Clinical Therapeutics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Review

Early Pharmacologic Approaches to Avert Anabolic Steroid-induced Male Infertility: A Narrative Review

André Rizzuti, MD[1], Conrado Alvarenga, MD[2], Gustavo Stocker, MD[3], Lucas Fraga, MD[4], Heitor O. Santos, MHS, RD, LDN[5,*]

[1] School of Medicine, Estácio de Sá University (UNESA), Rio de Janeiro, RJ, Brazil
[2] School of Medicine, Department of Urology, University of Sao Paulo (USP), Sao Paulo, Brazil
[3] School of Medicine, University Center Assis Gurgacz Foundation (FAG), Cascavel, PR, Brazil
[4] School of medicine, Santa Casa da misericordia de Vitorica (EMESCAM), Vitória, ES, Brazil
[5] School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, MG, Brazil

ARTICLE INFO

Key words:
Anabolic–androgenic steroids
Male infertility
Semen analysis
Testosterone

ABSTRACT

Purpose: To review the impact of testosterone and other androgenic-anabolic steroids (AASs) on male fertility, exploring potential drugs that can be used to preserve or restore male fertility upon AAS use or prior contact.
Methods: A review was performed to provide a unifying clinical link between drugs used to preserve or restore male fertility (ie, clomiphene citrate, human chorionic gonadotropin, selective estrogen receptor modulators, recombinant luteinizing and follicle-stimulating hormones, and human menopausal gonadotrophin) in the context of AAS-induced infertility and related aspects.
Findings: Human chorionic gonadotropin (125–500 IU every other day), clomiphene citrate (12.5–50 mg/d), recombinant luteinizing hormone (125–500 IU every other day), recombinant follicle-stimulating hormone (75–150 IU 1–3×/wk), and human menopausal gonadotrophin (75–150 IU 1–3×/wk) are promising early pharmacologic approaches to avert AAS-induced male infertility. Additionally, a full partner assessment is crucial to the success of a couple planning to have children. The partner's age and gynecopathies must be considered. Egg or sperm cryopreservation can also be alternatives for future fertility. Reinforcing AAS cessation is imperative to achieving better success in misusers.
Implications: The exponential increase in AAS misuse raises concerns about the impact on male fertility. This review suggests that gonadotropin analogs and selective androgen receptor modulators (clomiphene citrate) are viable approaches to early preserve or restore fertility in men on AAS use or with previous contact. However, proper standardization of doses and combinations is required and hence physicians should also be aware of patients' and partners' fertility.

Introduction

Testosterone (T) and its 5-alpha-reduced metabolite, dihydrotestosterone (DHT), are the main androgens and play a crucial role in sexual differentiation, reproductive function, and behavior, acting on sexual and nonsexual organs (eg, brain, heart, bone, muscle mass, among others).[1] In 1935, Butenandt and Hanisch, concomitantly with Ruzicka and Wettstein, were the pioneers in isolating androgens from urine and testes, affording the ensuing discussion in the clinical scenario.[2,3] Initial androgens indications were created for T replacement therapy (TRT), cachexia, osteosarcopenia, and aplastic anemia thanks to the role of T in enhancing muscle protein synthesis, bone mineral density, and erythropoietic capacity.[4–8] Currently, TRT is widely used as a means of improving the overall quality of life (mainly sexual function) in men with hypogonadism.[9,10] Interestingly, TRT can exert these benefits without increasing the risk of cardiovascular events, while ameliorating cardiometabolic parameters can be expected.[11,12]

Despite the benefits of TRT, the abuse of anabolic steroids (AASs), that is, a drug class including not only T but also DHT (oxandrolone and stanozolol) and nandrolone, has been considered an epidemiological health concern.[13] AAS misuse increases the risk of polycythemia, dyslipidemia, hypertension, left ventricular hypertrophy, and

* Address correspondence to: Heitor O. Santos, MHS, RD, LDN, School of Medicine, Federal University of Uberlandia (UFU), Avenue Pará, 1720, Minas Gerais, Uberlandia 38400-902, MG, Brazil.
E-mail address: heitoroliveirasantos@gmail.com (H.O. Santos).

https://doi.org/10.1016/j.clinthera.2023.09.003
Accepted 3 September 2023
Available online xxx
0149-2918/

Please cite this article as: A. Rizzuti, C. Alvarenga, G. Stocker et al., Early Pharmacologic Approaches to Avert Anabolic Steroid-induced Male Infertility: A Narrative Review, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2023.09.003

psychiatric disorders.[14–17] Overall, the risk of mortality can be 3 times higher in AAS users (particularly those without medical indications) compared to nonusers.[18] Equally important, AAS misuse has grown as a major contributor to the high prevalence of infertility in young and middle-aged individuals and hence cannot be underestimated.[19–21] AAS-induced infertility is a major concern especially for those planning to have children.[22,23] Moreover, many AAS misusers become drug dependent due to fear of coping with unsuccessful T recovery and related side effects, mainly sexual dysfunction and altered body composition in virtue of muscle wasting and increased fat mass.[24]

Further skepticism is warranted in the management of AAS-induced infertility, especially to avoid the unsubstantiated use of nature-based interventions such as some herbal medicines and dietary supplements in severe cases.[25–29] Instead, the focus must be on pharmacologic agents as first-line therapy to recover the hypothalamic–pituitary–testicular (HPT) axis. That said, a critical review to understand the prevalence of AAS-induced infertility and pharmacologic approaches to avert this condition is needed to aid clinical decision-making. Thus, we performed a review in an attempt to provide a more in-depth understanding of the impact of AAS misuse on male fertility, whereby proposals for early pharmacologic approaches are further discussed.

Methods

A review search was performed employing Medline, Embase, Scopus, Cochrane Library, and Web of Science from inception to May 2023. The following keywords were used: “testosterone replacement therapy” or “anabolic androgenic steroids” or “anabolic androgenic steroids abuse” or “anabolic androgenic steroids misuse” and “infertility” or “sperm parameters” or “sperm count” or "sperm quality” or “clomiphene citrate” or “human chorionic gonadotrophin or “hCG” or “selective estrogen receptor modulators” or “SERMs” or “recombinant FSH.” Then, the basic concepts and the clinical findings were discussed in order to unify traditional and recent evidence through a narrative review for practitioners and scientists in the area of andrology and urology.

Definition of Male Infertility

Semen analysis represents the most basic assessment of male infertility. According to the new 6th Edition of the World Health Organization (WHO) manual for human semen analysis, a seminal volume of 1.4 mL (1.3–1.5), sperm concentration of 39 million sperm per ejaculate (35–40), total motility of 42% (40–43), and normal forms of 4% (3.9–4) were reported as one-sided lower reference limits using the lower 5th percentile of fertile men (n = 3589 fertile men from 4 Europe, Americas and Oceania).[30]

Azoospermia, that is, complete absence of sperm in 2 centrifuged samples, affects almost 1% of the male population and about 10% to 15% of all males with infertility.[30,31] Oligozoospermia, in turn, is defined as less than 15 million sperm per milliliter (or 39 million sperm per ejaculate), and severe oligospermia refers to a very low number of sperm, typically less than 5 million per milliliter.[32]

Apart from male infertility per se, the definition of infertile couples must be detailed as well. Infertile couples are usually defined as the inability to conceive after 1 year of regular sexual intercourse without the use of contraceptive methods.[33] When the partner is over 35 years old, infertility may be considered when there is an inability to conceive within 6 months.[34] A recent WHO-funded systematic review with meta-analysis found a pooled lifetime and period prevalence of 12-month infertility of 17.5% and 12.6%, respectively.[35] In addition to the female factor, infertile couples may present both the male and the female factor as a cause, while only the male factor is identified in some cases.[36] However, due to different methodological biases, it is not possible to reliably determine the overall prevalence of male infertility and what is attributable to the male partner alone.[36]

