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Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse

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Objective: To report a case of symptomatic hypogonadism induced by the abuse of multiple steroid preparations that was subsequently reversed by clomiphene.

Design: Case report.

Setting: University-affiliated andrology practice within family practice clinic.

Patient(s): A 30-year-old male.

Intervention(s): Clomiphene citrate, 100-mg challenge for 5 days, followed by treatment at same dose for 2 months.

Main Outcome Measure(s): Clinical symptoms, androgen decline in aging male questionnaire, total T, FSH, LH.

Result(s): Reversal of symptoms, normalization of T levels with LH surge, restoration of pituitary–gonadal axis.

Conclusion(s): Clomiphene citrate is used typically in helping to restore fertility in females. This represents the first case report of the successful use of clomiphene to restore T levels and the pituitary–gonadal axis in a male patient. The axis was previously shut off with multiple anabolic steroid abuse. (Fertil Steril® 2003;79: 203–5. ©2003 by American Society for Reproductive Medicine.)

Key Words: Andropause, clomiphene, testosterone

Andropause can be defined as a biochemical state of low T or hypogonadism (1). It is frequently associated with the aging process. This hypogonadal state can be symptomatic or asymptomatic and symptoms can include loss of libido, energy, concentration, and memory. Long-term effects of hypogonadism include bone and muscle loss and possible effects on the brain and cardiovascular system. Premature andropause can result from excessive use of anabolic steroids, which lead to a shutdown of the pituitary–gonadal axis through interfering with LH and FSH. Other causes of premature andropause can include obesity, diabetes, and testicular infections.

CASE REPORT

A 30-year-old patient presented with severe depression and loss of libido and energy. He admitted to the use of steroids for bodybuilding purposes for several months. He had obtained nandrolone decanoate, deca Durabolin, primobolan depot, and Winstrol from a foreign country without a prescription. He is on an antidepressant, bupropion (Wellbutrin, Glaxo Smith Kline, Philadelphia, PA). While showering, he noticed that his testicles were gradually shrinking, despite a more muscular body. He does not report anosmia or any childhood orchitis. There was no history of galactorrhea or gynecomastia. There was no family history of hypogonadism.

Physical examination of the genitalia revealed fully descended testicular size of 4 × 2.5 × 1.5 cm on the right and 3.3 × 2.5 × 1.5 com on the left. He had no hypospadias nor abnormalities in the epididymis. There was no goiter, gynecomastia, or visual field defects. Muscle strength in all four limbs was grade 5 in both flexor and extensor groups. The androgen decline in aging male (A.D.A.M.) question-

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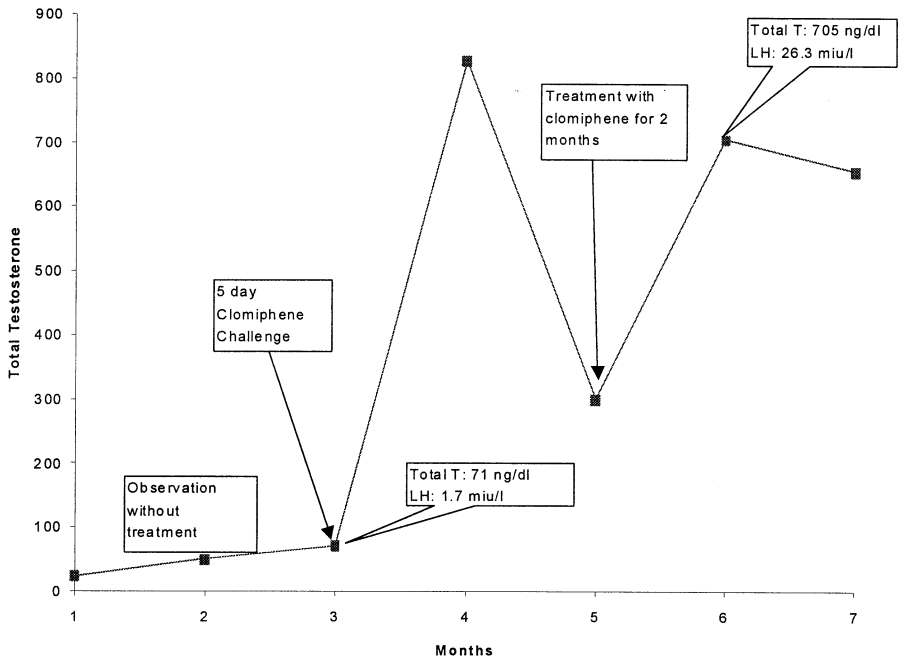
FIGURE 1

The effect of clomiphene citrate on T with time. *Filled square* = total T (ng/dL).



