QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

RZESZUTEK, Jakub, PEMPUŚ, Wiktoria, GRZYBOWSKA, Dominika, NIDERLA, Natalia, RACHWAŁ, Natalia, GRZYB, Weronika, KURNIK, Michał, JAŚLIKOWSKA, Adrianna, IDZIK, Kamil and KUBICKI, Adrian. Recovery of the Hypothalamic-Pituitary-Testicular Axis After Anabolic-Androgenic Steroid Cessation. A Review of Therapeutic Options and the Fundamental Role of the Primary Care Physician in Harm Reduction. Quality in Sport. 2026;56:72493. https://doi.org/10.12775/QS.2026.56.72493

ARTICLE TIMELINE
Received: 24.05.2026 Revised: 26.05.2026
Accepted: 26.05.2026 Published: 30.05.2026

INDEXING & EVALUATION
MEiN points: 20 Unique ID: 201398
Disciplines: Economics & Finance; Management & Quality Sciences

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Economics and Finance (Social Sciences); Management and Quality Sciences (Social Sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Recovery of the Hypothalamic-Pituitary-Testicular Axis After Anabolic-Androgenic Steroid Cessation. A Review of Therapeutic Options and the Fundamental Role of the Primary Care Physician in Harm Reduction.

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ABSTRACT

The recreational abuse of anabolic-androgenic steroids (AAS) is a major public health concern among amateur athletes. Supraphysiologic androgen exposure disrupts the hypothalamic-pituitary-testicular axis, inducing Anabolic Steroid-Induced Hypogonadism (ASIH). This study evaluates endocrine and spermatogenesis recovery timelines, reviews pharmacological interventions, and defines the role of primary care physicians (PCPs) in harm reduction. Based on a comprehensive literature review from 1990 to 2025, twenty key publications were analyzed. Results indicate that spontaneous axis recovery is prolonged. While serum testosterone normalizes within 3 months post-cessation, full spermatogenesis recovery averages 12 months. Up to 27 percent of former users exhibit persistent hypogonadism and psychiatric withdrawal symptoms years later. Combined off-label pharmacotherapy using human chorionic gonadotropin (hCG) alongside selective estrogen receptor modulators (SERMs) accelerates testosterone restitution and restores fertility in over 70 percent of azoospermic patients. General practitioners occupy the critical frontline to mitigate life-threatening complications through clinical surveillance.

Keywords: anabolic steroid-induced hypogonadism, harm reduction, primary health care, male infertility, human chorionic gonadotropin (hCG), clinical surveillance

1. INTRODUCTION: A NEW EPIDEMIC IN OUR CLINICS

Just a decade or so ago, when we thought of doping complications, we pictured a narrow group of elite athletes or professional bodybuilders. Today, as practicing physicians, we must completely revise this outdated paradigm. Modern medicine faces the challenge of a new, silent wave of endocrine, cardiovascular, and psychiatric disorders stemming from the non-medical, recreational use of anabolic-androgenic steroids (AAS). It is estimated that the global

prevalence of AAS use affects between 1% and 5% of the worldwide population [2]. What is most fascinating—and simultaneously terrifying—is that this problem has shifted from professional arenas to local neighborhood gyms. The primary target demographic today consists of young men, often teenagers and thirty-somethings, driven by the pressure of unrealistic physique standards perpetuated by social media [12, 14].

From a physiological standpoint, the administration of exogenous androgens in doses that are dozens, sometimes hundreds of times higher than the body's natural requirements leads to a catastrophic blockade of the hypothalamic-pituitary-testicular (HPTA) axis. This phenomenon is not merely a transient "side effect." It is a massive disruption of the most sensitive feedback loop in the male body, leading to the development of a clinical entity we refer to in the literature as Anabolic Steroid-Induced Hypogonadism (ASIH) [2, 8]. The clinical picture of a patient with ASIH is dominated by a dramatic drop in libido, erectile dysfunction, loss of hard-earned muscle mass, fat accumulation, and—something we often overlook—profound psychiatric complications, including treatment-resistant depression [9, 17]. From an andrological perspective, however, the most severe and burdensome problem remains the impairment of spermatogenesis, which in the vast majority of cases takes the form of severe oligozoospermia or complete azoospermia, leading to tragedies for couples trying to conceive [4, 15].

