

HORMONE AND METABOLIC MODULATORS, COMBINED PILL AND PROGESTOGEN ONLY PILL IN SPORT: STUDY OF THEIR USE

FILOMENA MAZZEO¹, DOMENICO TAFURI²

¹Department of Science and Technology, University of Naples "Parthenope", Italy - ²Department of Sport Sciences and Wellness, Parthenope University, Naples, Italy

ABSTRACT

The aim of this study was to examine the use of hormone and metabolic modulators (SARMs), that have the same effects of androgenic anabolic drugs and the use of selective estrogen receptor modulators (SERMs) as estrogen receptor agonists or antagonists. Examples of substances in this class include tamoxifen and clomiphene. In sport, these drugs are used by athletes as performance-enhancing drugs to stimulate anabolism, improve the strength and enhance muscle mass. These drugs are banned by the World Anti-Doping Agency and have negative side effects but not more of anabolic agents as testosterone and steroids.

The WADA list comprises a total of 10 different classes of banned substances (S0– S9), three different groups of prohibited methods (M1–M3), and two classes of drugs (P1 and P2). The latter are banned from selected sports only. We have analysed the doping's spread in Italy about S4 classes of substances since 2005. The data come from the databases of government and sports Italian institutions. The data show, in the last years, an moderate increase of utilize of this classes of drugs as performance-enhancing drugs.

Keywords: hormone and metabolic modulators, combined pill and progestogen only pill, sport, drugs.

DOI: 10.19193/0393-6384_2020_1_70

Received September 30, 2019; Accepted November 20, 2019

Introduction

The use of drugs in athletes should be carefully evaluated due to the limited margin of benefit and sometimes serious side effects that some of them present. Particularly intense training and competitive physical activity can induce amenorrhea and irregular menstrual cycles in numerous athletes^(1,2).

Certainly, menstrual disorders are common to young athletes and oral contraceptives are often recommended⁽³⁾. They generally have a benefit on body composition and may also be recommended "to prevent bone loss" in female athletes with permanent amenorrhea and estrogen deficiency⁽²⁾.

Combined pill and progestogen only pill (oral contraceptives) are sometimes prescribed to restore menstruation and can therefore be a valuable ally against the syndrome named in 1992 by the American College of Sports Medicine as "Female Athlete Triad", which describes a condition typical of some athletes, characterized by minor eating disorders, amenorrhea and osteoporosis, whose factors triggers seem

to be a low-calorie diet and a negative caloric balance, associated with excessive training^(4,5). However, minor information is available on the effects that oral contraceptives can have on physical performance and body composition. Therefore, the studies performed showed no improvement in muscle strength, nor did they highlight changes in lean mass. On the contrary, only a slight increase in fat mass is known^(2,6,7). This last effect could, however, negatively affect the performance of the athlete.

Currently, for therapeutic use, in addition to the estroprogestinic associations, the utilize of periodic injections (every 3 months) of high-dose progestins has spread⁽¹⁾. These hormonal therapies can be associated with consistent blood loss and iron deficiencies. Furthermore, estroprogestinic drugs can induce mood alterations, associated with states of depression, these reactions which can compromise the competitive spirit and have negative repercussions on the results of the competition^(8,3).

Nevertheless, among the factors that can interfere with the effectiveness of the combined pill and

progestogen only pill there is no physical activity⁹.¹⁰. Moderate intensity exercise has no significant effect on the menstrual cycle. There is no relationship, for example, between the coincidence of the time the oral contraceptives is taken with that of a sport activity such as aerobics and body building, practiced for about two hours. Indeed, physical activity could counteract any undesirable effects (metabolic effects) that may, although today more rarely due to the low dosages used, derive from them⁽¹¹⁾. About use of nutritional supplements such as creatine, there are no studies that correlate creatine supplementation with the oral contraceptives. However, it must be considered that this supplementation can generate an increase in water retention, a phenomenon which, as we have said, is also common to the use of combined pill and progestogen only pill⁽¹²⁾. This association could increase body hydration. The oral contraceptive, if taken simultaneously with creatine (administered especially to athletes who practice power sports), can lead to greater hydration and therefore greater sweating^(12,13).

In ministerial report among the most used and declared specific drugs by the athletes 55 declarations, equal to 2.1% of the total (2061) of all the declared preparations (drugs and other products) and to 3.9% of the total 1420 of the drugs used, concern the use of combined pill and progestogen only pill. Before starting to take a certain combined pill and progestogen only pill, the athlete consult the sports authorities and report the prescription in the appropriate form during the doping test. About concern others hormone and metabolic modulators they have been prohibited as doping agents in and out of competition since 2001 for men and since 2005 for women (classes S4). There are generally 5 different types prohibited substances in the S4 category list including : Aromatase inhibitors, selective estrogen receptors, Selective estrogen receptor modulators (SERMs), Other anti-estrogenic substances, Agents modifying myostatin functions and metabolic modulators.

