

## **Clinical effects assessment of clomiphene on young man hypogonadism patients for adjuvant therapy.**

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### **Abstract**

**It studied the treatment effect of clomiphene using a dosage of 25 mg/time. We recruited 30 young male volunteers of hypogonadism, aged from 22 to 40 y old. By orally once every two days for three months drug intervention, their increased scores of SILOH and IIEF-5 showed that clomiphene could treat they hypogonadism effectively, by increasing expression level of serum total testosterone. This drug could maintain the normal volume of testes, improve sperm motility and increase sperm count, after laboratory testing. So the clomiphene could be recommended to treat young male hypogonadism to improve patients' symptoms and maintain fertility.**

**Keywords:** Clomiphene, Hypogonadism, Young man, Clinical effect.

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### **Introduction**

Since, hypogonadism means diminished functional activity of the gonads, the testes in males that may result in diminished sex hormone bio-synthesis. Spermatogenesis in males may be impaired by hypogonadism, which, depending on the degree of severity, may result in partial or complete infertility [1,2].

Male primary or hypergonadotropic hypogonadism is often treated with testosterone replacement therapy if they are not trying to conceive. Adverse effects of testosterone replacement therapy include increased cardiovascular events (including strokes and heart attacks) and death, which had been warned by the Food and Drug Administration (FDA) [3,4].

Clomiphene was approved for medical use in the United States in 1967. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system [5,6]. It was first used to treat cases of oligomenorrhea but was expanded to include treatment of anovulation or other disease, which were analysed of clinic treatment effect on young male hypogonadism in this study.

Herein, we reported the clinical effects assessment of clomiphene in young man hypogonadism patients for adjuvant therapy. 30 young men hypogonadism patients were involved in this study, with clomiphene citrate orally once every two days for three months. The increased scores of SILOH and IIEF-5 showed that clomiphene could treat young man hypogonadism effectively, by increasing the expression level of serum total testosterone. After taking it with dose of 25 mg per two days, the patient's clinical symptoms have been effectively improved. This drug could maintain the normal volume of testes, improve sperm motility and increase sperm

count, through laboratory testing. The details of research case report were as following.

### **Patients and Diagnosis**

It collected 30 young men hypogonadism patients from the Jiangxi People's Hospital from January to December, 2016. They were received treatment and diagnosis from the Department of Andrology. The specific details of the diagnosis criteria were according to the guideline from International Society of Andrology (ISA) in 2005. We used this SILOH and IIEF-5 tool to assess the patient's disease severity. All initiatives of definition, diagnosis and classification of hypogonadism and their improvement were evaluated. All the collected patients were aging from 22 to 40, at average age of 34.7 y old. Case exclusion criteria: All cases should be excluded these diseases: Klinefelter syndrome, hypogonadotropic hypogonadism, testicular atrophy or no testicles.

### **Drug Intervention Procedure**

It designed citrate clomiphene capsules (clomiphene citrate) drug treatment program by once every two days for three consecutive months, which was purchased from Shanghai Hengshan Pharmaceutical Co., Ltd, (Shanghai, China). The dose of every time oral administration was treated with 25 mg. But it is not restrict the use of other direct or stimulate male hormone drugs in patients.

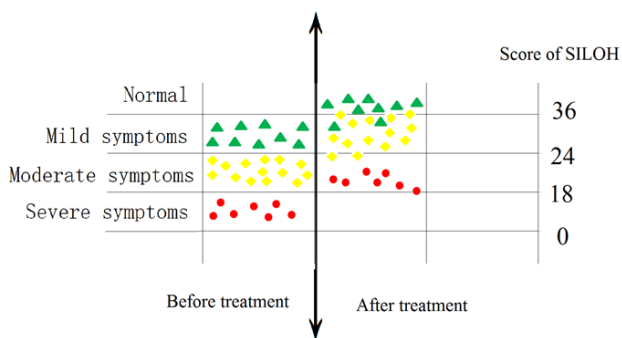
Improvement of clinical manifestations: After three months of clomiphene drug intervention, the patients' condition began to improve. There was no patient with fatigue after three months treatment. Other clinical manifestations had improved better

compared with before drug intervention ( $P<0.05$ ). And it needs this treatment timing to take the clomiphene effect on these patients (Table 1).

**Table 1.** The patients' condition had been improved during time treatment.

Clinical manifestations	Treatment timing			
	0 month	1 month	2 month	3 month
Fatigue	30	22	14	0
Muscle ache	28	21	13	0
Joint pain	26	20	13	1
Irritability	28	19	14	1
Memory loss	20	17	10	4
without morning erection	23	14	11	3
Pubic hair off	22	16	11	3
Beard off	23	16	11	2

All patients were evaluated by Schedule Table of Late Onset Hypogonadism (SILOH) and made scores. The scores changes were described in Figure 1. After three months of standardized treatment, the patients with different severe illness have been improved, especially for the moderate symptoms group.



