



Medical Treatment in Men with Infertility Can Be Misinterpreted as Doping Practice: A Case of Unintentional World Anti-doping Agency (WADA) Code Violation

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Abstract

Introduction: Clomiphene, a selective estrogen receptor modulator (SERM), is a drug which is primarily used for the treatment of anovulatory infertility in female patients. Although as an off-label use, some authorities and physicians use this drug for the treatment of idiopathic oligoasthenospermia in male patients. Clomiphene has two isomers and multiple metabolites, and its cis isomer (Zuclomiphene) can be detected in urine for as long as eight months in some cases.

Case Presentation: A 30-year-old male futsal player used clomiphene for infertility for two months. After 17 weeks from the last dose, his urine sample result came out as an adverse analytical finding for clomiphene. Despite the initial ruling on a four-year ban by the national anti-doping agency, the appeals committee reduced the athlete's ban to two years after receiving explanations from the athlete, his appropriate doping record, and the fact that no trace of other substances, such as anabolic androgenic steroids (AAS) was found in the player's sample.

Conclusions: In this article, the authors try to show the importance of athletes' familiarity with the anti-doping code and try to emphasize the importance of the fact that athletes should receive therapeutic use exemption (TUE) if they take any drugs with doping potential.

Keywords: Clomiphene, Hypogonadism, Doping in Sport, Sports Medicine

1. Introduction

Clomiphene, a triphenylethylene derivative and a selective estrogen receptor modulator (SERM), was first introduced as a treatment for the polycystic ovarian syndrome (PCOS) and other anovulatory conditions in 1967 (1).

Being a SERM, clomiphene exerts agonist and antagonist actions in different tissues that contain estrogen receptors (2).

Clomiphene is made of two isomers: Zuclomiphene (cis isomer) and Enclomiphene (trans isomer). These two isomers are usually found in clomiphene preparations with cis:trans ratio of 2:3. Enclomiphene with a half-life of 5 hours demonstrates estrogen antagonist activities, while Zuclomiphene with a half-life of roughly 24 hours exerts estrogen agonist and antagonist activities (3, 4).

It's been a relatively long time since clomiphene has been used as a treatment for female infertility due to ovulatory dysfunction. Clomiphene exerts its antagonizing

effect on estrogen receptors located on the hypothalamic arcuate nucleus causing inhibition of negative feedback of estrogen on the hypothalamus. This, in turn, causes the hypothalamus to secrete more gonadotropin-releasing hormone (GnRH) in a pulsatile fashion. Clomiphene may also increase pituitary sensitivity to GnRH and, consequently, an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by the pituitary gland. In addition, clomiphene may increase the sensitivity of granulosa cells to estrogen. All the aforesaid mechanisms result in ovulation (1).

Furthermore, off-label, clomiphene has been used to treat men with hypogonadism with normal/low FSH and normal testicular volume. In male individuals, testosterone is converted to estrogen via aromatase. This estrogen exhibits its effect on the hypothalamus and also pituitary gland by inhibiting them. Clomiphene, by means of antagonizing estrogen effects enhances the secretion of GnRH followed by secretion of LH and FSH. The increase in

secretion of these hormones, in turn, stimulates the testicular Leydig cells to produce more testosterone which in turn increases the production of sperm. Clomiphene therapy has been shown to be comparable to testosterone replacement therapy and better than aromatase inhibitors in increasing testosterone levels with a lower rate of side effects (5).

Clomiphene alone or in combination with vitamin E or L-carnitine can enhance the fertility of men with idiopathic oligoasthenospermia (6-8). As a result, the European Association of Urology (EAU), on its 2019 guidelines of male infertility, by citing the review article of Chua et al., claimed that clomiphene could be used as a treatment in male patients with idiopathic oligoasthenospermia (9).

Because of its testosterone-increasing properties, clomiphene has been considered as a muscle bulk-enhancing agent by athletes. For this reason, clomiphene has been prohibited by the world anti-doping agency (WADA) from its first prohibited list, which was published in 2004.