As doctors, we often operate under a myth instilled in us by patients: "I'll drop the gear, and everything will go back to normal on its own." Usually, after discontinuing a "cycle," the HPTA axis does exhibit a biological tendency toward spontaneous recovery [7]. The problem, however, lies in the duration of this process. For most patients, the return of normal semen parameters takes at least a year of patient waiting [1]. Even worse, recent data reveals that in up to 27% of men, post-AAS hypogonadism becomes persistent and chronic, rendering it irreversible without medical intervention [5, 6].

Given the broad spectrum of systemic complications—spearheaded by initially asymptomatic myocardial remodeling (left ventricular hypertrophy), atherosclerosis induced by drastic drops in HDL fractions, and drug-induced liver injury [13, 18]—the burden of initial diagnosis falls on primary care physicians (PCPs). Unfortunately, these patients rarely admit to doping. They frequently present to the clinic under the guise of minor infections, joint pain, or "spring fatigue," while a full-blown withdrawal syndrome and progressive organ failure develop in the background [16]. The situation is further complicated by the fact that the medical community

still lacks unified, global algorithms for treating ASIH [11], and patients' immense fears of stigmatization effectively hinder us from implementing harm reduction strategies [3, 10].

As a researcher and clinician, I believe we can no longer pretend this problem does not exist. The aim of this extensive review is to: (1) thoroughly systematize knowledge regarding the pathophysiology and recovery dynamics of the HPTA axis, (2) critically evaluate the efficacy of pharmacological interventions (including the often-controversial off-label use of hCG and SERMs) in salvaging the fertility and masculinity of our patients, and (3) redefine the role of the general practitioner in providing long-term, empathetic care for patients with a history of AAS abuse.

2. METHODS AND LITERATURE SELECTION: IN SEARCH OF HARD EVIDENCE

Studying the population of steroid users is incredibly frustrating from a researcher's perspective. Due to the illicit nature of many substances, the patients' propensity to hide the truth (the stigma effect), and ubiquitous polypharmacy (combining AAS with insulin, growth hormone, or stimulants), Evidence-Based Medicine (EBM) encounters major hurdles here. We cannot conduct a perfect, double-blind, randomized controlled trial administering toxic doses of androgens to young men. Therefore, we must rely on the highest quality observational studies, prospective cohort analyses, and meticulously documented case reports.

2.1. Search Strategy

The literature review underpinning this paper was conducted with rigorous use of PubMed, Scopus, and Google Scholar databases. The timeframe of the search covered the years 1990–2025. Why reach so far back? Because the first foundational papers on the reversibility of azoospermia (e.g., the studies by Turek and Jarow [20]) remain the cornerstones of andrology today, while publications from the last decade (especially 2019-2025) reflect the massive shift in the black market—the emergence of "designer steroids" and easy access to pharmaceuticals via the internet. I utilized a matrix of keywords including: *anabolic-androgenic steroids*, *hypogonadism recovery*, *ASIH*, *hCG off-label*, *harm reduction in primary care*.

2.2. and 2.3. Inclusion and Exclusion Criteria

For rigorous analysis, I included only those papers providing hard clinical data. I deemed studies assessing HPTA axis recovery time as crucial, with particular emphasis on the Dutch

HAARLEM study [1], which I consider an absolute game-changer in our field, as well as Scandinavian papers evaluating chronic ASIH [5, 6]. I included reviews documenting the use of pharmacotherapy in treating post-AAS azoospermia [2, 4, 15] and the latest UK guidelines for PCPs [3, 11, 16]. I firmly excluded animal-only studies, papers focusing on World Anti-Doping Agency (WADA) regulations—since elite sports medicine has little to do with the reality of the average gym-goer—and unscientific reports from bodybuilding forums, which often promote dangerous, pseudo-medical protocols.

2.4. Data Selection

Through a two-stage selection process, I ultimately isolated 20 key publications. During the analysis, I focused on extracting "hard endpoints": the average recovery time of physiological testosterone and gonadotropin concentrations, the dynamics of germinal epithelium renewal, and specific dosing regimens of adjunct medications, allowing me to draw conclusions that any physician can apply in their clinic tomorrow.

3. PATHOPHYSIOLOGY AND DYNAMICS OF HPTA RECOVERY: THE ANATOMY OF AN ENDOCRINE CATASTROPHE

To understand the patient with ASIH, we must first look at the perfect machinery of the male endocrine system and understand how brutally it is dismantled.

3.1. Mechanism of ASIH Development – Profound Hypothalamic Suppression

Physiologically, the hypothalamus releases gonadotropin-releasing hormone (GnRH) in a pulsatile manner, which stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on the Leydig cells in the testes, compelling them to produce endogenous testosterone. Meanwhile, FSH, in synergy with a massive concentration of intratesticular testosterone, stimulates the Sertoli cells to support spermatogenesis [2].