Methods

Data are originated from the report commissioned by the Italian Ministry of Health. The last years results have been collected and combined among them. The literature search was performed on the PubMed and Scopus databases and on the official website of the Italian Ministry of Health. The analysis of use the substances classified in S4 as “hormone and metabolic modulators” are reviewed and analyzed since 2005.

Results

The data show the anti-doping test took place in Italy during the last ten years: from 2003 to 2018. The literature search was performed on PubMed and Scopus database and Italy Anti-doping official website.

1. Aromatase inhibitors including, but not limited to:
2-Androst-enol (5 α -androst-2-en-17-ol)
2-Androst-enone (5 α -androst-2-en-17-one)
3-Androst-enol (5 α -androst-3-en-17-ol)
3-Androst-enone (5 α -androst-3-en-17-one)
4-androstene-3,6,17 trione (6-oxo)
Aminoglutethimide
Anastrozole
Androsta-1,4,6-triene-3,17-dione (androstatrienedione)
Androsta-3,5-diene-7,17-dione (arimistane)
Exemestane
Formestane
Letrozole
Testolactone
2. Selective estrogen receptor modulators (SERMs) including, but not limited to:
Raloxifene
Tamoxifen
Toremifene
3. Other anti-estrogenic substances including, but not limited to:
Clomifene
Cyclofenil
Fulvestrant
4. Agents preventing activin receptor IIB activation including, but not limited, to:
Activin A-neutralizing antibodies
Activin receptor IIB competitors (e.g. decoy activin receptors (e.g. ACE-031))
Anti-activin receptor IIB antibodies (bimagrumab)
Myostatin inhibitors (myostatin-neutralizing antibodies (e.g. domagrozumab, landogrozumab, stamulumab), myostatin-binding proteins (e.g. follistatin, myostatin propeptide); agents reducing or ablating myostatin expression)
5. Metabolic modulators:
Activators of the AMP-activated protein kinase (AMPK), eg. AICAR, SR9009;
Peroxisome Proliferator Activated Receptor δ (PPAR δ) agonists , e.g. 2-(2-methyl-4-((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methylthio)phenoxy) acetic acid (GW1516, GW501516);
Insulins , and insulin-mimetics;
Meldonium
Trimetazidine

Table 1: WADA 2018 list . The following classes of antiestrogenic substances, on the other hand, are always prohibited both in competition and out of competition.

Data showed are originated from the report commissioned by the Italian Ministry of Health.

The authors have compared the above mentioned data, but they have demonstrate and analyze all

the data but the only spread of S4 classes (Hormone and metabolic modulators).

First of all, it is important to know that hormone and metabolic modulators have been prohibited as doping agents in and out of competition since 2001 for men and since 2005 for women. Generally, irregular is the focus on the consumption of prohibited substances and considered that the control activities of the Anti-Doping Commission began in April 2003. Table 1 shows the lasses of antiestrogenic substances, on the other hand, are always prohibited both in competition and out of competition.

In table 2, the doped athletes from 2007 to 2017 breakdown by substance and by gender. In table 3 are reported the absolute and percentage values of the active substances recorded at the controls, divided by class according to the law 376/2000. In this table, since some (12 athletes) have taken more than one substance, the total number of active substances reported is greater than the number of positive athletes.

Substances Years 200.	7		8-9-10		11		12		13		14		15		16		17	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
cannabinoids	17	5			12	2	20	1	9	1	2	1	5	0	4	0	3	0
Stimulants	11	1			8	5	9	4	4	0	16	0	5	0	4	0	10	0
diuretics and masking agents	5	4			17	3	7	6	6	0	17	10	2	4	2	3	4	1
anabolic agents	3	0			14	2	5	1	20	1	23	0	14	0	3	2	27	1
hormones and related substances	3	0			3	0	7	1	11	0	16	0	3	0	4	0	2	0
corticosteroids	2	0			8	2	3	0	5	1	5	3	3	3	7	0	3	2
beta blockers	1	0						1	0		4	0						
beta agonists					4	0	1	0	1	1	2	1	1	0	2	1	2	1
narcotics											1	0						
hormonal and metabolic modulators													0	1	0	1	2	0

Table 2: Doped athletes from 2007 to 2017. Breakdown by substance and by gender.

cannabinoids (S8)	THC (5)	33.3% TOTAL 33.3%
anabolic agents (S1)	TIBOLONE (2) MESTEROLONE (1) CLOSTEBOL(1)	13.3% 6.7% 6.7% TOTAL 26.7 %
Stimulants (S6)	OXILOFRINA (1) EPHEDRINE (1) TUAMINOEPTANO (1) COCAINE(1)	6.7% 6.7% 6.7% 6.7% TOTAL 26.7 %
hormonal and metabolic modulators (S4)	MELDONIUM (1)	6.7% TOTAL 6.7 %
narcotics (S7)	METHADONE (1)	6.7% TOTAL 6.7 %

Table 3: Absolute and percentage values of active substances registered in 2018 years controls.