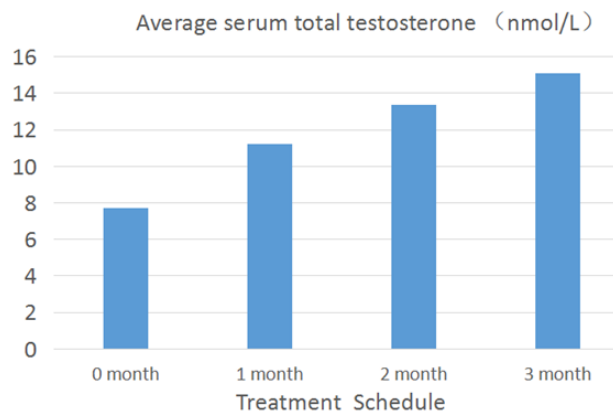
**Figure 1.** The scores changes of SILOH between before and after clomiphene drug intervention for 30 young men hypogonadism patients.

This standardised and validated 15-item self-evaluation scale provides pre-post treatment clinic evaluations of erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and general satisfaction. The IIEF-5 Sexual Health Inventory for Men, an abridged version of the IIEF, contains a shorter questionnaire of 5 items which takes into account the latest six months instead of the latest four weeks considered by the IIEF. All involved patients had the increasing scores of IIEF-5, compared with before treatment.

**Detection of serum total testosterone**

By patients' first time visiting hospital, it collected 2-3 ml fasting venous blood, then separated the serum by centrifugal for each experimental patient and collected it till the third

month after clomiphene treatment. Saved them in  $-20^{\circ}\text{C}$  for further detection. The serum total testosterone detection method was using ELISA. The human testosterone ELISA rapid detection kits were purchased from the Siemens Medical Diagnostic Products (Shanghai) Co., Ltd (Cat. No. 2402838). The testosterone standards were purchased from Sigma-Aldrich Company (Cat. No. T1500). According to these manual, it detected the patients' serum total testosterone.



**Figure 2.** The average serum total testosterone level had been increased significant after clomiphene treatment.

Figure 2 showed that increasing expression after clomiphene treatment. With the advance of treatment time this upward trend is more obvious for moderate symptoms patients. The drug intervention has a positive correlation with high degree of serum total testosterone by regression analysis ( $P<0.05$ ).

**Semen quality**

Semen quality is a measure of the ability of semen to accomplish fertilization. Thus, it is a measure of fertility in a man. It is the sperm in the semen that are of importance, and therefore semen quality involves both sperm quantity and quality. Decreased semen quality is a major factor of male infertility. A semen analysis typically measures the number of sperm per millilitre of ejaculate, and analyses the morphology (shape) and motility (ability to swim forward) of the sperm. We collected patients' semen by themselves masturbation method at first day and 90<sup>th</sup> d during the whole treatment schedule, and tested semen quality by two laboratory physicians. According to their reports, the average number of spermatozoa increased by 5.71 times, and the average sperm motility increased by 3.46 times under clomiphene treatment.

At the same time, there was no significant difference in the concentration of white blood cells, the level of fructose in the semen, and the volume, pH, and liquefaction time of the ejaculate between before and after treatment.

**Ultrasound scan of the scrotum**

At the patients' last visiting hospital, they were suggested to take ultrasound scan of the scrotum, for guarantee of healthy testicles. A Doppler ultrasound scan of the scrotum was used in

diagnosis of identifying the normal blood flow in the twisted testicle, without torsion or epididymitis. Initial images showed symmetric flow to the testes, and delayed images showed uniformly symmetric activity.

### **Research significance of summary**

Its introduction began the new therapeutic purposes of clomiphene for young male' hypogonadism. On the one hand it improved gonadal function, on the other hand so that patients maintained their fertility with sufficient number of sperm and enough viable sperm.

Clomiphene is in the Selective Estrogen Receptor Modulator (SERM) family of medication. It works by causing the release of gonadotrophin by the hypothalamus [7]. After drug intervention, their serum total testosterone levels increased steadily and maintained at an appropriate level. Furthermore, the patient received the appropriate scores of SILOH and IIEF-5, and harvested improvement of clinical manifestations.

This oral treatment method has higher feasibility, easy operation, and high rate of patient compliance. Additional, clomiphene is available as a generic medication. The wholesale cost in the developing world is about 0.79 to 2.00 USD for a course of treatment, so patients' economic burden is not heavy [8]. Clomiphene should be used for more suitable hypogonadism young male cases in the future.

### **Limitations**

There were few patients enrolled in this study. An adequate following-up would be taken for longer time in the future.

### **Conflict of Interest Statement**

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our hospital concerning intellectual property.

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