Impaired Sperm Analysis Induced by Supraphysiological Doses of Testosterone

High levels of intratesticular T secreted by Leydig cells are required for spermatogenesis.[37] Infertility often occurs during and after AAS misuse due to negative feedback of androgens on the HPT axis,[38] where high serum T levels reduce the secretion of gonadotropin release hormone by the hypothalamus and consequently decrease or even completely inhibit the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[39,40]

While serum T levels may be high in the bloodstream on T administration, the accompanied low LH and FSH levels decrease intratesticular T, which is needed for synthesis and maturation of sperm cells.[41] In addition to the reduced intratesticular T production, low FSH levels can also reduce the testicular cells capacity to uptake T, since FSH stimulates the production of androgen-binding protein, a protein responsible for sequestering T in the testis.[42] Not surprisingly, only ~18% of men with a history of AAS misuse have any morphologically normal sperm.[41]

The effect of supraphysiological doses of T on fertility was evaluated in a series of studies, starting in the 90s.[43–45] In 1990, Matsumoto et al. revealed supraphysiological T regimens (ie, ≥ 100 mg weekly) maximally suppress sperm count.[45] Healthy men were divided into 5 groups: one receiving placebo and the others receiving T enanthate at 25, 50, 100, and 300 mg weekly for 6 months.[45] While T at 25 and 50 mg partially suppressed sperm count, 100 and 300 mg maximally suppressed the spermatogenesis in the subjects leading to severe oligospermia or azoospermia.[45]

Two studies by the World Health Organization Task Force on Methods for the Regulation of Male Fertility, published in 1990 and 1996, evaluated the use of 200 mg of intramuscular T enanthate for male contraception in previously eugonadal men and the average time to occurrence of severe oligospermia or azoospermia was 91 to 120 days.[43,44] In the 1990 WHO study, more than 70% of the patients developed azoospermia in the hormone suppression phase, and those who did not become azoospermic had severe oligozoospermia.[43] In the 1996 WHO study, only 2.2% did not reach azoospermia after the hormone suppression phase.[44]

T undecanoate elicits severe oligozoospermia or zoosperm.[46–48] In 2003, Gu et al.,[47] in healthy fertile Chinese men, evaluated the efficacy of T undecanoate for achieving male contraception at an initial dose of 1000 mg followed by monthly doses of 500 mg for 12 months. An overall contraceptive efficacy of 94.8% was reported, but spermatogenesis in all participants returned to the normal reference range during the recovery period, which covered 12 months after cessation of T undecanoate.[47] Moreover, in 2009, Gu et al.,[46] employing an intervention of monthly T undecanoate at 500 mg for 30 months observed a pregnancy rate in the partners of 6.1%, of which 4.8% and 1.3% accounted for inadequate suppression and postsuppression sperm rebound, respectively.

Taken together, the time to reach azoospermia or oligozoospermia on supraphysiological T doses through the above-mentioned RCTs can be seen in Table 1.

Beyond Testosterone: The Impact of Other AASs on Sperm Analysis

In addition to T misuse, other AASs contribute to the burden of impaired sperm parameters. However, there is a lack of RCTs focusing on the impact of particular AASs on sperm analysis other than T. Regardless of being T derivative (eg, methandienone and boldenone), DHT derivative (eg, oxandrolone, oxymetholone, and stanozolol), or 19-nortestosterone (eg, trenbolone and nandrolone), AASs seemingly inhibit the HPT axis proportionally to dose and time of use, causing severe inhibition of LH and FSH and thus impairing sperm parameters.[7]

Nandrolone misuse and its negative effects on the HPT axis and sperm parameters are widely reported.[49–54] Correspondingly, nandrolone doses at 100 mg to 200 mg weekly induced azoospermia within

Table 1
Time to reach azoospermia or oligozoospermia on supraphysiological intramuscular T doses (intramuscular injection) through randomized clinical trials.

Studies	T Ester	Dose	Time to Reach Azoospermia or Oligozoospermia (<3 Million Sperm/mL)
WHO[43]	Enanthate	200 mg weekly	120 days
WHO[44]	Enanthate	200 mg weekly	91–112 days
Gu et al.[47]	Undecanoate	1000 mg initial + 500 mg monthly for 6 months	150 days
Gu et al.[46]	Undecanoate	1000 mg initial + 500 mg monthly for 6 months	108 days
Matsumoto et al.[45]	Enanthate	25 mg, 50 mg, 100 mg, 300 mg weekly for 6 months	100 mg and 300 mg weekly lead to oligo/azoospermia after 180 days

7 to 13 weeks of administration.[53] Moreover, methandienone, a T derivative, at 15 mg/d, decreased sperm density by 46% in the first month and by 73% after 2 months.[55]

Collectively, LH and FSH levels are expected to increase after AAS cessation, but low T levels and impaired sperm analysis can be observed even at 8 to 30 weeks of AAS withdrawal.[13,45,56–58] At best, according to many reports, sperm quality tends to spontaneously normalize within 4 to 12 months after cessation of AAS misuse.[23,59,60] Furthermore, fertility restoration has been reported even in situations of persistent azoospermia up to 5 years after the AAS cessation, however, the negative effect on sperm quality can persist for long periods in many patients and requires pharmacologic induction of spermatogenesis.[13,61]

Illicit AAS Use for Performance in Athletes and Nonathlete Exercisers

The off-label and illicit AAS use has gained interest in sports and fitness circles aiming at enhancing performance and body composition—that is, incrementing muscle mass while decreasing fat mass.[62,63] In the late 1980s, scandals became more frequent until the creation of the World Anti-Doping Agency (WADA) in 1999.[64–66] WADA reported T and nandrolone as the most tested compounds classified as banned substances in class S1.[67]

The global lifetime prevalence rate of AAS use is estimated at ~3% in the general public and at ~6% in males.[68] Estimates can rise to ~32% to 40% or more in gym-goers, particularly the highly experienced ones.[69,70] No wonder AAS misuse is closely associated with an impaired reproductive system of athletes and nonathletes alike aiming at improving body composition and strength.[13] Currently, bodybuilding is a sport whereby AAS-induced infertility is an issue, as the main competition is doping-free. The common profile of an AAS user comprises male individuals, aged between 20 and 40 years, and who practice bodybuilding or seek to behave like a bodybuilder.[71] Correspondingly, reduced fertility was one of the most significant long-term adverse effects in 20 male bodybuilders on AAS misuse over a 2-year period.[56,69]

Although male bodybuilders and other athletes of drug-free sports such as strongmen and power lifters may neglect infertility in the middle term, as competition tends to be a life priority, infertility and related changes in sperm parameters can be an issue in the long term over the AAS abuse.

Despite the satisfactory restoration of spermatogenesis observed in the studies described in Table 1, well-designed and controlled long-term studies in athletes and nonathlete exercisers using higher doses of T and combinations with other AASs and performance-enhancing drugs are lacking, as this is unethical due to the plausibility of deleterious effects.

At best, personalized pharmacologic approaches in an attempt to avert AAS-induced infertility in athletes of drug-free sports and nonathlete exercisers are proposed below.