Clomiphene is placed under class 4.2 and as a specified substance in WADA prohibited list. Its use is prohibited in and out of competition for athletes competing under WADA rules (10).

Parallel to its use as a doping agent, clomiphene has other uses among athletes:

(1) Prevention of gynecomastia: Athletes who use anabolic androgenic steroids (AAS) are prone to gynecomastia. It's because of the conversion of AAS to estrogen by aromatase. Hence for the prevention of gynecomastia, they either use aromatase inhibitors or SERMs (11).

(2) Resuming fertility: Athletes who use AAS for long times have suppressed levels of LH and FSH. After discontinuation of AAS, the body gradually starts to turn back to its normal function of producing FSH, LH, and testosterone, a process that takes time. Using clomiphene upon AAS withdrawal reduces the time for the body to return to its normal function of producing testosterone (12).

2. Case Presentation

A 30-year-old male futsal player referred to urology clinic for consultation on infertility. After normal physical examination, the physician requested a semen analysis and hormonal profile. After normal hormonal profile and investigation the semen analysis result, he was diagnosed with idiopathic oligoasthenospermia. The urologist considered treating the patient with clomiphene for two months. Seventeen weeks after the last dose of clomiphene, he participated in a futsal match and at the end, he was invited to take the doping test. Based on the result of the urinary sample, his results were adverse analyt-

ical finding for clomiphene. Citing article 2.1 (presence of a prohibited substance or its metabolites or markers in an athlete sample) and article 10.2.1.2 (intentional use of specified substance) of WADA code, (13) he was convicted to 4 years of ineligibility to participate in any sports event by national anti-doping organization (NADO).

3. Discussion

Clomiphene has been shown to increase testosterone by 150% for multiple weeks after use, and it also increases two other types of androgens, epitestosterone, and 4-androstenedione (3, 14). These effects are mostly seen in males while females show a smaller effect, because most female androgens are made by non-gonadal organs, and these productions are independent of pituitary hormones (14).

Clomiphene has several markers and metabolites which can be found in urine; 4-hydroxyclophene and 3-methoxy-4hydroxyclophene being the most common metabolites being tested in doping labs as well as clomiphene isomers, namely Zuclomiphene and Enclomiphene (3, 15, 16). In a study in 2019, Miller et al. showed that Zuclomiphene can be found in urine for an average of 98 days and, in some cases, up to 8 months after the final dose of clomiphene (3).

Our patient used clomiphene for his infertility for two months. It is noteworthy to know that the recommended treatment for male hypogonadism by WADA is human chorionic gonadotropin and testosterone (17). Due to ethnic and cultural issues, the player did not inform the coaching and medical staff about the use of clomiphene. Therefore, he failed to apply for a therapeutic use exemption (TUE) for the medicine he used. On the other hand, on the day of testing, the player was provided with a form asking about the medicines the player used in the past week, which the player didn't use any medicine in the time given. Last but not least, the player didn't think that a doping test on a urine sample would be positive for a drug which he last used four months ago.

Following the initial verdict, the player appealed the verdict. The Appeals Committee, taking into account all the above conditions, the player's favorable record on doping and the fact that no trace of other substances such as AAS was found in the player's sample, concluded that the player's ban on participating in sports events could be reduced to 2 years under Article 10.6.1.1 of the WADA code. Article 10.6.1.1. states that "Where the anti-doping rule violation involves a specified substance (other than a substance of abuse) or specified method, and the athlete or other person can establish no significant fault or negligence, then the period of ineligibility shall be, at a mini-

mum, a reprimand and no period of ineligibility, and at a maximum, two years of ineligibility, depending on the athlete's or other person's degree of fault." (13).

Footnotes

Authors' Contribution: Tohid Seif Barghi: Gathering case information, critical revision of the manuscript, supervisor; Mohammad Mahdi Tavana: Drafting the manuscript; Erfan Omid: Consultant on urologic issues.

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