20-year fact-finding process, inferred regarding the mechanism of TU's action, that its administration resulted in a sharp rise in dihydrotestosterone levels, which itself is a epididymal function promoter. The pre-existing concepts about the action of androgens on spermatogenesis, namely the Direct Stimulatory Theory and the Rebound Theory appear to have been validated, given the lack of contraceptive efficacy of TU at low doses and the incidents of pregnancy reported in various contraceptive trials after cessation of treatment.[14]

CONCLUSIONS:

Testosterone undecanoate showed improvement in seminal parameters in men diagnosed with subfertility due to idiopathic oligoasthemozoospermia.

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