Pharmacologic Approaches

Despite the miscellaneous benefits of TRT for men with hypogonadism, guidelines of the *European Journal of Endocrinology and Endocrine Society* contraindicate TRT for men with hypogonadism who desire fertility.[19,21] Not surprisingly, TRT has been studied as a contraceptive method,[43,44,72] although it cannot be considered as efficient and safe as condoms and vasectomy.[73]

Different pharmacologic regimens are described to avert AAS-induced male infertility, for example, selective estrogen receptor modulators (SERMs) such as clomiphene citrate and tamoxifen, human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and even recombinant FSH.[39,74] Interestingly, recent studies have suggested the use of hCG during TRT for fertility maintenance.[75–77]

SERMs

SERMs are a class of drugs that bind with high affinity to the estrogen receptor and act as estrogen receptor agonists or antagonists depending on the tissue.[78,79]

Clomiphene citrate (38% zuclomiphene citrate plus 62% enclomiphene citrate) is the most widely drug used in the fertility field.[80] As an estrogen agonistic, clomiphene citrate competes with estradiol (E2) for estrogen receptors in the hypothalamus and blocks the negative feedback of circulating E2 on the HPT axis, thereby increasing LH levels, endogenous T, and spermatogenesis.[81,82] The dosing regimen used varies from 12.5 to 50 mg/d, with most studies using 12 to 25 mg/d.[83–85] Doses higher than 50 mg/d apparently does not lead to a better response because zuclomiphene agonist effect can blunt the antagonist effect on estrogen receptor responsible to increase the positive feedback on the HPT axis.[80]

The benefits are not indisputable insofar as impaired semen analysis can be presented in some subjects on clomiphene. As reported by a systematic review including 384 sub-fertility men from 11 cohorts, 19%, 21%, 17%, and 24% of clomiphene-treated subjects suffered from a decrease in sperm count, concentration, motility and total motile sperm count, respectively.[86] Moreover, after clomiphene discontinuation, deterioration in semen parameters did not recover in up to 17% of subjects.

The side effects of clomiphene seem to be mild and well tolerated. The most common ones include headaches, dizziness, blurred vision, nausea, vomiting, gynecomastia, weight gain, hypertension, and even a paradoxical decrease in total T levels.[86,87]

LH Receptor Agonists: hCG and Recombinant LH

Urinary hCG is obtained by collecting urine from early-stage pregnant women for medical use.[88,89] Urine is filtered, concentrated, and purified using techniques such as ion exchange or affinity chromatography to extract the hCG hormone.[88,89] hCG acts as an LH analog, with the added benefit of a longer half-life.[89] By mimicking LH, hCG acts on Leydig cells by stimulating the production and release of intratesticular T.[75,88,90]

An RCT of healthy males using 200 mg of intramuscular T enanthate weekly to suppress intratesticular T found that low doses of hCG (125–500 IU every other day) for 3 weeks dose-dependently preserved intratesticular T, while the group using T alone had a 94% reduction in intratesticular T production.[76] In an observational study of men (n = 29) on TRT, combined hCG therapy (500 IU every other day) for approximately 1 year preserved semen analysis values and 9 patients were able to get their partners pregnant.[77]

Recombinant LH, a synthetic form of LH produced naturally in the pituitary gland, is another way to bind directly to LH receptors.[91] Such a

drug is produced using recombinant DNA technology, in which the DNA sequence that encodes the hormone is inserted into culture cells capable of producing large amounts of recombinant LH.[91] Recombinant LH is used in fertility treatments to stimulate ovulation in women who do not ovulate normally.[91] Recombinant LH is administered by subcutaneous injection and differs from urinary hCG in that it has greater potency in modulating LH receptors.[91,92] To date, however, there are no RCTs using recombinant LH rather than urinary hCG to assess intratesticular T levels on TRT.[92,93]

The most common side effect of subcutaneous hCG and recombinant LH was local swelling at the injection site after injection, mild gynecomastia, acne, headache, restlessness, tiredness, swelling of the ankles and feet, and mood changes.[94]

hMG

Human menopausal gonadotropin is a natural derivative of urine with action on LH and FSH receptors.[95] The evolution of isolation and filtration methods has afforded a highly purified hMG with greater actions on the FSH receptor, reducing the number of inactive proteins present in less purified hMG.[96] The FSH-like effect is important for providing indirect structural and metabolic support for spermatogenesis via FSH receptors on Sertoli cells, regulating structural genes involved in the organization of cell junctions and genes required for the metabolism and transport of regulatory and nutritional substances from Sertoli to germ cells.[97,98] In the testes, endothelial FSH receptors mediate the FSH transport across the gonadal endothelial barrier.[99,100] FSH also has a regulatory role in Sertoli cell number that is critical for maintaining spermatogenesis.[100]

Taken together, hMG therapy ranges from 75 to 150 IU once to 3 times a week and is commonly added to the fertility recovery protocol if the response to urinary hCG or recombinant LH alone fails to improve sperm count and quality satisfactorily.[43,44,101] In men with AAS-induced infertility, that is, a hypogonadotropic hypogonadism pattern, combined therapy of hCG and hMG (1500–5000 IU for hCG and 75–150 IU for hMG, 3× weekly) for a median of 26 months (range 6–57) allowed 40% of patients (35 of 87) to achieve one or more pregnancies.[102]

As above-mentioned, studies assessing the effects of hMG in men have combined the therapy with other pharmacologic agents such as hCG. Case reports associate hMG administration with gynecomastia, dizziness, fainting, headache, loss of appetite, and irregular heartbeat.[103] However, it is difficult to infer the side effects of a specific medication with the coexistence of other drugs. Correspondingly, hCG administration could be responsible for most of the effects such as gynecomastia, acne, and mood changes due to the rapid rise in T levels and subsequent fluctuations.[94,95,103]

Recombinant FSH

Recombinant FSH, also known as follitropin alpha, is an alternative to hMG. The technology is based on the human FSH gene insertion into a host cell and purified from the culture medium, resulting in a highly pure drug biologically identical to human FSH.[104–106] However, its cost can be an obstacle for the patient and hence may be included later in the protocol in the absence of response to hCG and clomiphene.[75]

Considering its higher biological activity and cost, recombinant FSH administration at 75–150 IU 3 times weekly has become an option when LH agonists fail to improve sperm parameters.[101] Research on recombinant FSH also combines treatment with LH analogs, making it challenging to specifically attribute isolated effects.[88,102,107] Nevertheless, findings consistently indicate that elevated T levels are a causal factor.[108] Recombinant FSH presents a similar profile to hMG, with studies describing mild reactions at the injection site and increases in red blood cell count, hemoglobin, hematocrit, and creatinine levels.[102]

Aromatase Inhibitors

Aromatase inhibitors are a class of drugs used in hormone therapy to treat hormone receptor-positive breast cancer, as well as certain conditions such as endometriosis and infertility.[109] The primary function of aromatase inhibitors is to block the activity of aromatase, an enzyme responsible for converting androgens into estrogens, particularly E2.[110] Anastrozole and letrozole are 2 commonly used aromatase inhibitors that reversibly bind to the aromatase active site, thereby inhibiting its function.[109]

Recent studies have been conducted with letrozole in men with a T/E2 ratio lower than 10 and even with a normal T/E2 ratio, in which aromatase inhibitors appear to assist in the recovery of the HPT axis and improvement of sperm parameters.[111–113] The use of letrozole in combination with hCG appears to favor a more significant improvement in semen analysis compared to using both substances individually.[111] The proposed mechanism involves enhancing positive feedback and reducing negative feedback caused by the imbalance between T/E2.[112,113]

Common side effects of aromatase inhibitors may include hot flashes, joint pain, fatigue, and increased susceptibility to osteoporosis and fractures in women due to reduced estrogen levels.[109] In males, hypoestrogenism can induce similar effects, particularly joint pain, and sexual dysfunction.[114–116] Therefore, the administration of these medications should be exercised with caution to prevent the development of a hypoestrogenic state.[114,117]

Proposed Dosing Regimens and Clinical Considerations

Taken together, the proposed pharmacologic regimens discussed here to avert AAS-induced male infertility, along with clinical considerations, are summarized in Figure 1.