In 2018, the highest percentage of active ingredients detected in doping controls belongs to the S8 class of cannabinoids with 33.3%, followed by anabolic agents (26.7% class S1) and stimulants (class S6) with 26.7%.

During 2018, the most controlled events concerned events relating to basketball (21.1%), to football (13.3%) and to swimming (10.2%). The S4 substances have a peak of consumption in 2006 and 2016-2018. In the last years, their use in the is characterized by ups and downs. The statement of employment of combined pill and progestogen only pill in 2018 was 4.5% of all drugs intake.

Conclusion

The Prohibited List category of “Hormone and metabolic modulators” comprises five sub-categories and substances of for the most part diverse physicochemical nature. Amongst these, aromatase inhibitors as well as selective estrogen receptor modulators (SERMs) and other anti-estrogens were measured in particular concerning the possibility to test for their presence in human urine^(14,15). Therefore, strength and combat sports, weightlifting, boxing as well as endurance sports such as cycling and cross-country skiing are affected, but the most widespread abuse occurs in the body building⁽⁹⁾. Hormone and metabolic modulators are substances which influence the hormones and thus modify their effects and which act on the body's metabolism. They have anti-estrogenic effect and are used to prevent the adverse effects of anabolic agents. In the last years, anabolic agents experienced a pointed increase in their consumption in 2008 and 2013, respectively with 37.1% and 35%. The average consumption is 16.9%. Constantly there is an evolution of doping substances and methods⁽¹⁵⁾.

Therefore, each historical period is marked by the use of one or more specific substances or methods, which usually become prohibited only after being identified by the competent anti-doping entities. Current anti-doping strategy is to eliminate the doping in sport, especially in the elite sport.

References

- 1) Kazis K, Iglesias E. (2003).The female athlete triad. Adolesc Med14(1): 87-95
- 2) Montesano, P. (2016). Goalkeeper in soccer: performance and explosive strength. Journal of Physical Education and Sport, 16(1), 230
- 3) Hee L, Kettner LO, Vejtorp M. (2013). Continuous use of oral contraceptives: an overview of effects and side-effects. Acta Obstet Gynecol Scand , 92(2): 125-36. doi: 10.1111/aogs.12036.
- 4) Loveless MB. (2017). Female athlete triad. Curr Opin Obstet Gynecol., 29(5):301-305. doi: 10.1097/GCO.0000000000000396.

- 5) Gibala MJ, Gillen JB, Percival ME (2014) Physiological and health-related adaptations to low-volume interval training: influences of nutrition and sex. *Sports Med*, 44 Suppl 2: S127-37. doi: 10.1007/s40279-014-0259-6.
- 6) Gillen JB, Martin BJ, MacInnis MJ, Skelly LE, Tarnopolsky MA, Gibala MJ (2016) .Twelve Weeks of Sprint Interval Training Improves Indices of Cardiometabolic Health Similar to Traditional Endurance Training despite a Five-Fold Lower Exercise Volume and Time Commitment. *PLoS One*. 2016; 11(4): e0154075.
- 7) Julian R, Hecksteden A, Fullagar HH, Meyer T. (2017) The effects of menstrual cycle phase on physical performance in female soccer players *PLoS One*. 13;12(3):e0173951. doi: 10.1371/journal.pone.0173951.
- 8) Oosthuysen T, Bosch AN (2010) The effect of the menstrual cycle on exercise metabolism: implications for exercise performance in eumenorrhoeic women . *Sports Med*. Mar 1; 40(3): 207-27.
- 9) Chen MN, Lin CC, Liu CF (2015) Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric.*; 18(2): 260-9. doi: 10.3109/13697137.2014.966241
- 10) Constantini NW, Dubnov G, Lebrun CM.(2005) The menstrual cycle and sport performance. *Clin Sports Med*.24(2): 51-82
- 11) Hartgens F, Kuipers H. (2004) Effects of androgenic-anabolic steroids in athletes. *Sports Med.*;34(8):513-54.
- 12) Oosthuysen T, Bosch AN (2017) The Effect of Gender and Menstrual Phase on Serum Creatine Kinase Activity and Muscle Soreness Following Downhill Running. *Antioxidants (Basel)* 23;6(1). pii: E16. doi: 10.3390/antiox6010016
- 13) Deldicque L, Francaux M. (2016) Potential harmful effects of dietary supplements in sports medicine. *Curr Opin Clin Nutr Metab Care* 19(6): 439-445
- 14) Thevis, M., Kuuranne, T., & Geyer, H. (2019). Annual banned-substance review: Analytical approaches in human sports drug testing. *Drug Testing and Analysis*, 11(1), 8-26. doi:10.1002/dta.2549
- 15) Mazzeo, F., Monda, M., Messina, G., Santamaria, S., Messina, A., et al. (2016). Doping in Italy: An analysis of its spread in ten years. *Biology and Medicine*, 8(1) doi:10.4172/0974-8369.1000263

Corresponding Author:
???????