Tan. Premature andropause reversed with CC. Fertil Steril 2003.

naire was applied, and he scored 8/10. For standardization purposes, blood work was done at 9 AM. Just before clomiphene citrate administration, laboratory examination revealed a total T of 71 ng/dL (reference range, 260–1000 ng/dL), free T of 29 pg/dL (reference range, 34–194 pg/dL), bioavailable T of 61 ng/dL (reference range, 84–402 ng/dL), LH of 3.7 miu/mL (reference range, 1.5–9.3 miu/mL), FSH of 2.4 miu/mL (reverence range 1.4–18.1 miu/mL), prolactin of 5 ng/mL (reference range, 2–18 ng/mL), and TSH of 1.36 miu/mL (reference range, 0.40–5.50 miu/mL). Free and total Ts were measured by radioimmunoassay methods. Magnetic resonance imaging did not show any abnormality in the pituitary area. Cortisol and thyroxine were also in the normal ranges. Sperm samples were not collected as the patient declined. Total T levels rather than free or bioavailable T were used for follow-up.

He was challenged with 100 mg of clomiphene citrate for 5 days. Two weeks later, his total T was 828 ng/dL. The patient reported better moods and return of libido and energy, but still continued on his antidepressant. The patient was followed up, and 2 months after clomiphene citrate challenge, he had a relapse of symptoms including tiredness and loss of libido. At this time, his total T dropped again to 301 ng/dL. A decision was made to continue treatment with clomiphene citrate for 2 months. At the end of 2 months, his total T was 705 ng/dL, and LH was 26.3 miu/L (Fig. 1). The magnetic resonance imaging of the pituitary was repeated and remained normal. Symptoms resolved and the patient continues to be followed up.

Institutional review board approval was obtained for writing this case report.

DISCUSSION

Clomiphene citrate is an orally administered, nonsteroidal ovulatory drug typically used in female infertility management. It has both estrogenic and antiestrogenic properties. Clomiphene citrate initiates a series of endocrinologic events that cause a gonadotropin surge, which in turn causes an increase in steroidogenesis. Clomiphene citrate is thought not to have any inherent androgenic or anti-androgenic effect. In this case, we were challenging the pituitary gland to produce a surge of gonadotropins to help restore function to the Leydig cells to produce T.

Clomiphene citrate has been shown to increase T levels in both normal and impotent hypogonadal men probably reflecting the primacy of estrogen over T in the feedback regulation of male gonadal function. In a small, double-blind, placebo-controlled, crossover study of clomiphene against placebo in impotent men with secondary hypogonadism, there was a significant rise of LH, FSH, and T with clomiphene (2). However, the study in these 17 men did not

reveal any improvement of sexual function as measured with questionnaires and penile tumescence and rigidity testing. Another study investigated the hormonal response to clomiphene in alcoholics with hypogonadism (3) and found that clomiphene can increase androgens and estrogens. The rise in estrogens was thought to be due to peripheral conversion of androgens to estrogens. Paradoxically, one study failed to show that clomiphene could restore pituitary testicular responsiveness in hypogonadotrophic hypogonadism but succeeded with human chorionic gonadotropin (4).

Clomiphene citrate has been used successfully in the treatment of idiopathic hypogonadotrophic hypogonadism induced by excessive exercise such as marathon running (5). In that case report, reestablishment of the physiologic hypothalamic–pituitary–gonadal axis with the return of normal T and gonadal function was achieved with clomiphene citrate (50 mg, 2 times per day) over 5 months. In our case, the reestablishment of eugonadal status was achieved with just a short challenge of clomiphene citrate 100 mg over 2 weeks, but the patient relapsed. He needed a longer course of 2 months of clomiphene citrate to maintain eugonadal status. Both cases, including ours, suggest that early intervention with clomiphene can restore the hypothalamic–pituitary–gonadal axis. We are still continuing to follow up our patient to establish long-term effects. The patient did not suffer from any hot flashes or other side effects from clomiphene citrate.

There have been no previously documented cases of clomiphene citrate improving exogenous steroid–induced testicular failure. The mechanism of initial testicular failure could be due to the suppression of LH due to the use of exogenous steroids, which in turn leads to decreased T levels. We postulate that clomiphene citrate can reestablish the axis even after steroid abuse has initially shut down the axis. It can induce the gonadotropin surge, initiate T levels to increase, and improve gonadal function and reverse symptoms. This was possible in this case as the patient was relatively young and presumably had a more elastic axis.

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