Behavioral Approach

The proposed interventions in the flowchart of Figure 1 consider the main factors associated with the male and couple´s fertility. The initial step toward successful treatment and recovery from AAS misuse must be a behavioral approach. This has been recognized by the guidelines for treating AAS misuse[119]; however, the way physicians deal with patients in the real-world scenario is far from ideal.[119–121]

In light of this, motivational interviewing (MI) can be a useful tool for AAS misusers who show signs of infertility awareness. MI is a person-centered strategy originating in the field of addiction which mixes components of cognitive-behavioral therapy and elements that encourage and strengthen the relationship between patient and professional to build trust.[122–124] MI is the opposite of vertical care, in which the professional is the authority over the patient.[122] This approach keeps the clinician closer to the patient, allowing greater patient's motivation for change through reflections on life goals and values.[122]

Pharmacologic Regimens

In addition to the behavioral approach, the pharmacologic approach is of crucial importance, and both should be implemented together. Pharmacologic protocols consist of LH analogs such as hCG with or without SERMs even before discontinuing AASs.[39,101,102] Collectively, pharmacologic approach can be useful for future success in achieving couples pregnancy, especially when considering the partner's age, gynecological status, and the time to recovery of male spermatogenesis, whose severity of the latter depends on patients' age and time of AAS misuse.[125]

The use of clomiphene is the starting point for restoring the HPT axis and fertility in hypogonadotropic hypogonadism, particularly considering cost.[126] The usual dose regimen varies from 12.5 to 25 mg/d or every other day.[127] Conversely, its effectiveness seems to be limited

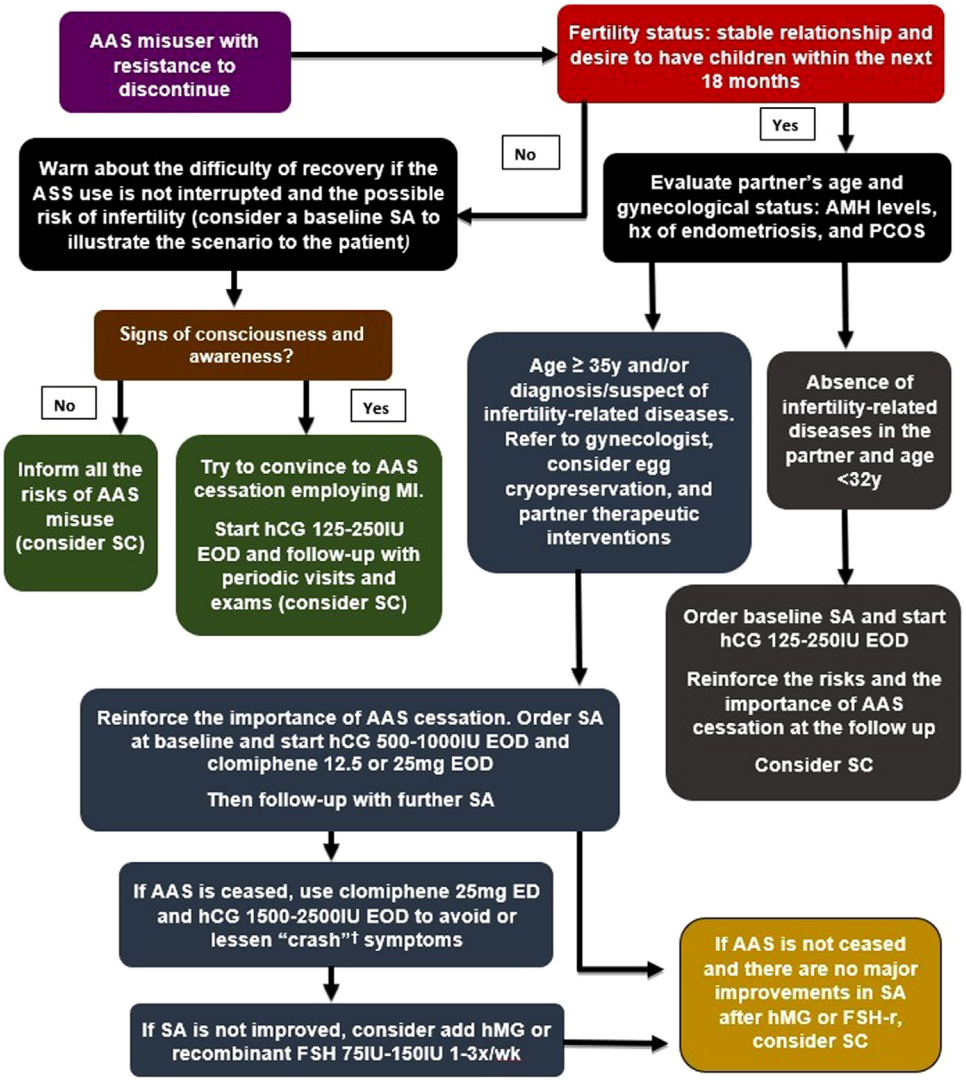

Figure 1. Proposed pharmacologic regimens to restore male fertility after AAS use. AAS = anabolic androgenic steroids; AI = aromatase inhibitors; AMH = anti-Müllerian hormone; E2 = estradiol; ED = every day; EOD = every other day; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; hx = medical history; MI = motivational interview; PCOS = polycystic ovary syndrome; SA = semen analysis; SC = sperm cryopreservation; T = testosterone. † "Crash" symptoms can occur after AAS withdrawal; when androgen levels drop to deficiency levels and hence lead to mood disorders, low libido, and sexual problems.[118]

concerning the duration of use and may even lead to a paradoxical worsening of the semen analysis.[86,128] A plateau effect can occur within 3 to 6 months of use[128]; nevertheless, combining clomiphene citrate with an LH agonist or switching one for the other may overcome this potential desensitization due to the direct binding mechanism of a LH agonist as hCG.[129]

The dosing regimen of urinary hCG or recombinant LH, both at 125–500 IU every other day, can be prescribed early to improve sperm parameters. These drugs can be combined with clomiphene citrate or alone after screening for sperm analysis during follow-up.[76,77]

Combining hMG with recombinant FSH, both at 75–150 IU 1 to 3 times a week, is also conceivable in an attempt to enhance spermatogenesis recovery intra-AAS use or after cessation.[23,39,75–77,101,102] If cost is not an issue, an early introduction of recombinant FSH may help a faster recover given its direct effect on FSH receptors, but this strategy is not mandatory.[130,131]

Aromatase inhibitors can be combined with gonadotrophin analogs and SERMs since the rise in T levels by these drugs can increase E2 levels disproportionally due to negative feedback.[132] Aromatase inhibitors may be used when the ratio of T (ng/dL) to E2 (pg/mL) falls above 10.[39,111,112,133] Anastrozole can reduce E2 levels by approximately 70% to 80% at 1 mg per day.[110,134,135] Letrozole at 2.5 mg per day can achieve a similar degree of E2 suppression, approximately 80% to 90%.[109,110,112] In contrast, it is important to monitor E2 levels when taking aromatase inhibitors, as low E2 levels can cause problems such as sexual dysfunction.[116] Lower doses must be considered if compounding medications are available.[114,136]

Full Partner Assessment

A full partner assessment is crucial to the success of the couple planning to have children.[33] The partner's age is one of the main factors to consider. Women under 30 years have an 85% and 75% chance of conceiving at 12 and 30 months, respectively, and this progressively declines to 66% and 44% at ages 35 and 40 years, respectively.[137] The presence of gynecopathies such as endometriosis and polycystic ovary syndrome are important factors in the partner assessment, as they are associated with women's infertility.[138,139] Thus, age and gynecopathies must be approached together.[33]

Complementary Laboratory Markers

The anti-Müllerian hormone (AMH) is an important marker of female fertility that has recently gained attention as a potential marker of ovarian reserve and gonadotropin response.[140,141] Since AMH is secreted by the ovary,[142] its serum levels essentially reflect the ovarian follicular pool, such that a reduction in the number of small growing follicles may be followed by low circulating AMH levels, whose phenomena can diminish lifespan.[143]

Regarding younger partners without gynecopathies, if the man is approached with an early intervention with hCG or recombinant LH agonist to partially maintain testicular function, intratesticular T can be monitored through 17OH-progesterone levels.[75,144,145]

Cryopreservation

Sperm cryopreservation can also be an alternative for men who desire future fertility without a stipulated period.[146] The sample can be collected after introducing a protocol with hCG, SERMs, and other gonadotropin analogs if necessary.[146,147] Sperm cryopreservation techniques have been increasingly developed and have proven to be effective and safe in maintaining the integrity of sperm DNA.[148,149]

Oocyte cryopreservation can be a safe option as an alternative line for the couple if the man has difficulties in improving sperm parameters in a short-time window and the partner is ≥35 years old.[137,150] However, oocyte cryopreservation is a relatively new procedure for nonfemale factor and there are ethical implications to be debated, in which the potential for women to chronically delay childbearing may increase the risk of pregnancy and childbirth complications.[151,152] The commodification of female bodies and the social background impact children born from cryopreserved eggs more than children born to younger mothers, hence raising caveats against child's identity and sense of belonging.[151,152] Other concerns involve the cost of oocyte cryopreservation and the success rate of the procedure.[151]

AAS Misuse

Practitioners must exercise empathetic skills in order not to judge AAS misusers, but is it crucial to reinforce AAS misuse as a potential concern that adds to others related to male infertility, as ceasing AAS misuse is a clinical barrier in the long term. The intervention can change the patient's prognosis especially if it is done early and evaluating the partner's status, which is often not approached earlier.

Ultimately, beyond fertility, concurrent nonpharmacologic approaches can be adopted to minimize muscle loss after discontinuing AASs, for example, high protein intake (~1.6–2.2 g/kg/d),[153,154] creatine supplementation (~5 g/d),[155] and a proper volume of resistance training.[156,157]

Conclusion

SERMs (clomiphene citrate), hCG, or recombinant LH agonists associated or not with hMG or recombinant FSH may be useful and effective approaches to early avert AAS-induced male infertility. Thus, dosing regimens can be personalized during AAS use or after cessation according to a series of factors beyond the reproductive wish time. Early assessment of partners' fertility is essential to formulate individualized recommendations and increase success in conceiving in couples when this is a goal. Time is crucial and the partner component of fertility and/or cryopreservation of sperm and eggs must also be considered according to particular situations.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgments

HOS has been supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brazil (CAPES).

Author Contributions

The authors' responsibilities were as follows—AR: design, data management, and writing; CA: writing; GS: writing; LF: writing; HOS: design, writing, and final content of the paper; and all authors: read and approved the final manuscript.

References

1. Wilson JD. The role of 5alpha-reduction in steroid hormone physiology. *Reprod Fertil Dev*. 2001;13:673–678.
2. Butenandt A, Hanish G, Butenandt A, Hanisch G. Umwandlung des Dehydroandrosterons in Androstendiol und Testosteron; ein Weg zur Darstellung des Testosterons aus Cholesterin. *Hoppe-Seyler Z Physiol Chem*. 1935;237:89–98.
3. Ružička L, Wettstein A. Über die kunstliche Herstellung des Testikelhormons Testosteron (Androsten-3-on-17-ol).[Synthesis of the testicular hormone (testosterone)(androstene 3-on-17-ol)]. *Helv Chim Acta*. 1935;18:1264–1275.
4. Nieschlag E, Behre HM, Nieschlag S. *Testosterone: Action, Deficiency, Substitution*. Cambridge University Press; 2012.
5. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men: a clinical research center study. *J Clin Endocrinol Metab*. 1996;81:3469–3475.
6. Katznelson L, Finkelstein JS, Schoenfeld DA, et al. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab*. 1996;81:4358–4365.
7. Kicman AT. Pharmacology of anabolic steroids. *Br J Pharmacol*. 2008;154:502–521.
8. Gardner FH. Androgen therapy of aplastic anaemia. *Clin Haematol*. 1978;7:571–585.
9. Khera M, Bhattacharya RK, Blick G, et al. Improved sexual function with testosterone replacement therapy in hypogonadal men: real-world data from the Testim Registry in the United States (TRiUS). *J Sex Med*. 2011;8:3204–3213.
10. Rizzuti A, Stocker G, Santos HO. Exploring the role of testosterone replacement therapy in benign prostatic hyperplasia and prostate cancer: a review of safety. *URO*. 2022;2:30–39.
11. Shores MM, Walsh TJ, Korpak A, et al. Association between testosterone treatment and risk of incident cardiovascular events among US male veterans with low testosterone levels and multiple medical comorbidities. *J Am Heart Assoc*. 2021;10:e020562.
12. Li SY, Zhao YL, Yang YF, et al. Metabolic effects of testosterone replacement therapy in patients with type 2 diabetes mellitus or metabolic syndrome: a meta-analysis. *Int J Endocrinol*. 2020;2020:4732021.
13. Christou MA, Christou PA, Markozannes G, et al. Effects of anabolic androgenic steroids on the reproductive system of athletes and recreational users: a systematic review and meta-analysis. *Sports Med*. 2017;47:1869–1883.
14. Achar S, Rostamian A, Narayan SM. Cardiac and metabolic effects of anabolic-androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm. *Am J Cardiol*. 2010;106:893–901.
15. Kanayama G, Hudson JI, Pope Jr HG. Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse: a looming public health concern? *Drug Alcohol Depend*. 2008;98:1–12.
16. de Souza GL, Hallak J. Anabolic steroids and male infertility: a comprehensive review. *BJU Int*. 2011;108:1860–1865.
17. Harvey O, Keen S, Parrish M, van Teijlingen E. Support for people who use anabolic androgenic steroids: a systematic scoping review into what they want and what they access. *BMC Public Health*. 2019;19:1024.
18. Horwitz H, Andersen JT, Dalhoff KP. Health consequences of androgenic anabolic steroid use. *J Intern Med*. 2019;285:333–340.
19. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103:1715–1744.
20. van Hulsteijn LT, Pasquali R, Casanueva F, et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. *Eur J Endocrinol*. 2020;182:11–21.
21. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization: European Society of Endocrinology. *androl*. 2020;8:970–987.
22. Kanayama G, Hudson JI, DeLuca J, et al. Prolonged hypogonadism in males following withdrawal from anabolic-androgenic steroids: an under-recognized problem. *Addiction*. 2015;110:823–831.
23. Al Hashimi M. The deleterious effects of anabolic androgenic steroid abuse on sexual and reproductive health and comparison of recovery between treated and untreated patients: single-center prospective randomized study. *Andrologia*. 2022;54:e14576.
24. Kanayama G, Hudson JI, Pope Jr HG. Anabolic-androgenic steroid use and body image in men: a growing concern for clinicians. *Psychother Psychosomat*. 2020;89:65–73.
25. Santos HO, Cadegiani FA, Forbes SC. Nonpharmacological interventions for the management of testosterone and sperm parameters: a scoping review. *Clin Ther*. 2022;44:1129–1149.
26. Santos HO, Howell S, Nichols K, Teixeira FJ. Reviewing the evidence on vitamin D supplementation in the management of testosterone status and its effects on male reproductive system (testis and prostate): mechanistically dazzling but clinically disappointing. *Clin Ther*. 2020;42:e101–e114.
27. Santos HO, Teixeira F. Use of medicinal doses of zinc as a safe and efficient coadjutant in the treatment of male hypogonadism. *The Aging Male*. 2020;23:669–678.
28. Santos HO, Howell S, Teixeira FJ. Beyond tribulus (Tribulus terrestris L.): the effects of phytotherapics on testosterone, sperm and prostate parameters. *J Ethnopharmacol*. 2019;235:392–405.

29. Santos HO. Ketogenic diet and testosterone increase: is the increased cholesterol intake responsible? To what extent and under what circumstances can there be benefits? *Hormones (Athens, Greece)*. 2017;16:266–270.
30. Boitrelle F, Shah R, Saleh R, et al. The sixth edition of the WHO manual for human semen analysis: a critical review and SWOT analysis. *Life (Basel, Switzerland)*. 2021;12:1368.
31. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. *J Urol*. 1989;142:62–65.
32. Aziz N. The importance of semen analysis in the context of azoospermia. *Clinics (Sao Paulo, Brazil)*. 2013;68(suppl 1):35–38.
33. Carson SA, Kallen AN. Diagnosis and management of infertility: a review. *JAMA*. 2021;326:65–76.
34. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril*. 2008;90:S60.
35. Cox CM, Thoma ME, Tchangalova N, et al. Infertility prevalence and the methods of estimation from 1990 to 2021: a systematic review and meta-analysis. *Hum Reprod Open*. 2022;2022:hoac051.
36. Barratt CLR, Björndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities. *Hum Reprod Update*. 2017;23:660–680.
37. Sidhom K, Panchendrabose K, Mann U, Patel P. An update on male infertility and intratesticular testosterone-insight into novel serum biomarkers. *Int J Imp Res*. 2022;34:673–678.
38. El Osta R, Almont T, Diligent C, Hubert N, Eschwège P, Hubert J. Anabolic steroids abuse and male infertility. *Basic Clin Androl*. 2016;26:2.
39. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. *Asian J Androl*. 2016;18:373–380.
40. Oduwole OO, Huhtaniemi IT, Misrahi M. The roles of luteinizing hormone, follicle-stimulating hormone and testosterone in spermatogenesis and folliculogenesis revisited. *Int J Mol Sci*. 2021;23:12735.
41. Esposito M, Salerno M, Calvano G, et al. Impact of anabolic androgenic steroids on male sexual and reproductive function: a systematic review. *Panminerva Med*. 2023;65:43–50.
42. Hall SH, Conti M, French FS, Joseph DR. Follicle-stimulating hormone regulation of androgen-binding protein messenger RNA in Sertoli cell cultures. *Mol Endocrinol (Baltimore, MD)*. 1990;4:349–355.
43. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet (London, England)*. 1990;336:955–959.
44. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril*. 1996;65:821–829.
45. Matsumoto AM. Effects of chronic testosterone administration in normal men: safety and efficacy of high dosage testosterone and parallel dose-dependent suppression of luteinizing hormone, follicle-stimulating hormone, and sperm production. *J Clin Endocrinol Metab*. 1990;70:282–287.
46. Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. *J Clin Endocrinol Metab*. 2009;94:1910–1915.
47. Gu YQ, Wang XH, Xu D, et al. A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab*. 2003;88:562–568.
48. Zhang GY, Gu YQ, Wang XH, et al. A clinical trial of injectable testosterone undecanoate as a potential male contraceptive in normal Chinese men. *J Clin Endocrinol Metab*. 1999;84:3642–3647.
49. Bijlsma JW, Duursma SA, Thijssen JH, Huber O. Influence of nandrolondecanoate on the pituitary-gonadal axis in males. *Acta Endocrinol (Copenh)*. 1982;101:108–112.
50. Barone R, Pitruzzella A, Marino Gammazza A, et al. Nandrolone decanoate interferes with testosterone biosynthesis altering blood-testis barrier components. *J Cell Mol Med*. 2017;21:1636–1647.
51. Karbalay-Doust S, Noorafshan A, Ardekani FM, Mirkhani H. The reversibility of sperm quality after discontinuing nandrolone decanoate in adult male rats. *Asian J Androl*. 2007;9:235–239.
52. Hemmersbach P, Grosse J. Nandrolone: a multi-faceted doping agent. *Handb Exp Pharmacol*. 2010:127–154.
53. Schürmeyer T, Knuth UA, Belkien L, Nieschlag E. Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. *Lancet (London, England)*. 1984;1:417–420.
54. Knuth UA, Behre H, Belkien L, et al. Clinical trial of 19-nortestosterone-hexoxyphenylpropionate (Anadur) for male fertility regulation. *Fertil Steril*. 1985;44:814–821.
55. Holma PK. Effects of an anabolic steroid (metandienone) on spermatogenesis. *Contraception*. 1977;15:151–162.
56. Bonetti A, Tirelli F, Catapano A, et al. Side effects of anabolic androgenic steroids abuse. *Int J Sports Med*. 2008;29:679–687.
57. Karila T, Hovatta O, Seppälä T. Concomitant abuse of anabolic androgenic steroids and human chorionic gonadotrophin impairs spermatogenesis in power athletes. *Int J Sports Med*. 2004;25:257–263.
58. Knuth UA, Maniera H, Nieschlag E. Anabolic steroids and semen parameters in bodybuilders. *Fertil Steril*. 1989;52:1041–1047.
59. Turek PJ, Williams RH, Gilbaugh 3rd JH, Lipshultz LI. The reversibility of anabolic steroid-induced azoospermia. *J Urol*. 1995;153:1628–1630.
60. de la Torre Abril L, Ramada Benlloch F, Sánchez Ballester F, et al. Management of male sterility in patients taking anabolic steroids. *Arch Esp Urol*. 2005;58:241–244.
61. Dohle GR, Smit M, Weber RF. Androgens and male fertility. *World J Urol*. 2003;21:341–345.
62. Kanayama G, Pope Jr HG. History and epidemiology of anabolic androgens in athletes and non-athletes. *Mol Cell Endocrinol*. 2018;464:4–13.
63. Santos HO and Haluch CEJM. Downregulation of androgen receptors upon anabolic-androgenic steroids: a cause or a flawed hypothesis of the muscle-building plateau? 2022;1:92-101.
64. Ljungqvist A. Brief history of anti-doping. *Med Sport Sci*. 2017;62:1–10.
65. Fitch K. Proscribed drugs at the Olympic Games: permitted use and misuse (doping) by athletes. *Clin Med (Lond)*. 2012;12:257–260.
66. Fraser AD. Doping control from a global and national perspective. *Ther Drug Monit*. 2004;26:171–174.
67. Saudan C, Baume N, Robinson N, et al. Testosterone and doping control. *Br J Sports Med*. 2006;40(suppl 1):i21–i24.
68. Sagoe DJIJoE. Abstract#: 2190 The global epidemiology of anabolic steroid use. Ann Epidemiol. 2015;44:1.
69. Tahtamouni LH, Mustafa NH, Alfaouri AA, et al. Prevalence and risk factors for anabolic-androgenic steroid abuse among Jordanian collegiate students and athletes. *Eur J Public Health*. 2008;18:661–665.
70. Abrahin OSC, Souza NSF, ECd Sousa, et al. Prevalência do uso e conhecimento de esteroides anabolizantes androgênicos por estudantes e professores de educação física que atuam em academias de ginástica %. *J Rev Brasil Med Esport*. 2013;19:27–30.
71. de Ronde W, Smit DL. Anabolic androgenic steroid abuse in young males. *Endocr Connect*. 2020;9:R102–r111.
72. Patel AS, Leong JY, Ramos L, Ramasamy R. Testosterone is a contraceptive and should not be used in men who desire fertility. *World J Mens Health*. 2019;37:45–54.
73. Abbe CR, Page ST, Thirumalai A. Male contraception. *Yale J Biol Med*. 2020;93:603–613.
74. Boyadjiev NP, Georgieva KN, Massaldjieva RI, Gueorguiev SI. Reversible hypogonadism and azoospermia as a result of anabolic-androgenic steroid use in a bodybuilder with personality disorder. A case report. *J Sports Med Phys Fitness*. 2000;40:271–274.
75. Lee JA, Ramasamy R. Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men. *Transl Androl Urol*. 2018;7:S348–s352.
76. Coviello AD, Matsumoto AM, Bremner WJ, et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. *J Clin Endocrinol Metab*. 2005;90:2595–2602.
77. Hsieh TC, Pastuszak AW, Hwang K, Lipshultz LI. Concomitant intramuscular human chorionic gonadotropin preserves spermatogenesis in men undergoing testosterone replacement therapy. *J Urol*. 2013;189:647–650.
78. Mirkin S, Pickar JH. Selective estrogen receptor modulators (SERMs): a review of clinical data. *Maturitas*. 2015;80:52–57.
79. An KC. Selective estrogen receptor modulators. *Asian Spine J*. 2016;10:787–791.
80. Fontenot GK, Wiehle RD, Podolski JS. Differential effects of isomers of clomiphene citrate on reproductive tissues in male mice. *BJU Int*. 2016;117:344–350.
81. Puia D, Pricop C. Effectiveness of clomiphene citrate for improving sperm concentration: a literature review and meta-analysis. *Cureus*. 2022;14:e25093.
82. Liao Y, Chang YK, Wang SM, Chang HC. Ceiling effect of clomiphene citrate on the testosterone to estradiol ratio in eugonadal infertile men. *PLoS One*. 2022;17:e0262924.
83. Sharma D, Zillioux J, Khourdaji I, et al. Improvements in semen parameters in men treated with clomiphene citrate: a retrospective analysis. *Andrologia*. 2019;51:e13257.
84. Kim ED, McCullough A, Kaminetsky J. Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. *BJU Int*. 2016;117:677–685.
85. Mićić S, Dotlić R. Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men. *J Urol*. 1985;133:221–222.
86. Gundewar T, Kuchakulla M, Ramasamy R. A paradoxical decline in semen parameters in men treated with clomiphene citrate: a systematic review. *Andrologia*. 2021;53:e13848.
87. Patel DP, Brant WO, Myers JB, et al. The safety and efficacy of clomiphene citrate in hypoandrogenic and subfertile men. *Int J Imp Res*. 2015;27:221–224.
88. Madhusoodanan V, Patel P, Lima TFN, et al. Human chorionic gonadotropin monotherapy for the treatment of hypogonadal symptoms in men with total testosterone >300 ng/dL. *Int Braz J Urol*. 2019;45:1008–1012.
89. Nwabuobi C, Arlier S, Schatz F, et al. hCG: biological functions and clinical applications. *Int J Mol Sci*. 2017;10:2037.
90. Cole LA. Biological functions of hCG and hCG-related molecules. *Reprod Biol Endocrinol*. 2010;8:102.
91. Nedresky D, Singh G. *StatPearls*. Physiology, luteinizing hormone. Treasure Island, FL: StatPearls Publishing LLC.; 2023.
92. Trinchard-Lugan I, Khan A, Porchet HC, Munafo A. Pharmacokinetics and pharmacodynamics of recombinant human chorionic gonadotrophin in healthy male and female volunteers. *Reprod Biomed Online*. 2002;4:106–115.
93. Orvieto R. HMG versus recombinant FSH plus recombinant LH in ovarian stimulation for IVF: does the source of LH preparation matter? *Reprod Biomed Online*. 2019;39:1001–1006.
94. Jones TH, Darne JF, McGarrigle HH. Diurnal rhythm of testosterone induced by human chorionic gonadotrophin (hCG) therapy in isolated hypogonadotrophic hypogonadism: a comparison between subcutaneous and intramuscular hCG administration. *Eur J Endocrinol*. 1994;131:173–178.
95. Deeks ED. Highly purified human menopausal gonadotropin (Menopur(®)): a profile of its use in infertility. *Clin Drug Investig*. 2018;38:1077–1084.
96. Lehert P, Schertz JC, Ezcurra D. Recombinant human follicle-stimulating hormone produces more oocytes with a lower total dose per cycle in assisted reproductive

technologies compared with highly purified human menopausal gonadotrophin: a meta-analysis. *Reprod Biol Endocrinol*. 2010;8:112.
97. Oduwole OO, Peltoketo H, Huhtaniemi IT. Role of follicle-stimulating hormone in spermatogenesis. *Front Endocrinol*. 2018;9:763.
98. Santi D, Crépieux P, Reiter E, et al. Follicle-stimulating hormone (FSH) action on spermatogenesis: a focus on physiological and therapeutic roles. *J Clin Med*. 2020;4:1014.
99. Vu Hai MT, Lescop P, Loosfelt H, Ghinea N. Receptor-mediated transcytosis of follicle-stimulating hormone through the rat testicular microvasculature. *Biol Cell*. 2004;96:133–144.
100. Simoni M, Gromoll J, Nieschlag E. The follicle-stimulating hormone receptor: biochemistry, molecular biology, physiology, and pathophysiology. *Endocr Rev*. 1997;18:739–773.
101. Liu PY, Baker HW, Jayadev V, et al. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. *J Clin Endocrinol Metab*. 2009;94:801–808.
102. Farhat R, Al-zidjali F, Alzahrani AS. Outcome of gonadotropin therapy for male infertility due to hypogonadotrophic hypogonadism. *Pituitary*. 2010;13:105–110.
103. Rubin SO. Malignant teratoma of testis in a subfertile man treated with Hcg and Hmg: a case report. *Scand J Urol Nephrol*. 1973;7:81–84.
104. Levi Setti PE, Alviggi C, Colombo GL, et al. Human recombinant follicle stimulating hormone (rFSH) compared to urinary human menopausal gonadotropin (HMG) for ovarian stimulation in assisted reproduction: a literature review and cost evaluation. *J Endocrinol Invest*. 2015;38:497–503.
105. Prevost RR. Recombinant follicle-stimulating hormone: new biotechnology for infertility. *Pharmacotherapy*. 1998;18:1001–1010.
106. Lunenfeld B, Bilger W, Longobardi S, et al. The development of gonadotropins for clinical use in the treatment of infertility. *Front Endocrinol*. 2019;10:429.
107. Liu Y, Ren XY, Peng YG, et al. Efficacy and safety of human chorionic gonadotropin combined with human menopausal gonadotropin and a gonadotropin-releasing hormone pump for male adolescents with congenital hypogonadotropic hypogonadism. *Chin Med J (Engl)*. 2021;134:1152–1159.
108. Bouloux P, Warne DW, Loumaye E. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. *Fertil Steril*. 2002;77:270–273.
109. Buzdar AU, Robertson JF, Eiermann W, Nabholtz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. *Cancer*. 2002;95:2006–2016.
110. Miller WR. Biology of aromatase inhibitors: pharmacology/endocrinology within the breast. *Endocr Relat Cancer*. 1999;6:187–195.
111. Ahmadi-Asrbadr Y, Hemmati-Ghavshough M, Khanzadeh N, et al. Comparison of the effect of combined therapy of HCG ampule and letrozole tablet with each method separately on the spermogram parameters in the obese men with idiopathic infertility: a clinical trial. *Am J Clin Exp Urol*. 2022;10:258–265.
112. Peivandi S, Jafarpour H, Abbaspour M, Ebadi A. Effect of letrozole on spermogram parameters and hormonal profile in infertile men: a clinical trial study. *Endocr Regul*. 2019;53:231–236.
113. Shuling L, Sie Kuei ML, Saffari SE, et al. Do men with normal testosterone-oestradiol ratios benefit from letrozole for the treatment of male infertility? *Reprod Biomed Online*. 2019;38:39–45.
114. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013;369:1011–1022.
115. Hammes SR, Levin ER. Impact of estrogens in males and androgens in females. *J Clin Invest*. 2019;129:1818–1826.
116. Cooke PS, Nanjappa MK, Ko C, et al. Estrogens in male physiology. *Physiol Rev*. 2017;97:995–1043.
117. de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol*. 2011;9:93.
118. Sharma A, Grant B, Islam H, et al. Common symptoms associated with usage and cessation of anabolic androgenic steroids in men. *Best Pract Res Clin Endocrinol Metab*. 2022;36:101691.
119. Arver S, Borjesson A, Bottiger Y, Edin A, Garevic N, Lundmark J. *Swedish clinical guidelines on: The abuse of anabolic androgenic steroids and other hormonal drugs*. Stockholm: Karolinska University Hospital; 2013.
120. Anawalt BD. Diagnosis and management of anabolic androgenic steroid use. *J Clin Endocrinol Metab*. 2019;104:2490–2500.
121. Bonnecaze AK, O'Connor T, Burns CA. Harm reduction in male patients actively using anabolic androgenic steroids (AAS) and performance-enhancing drugs (PEDs): a review. *J Gen Intern Med*. 2021;36:2055–2064.
122. Bischof G, Bischof A, Rumpf HJ. Motivational interviewing: an evidence-based approach for use in medical practice. *Deutsches Arzteblatt Int*. 2021;118:109–115.
123. Miller WR, Baca LMJBT. Two-year follow-up of bibliotherapy and therapist-directed controlled drinking training for problem drinkers. *Behavior Therapy*. 1983;14:441–448.
124. Miller WR, Rollnick S. Motivierende Gesprächsführung: Motivational Interviewing: 3. Auflage des Standardwerks in Deutsch:. Lambertus-Verlag; 2015.
125. Kohn TP, Louis MR, Pickett SM, et al. Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. *Fertil Steril*. 2017;107:351–357.e1.
126. Habous M, Giona S, Tealab A, et al. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short–course randomized study. *BJU Int*. 2018;122:889–897.
127. Huijben M, Huijsmans RLN, Lock M, et al. Clomiphene citrate for male infertility: a systematic review and meta-analysis. *Andrology*. 2023;6:987–989.
128. Jiang T, Sigalos JT, Osadchiy V, et al. Temporal changes of clomiphene on testosterone levels and semen parameters in subfertile men. *World J Mens Health*. 2023;41:198–203.
129. Trinh TS, Hung NB, Hien LTT, et al. Evaluating the combination of human chorionic gonadotropin and clomiphene citrate in treatment of male hypogonadotropic hypogonadism: a prospective study. *Res Rep Urol*. 2021;13:357–366.
130. Balasch J, Barri PN. Reflections on the cost-effectiveness of recombinant FSH in assisted reproduction. The clinician's perspective. *J Assist Reprod Genet*. 2001;18:45–55.
131. Casarini L, Crépieux P, Reiter E, et al. FSH for the treatment of male infertility. *Int J Mol Sci*. 2020;7:2270.
132. Hayes FJ, Seminara SB, Decruz S, et al. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. *J Clin Endocrinol Metab*. 2000;85:3027–3035.
133. Cakan M, Aldemir M, Topcuoglu M, Altuğ U. Role of testosterone/estradiol ratio in predicting the efficacy of tamoxifen citrate treatment in idiopathic oligoasthenoteratozoospermic men. *Urol Int*. 2009;83:446–451.
134. Geisler J. Neoajuvant treatment with anastrozole ('Arimidex') causes profound suppression of intra-tumor estrogen levels (abstract 311). *Proc Am Soc Clin Oncol*. 1999;18:82A.
135. Grimm SW, Dyroff MC. Inhibition of human drug metabolizing cytochromes P450 by anastrozole, a potent and selective inhibitor of aromatase. *Drug Metab Dispos*. 1997;25:598–602.
136. Goss PE. Risks versus benefits in the clinical application of aromatase inhibitors. *Endocr Relat Cancer*. 1999;6:325–332.
137. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. *Hum Reprod*. 2004;19:1548–1553.
138. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil Steril*. 2008;89:505–522.
139. Collée J, Mawet M, Tebache L, et al. Polycystic ovarian syndrome and infertility: overview and insights of the putative treatments. *Gynecol Endocrinol*. 2021;37:869–874.
140. Seifer DB, Golub ET, Lambert-Messerlian G, et al. Variations in serum Müllerian inhibiting substance between white, black, and Hispanic women. *Fertil Steril*. 2009;92:1674–1678.
141. Oh SR, Choe SY, Cho YJ. Clinical application of serum anti-Müllerian hormone in women. *Clin Exp Reprod Med*. 2019;46:50–59.
142. di Clemente N, Racine C, Pierre A, Taieb J. Anti-Müllerian hormone in female reproduction. *Endocr Rev*. 2021;42:753–782.
143. van Rooij IA, Broekmans FJ, te Velde ER, et al. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod (Oxford, England)*. 2002;17:3065–3071.
144. Amory JK, Coviello AD, Page ST, et al. Serum 17-hydroxyprogesterone strongly correlates with intratesticular testosterone in gonadotropin-suppressed normal men receiving various dosages of human chorionic gonadotropin. *Fertil Steril*. 2008;89:380–386.
145. Lima TFN, Rakitina E, Blachman-Braun R, Ramasamy R. Evaluation of a serum 17-hydroxyprogesterone as a predictor of semen parameter improvement in men undergoing medical treatment for infertility. *Can Urol Assoc J*. 2021;15:E340–e345.
146. Hughes G, Martins da Silva S. Sperm cryopreservation for impaired spermatogenesis. *Reprod Fertil*. 2022.
147. Di Santo M, Tarozzi N, Nadalini M, Borini A. Human sperm cryopreservation: update on techniques, effect on DNA integrity, and implications for ART. *Adv Urol*. 2012;2012:854837.
148. Liu S, Li F. Cryopreservation of single-sperm: where are we today? *Reprod Biol Endocrinol*. 2020;18:41.
149. Feldschuh J, Brassel J, Durso N, Levine A. Successful sperm storage for 28 years. *Fertil Steril*. 2005;84:1017.
150. Delbaere I, Verbiest S, Tydén T. Knowledge about the impact of age on fertility: a brief review. *Ups J Med Sci*. 2020;125:167–174.
151. Anderson RA, Amant F, Braat D, et al. ESHRE guideline: female fertility preservation. *Hum Reprod Open*. 2020;2020:hoaa052.
152. Patrizio P, Molinari E, Caplan A. Ethics of medical and nonmedical oocyte cryopreservation. *Curr Opin Endocrinol Diabetes Obes*. 2016;23:470–475.
153. Stokes T, Hector AJ, Morton RW, et al. Recent perspectives regarding the role of dietary protein for the promotion of muscle hypertrophy with resistance exercise training. *Nutrients*. 2018;10.
154. Teixeira FJ, Santos HO, Howell SL, Pimentel GD. Whey protein in cancer therapy: a narrative review. *Pharmacol Res*. 2019;144:245–256.
155. Delpino FM, Figueiredo LM, Forbes SC, et al. Influence of age, sex, and type of exercise on the efficacy of creatine supplementation on lean body mass: a systematic review and meta-analysis of randomized clinical trials. *Nutrition*. 2022;103-104:111791.
156. Schoenfeld BJ, Contreras B, Krieger J, et al. Resistance training volume enhances muscle hypertrophy but not strength in trained men. *Med Sci Sports Exerc*. 2019;51:94–103.
157. Schoenfeld BJ, Grgic J, Van Every DW, Plotkin DL. Loading recommendations for muscle strength, hypertrophy, and local endurance: a re-examination of the repetition continuum. *Sports (Basel)*. 2021;9.