Introducing supraphysiological doses of testosterone or its synthetic, non-aromatizing derivatives (e.g., trenbolone or nandrolone) triggers a cascade of changes. The excess androgens activate a negative feedback mechanism at the hypothalamic level. Furthermore, classic testosterone undergoes peripheral aromatization via the aromatase enzyme, creating high levels of estradiol. In men, estradiol is a remarkably potent hypothalamic suppressor. As

a result, the hypothalamus completely shuts down the pulsatile release of GnRH. The pituitary goes silent [2, 8].

The lack of LH causes the Leydig cells to effectively "fall asleep." Intratesticular testosterone (ITT) concentrations, which are physiologically nearly 100 times higher than in peripheral blood, drop to zero. The lack of FSH prevents Sertoli cells from properly guiding sperm maturation. Clinically and macroscopically, this results in reduced testicular volume (atrophy) and profound hypogonadism immediately after stopping exogenous injections [2, 15]. Contrary to popular belief, the return of endogenous hormone production does not happen a few days after "coming off a cycle." As Kanayama et al. emphasize, the post-cessation period is a time of a massive "crash"—severe, clinical hypogonadotropic hypogonadism, which represents a period of immense physical and psychological suffering for the patient [6].

3.2. Time to Eugonadism – Myths vs. Hard Science (The HAARLEM Study)

How long must a patient wait to recover? These timelines are incredibly heterogeneous. The speed of HPTA axis regeneration is determined by age, the "cumulative dose" (how many grams of steroids the patient has taken in their lifetime), and the pharmacokinetics of specific esters (long-ester forms of testosterone or nandrolone metabolites can continue to suppress the axis for many weeks post-injection).

A fascinating, highly precise look into this process was provided by the recent Dutch HAARLEM study by Smit and colleagues [1]. This prospective observational study tracked 100 men using AAS recreationally—before, during, and after a cycle. The authors demonstrated that in the majority of men, the hormonal profile (serum LH, FSH, and total testosterone) returned to the lower limits of the reference range within approximately 3 months (12 weeks) of ceasing doping. This might seem short. However, and we must emphasize this clearly to our patients, urologists, and andrologists: semen parameters required significantly more time to recover. The return of full spermatogenesis took an average of 12 months, and in many patients, it took even longer [1]. This aligns with studies by Shankara-Narayana et al. (2020), who confirmed that while the reproductive system can eventually regenerate, the process demands patience [7].

3.3. Chronic ASIH – When the Testes Forget How to Work

From a clinical perspective, my greatest concern lies with patients in whom the "reboot" never spontaneously occurs. The myth of "total reversibility" is shattered by the outstanding work of Rasmussen et al. (2016). They conducted a case-control study demonstrating that in the serum of former AAS users, even an average of 2.5 years (!) after stopping doping, total testosterone levels remained significantly and statistically lower compared to a control group of men who had never touched steroids. In this study, a staggering 27.2% of former users still presented with testosterone levels below 12.1 nmol/L, meeting the biochemical criteria for hypogonadism [5].

What does this mean for us? It means that in nearly 1/3 of patients, ASIH is not a transient state but a chronic disease induced by toxic damage to the Leydig cells. This entails dramatic drops in libido, constant fatigue, and an extreme psychiatric burden [6, 9]. The frustration over the body's powerlessness often tempts patients in this phase to return to injections just to feel "normal"—creating the classic vicious cycle of AAS dependence extensively described by Harrison Pope [12].

4. PHARMACOLOGICAL TREATMENT OF ASIH AND INFERTILITY: SALVAGING MASCULINITY AND FERTILITY

Given the formidable pathophysiological knowledge we are faced with, we must ask ourselves: what can we offer the patient in the clinic?

4.1. The Clinic Dilemma: Watchful Waiting or Aggressive Intervention?

As I mentioned in the introduction, the lack of a global consensus is a massive problem. This is perfectly illustrated by a 2023 survey conducted by Grant's team among British endocrinologists. The medical community is deeply divided. A significant portion of physicians still advocates for a "watchful waiting" strategy, simply telling the patient to stop the drugs, live healthily, and return for a check-up in a few months [11].

From a practitioner's perspective, this approach often borders on cruelty and is medically unjustified in specific cases. Passive observation is unacceptable for a young man with severe suicidal ideation due to a lack of testosterone, and even more so for a couple that has been unsuccessfully trying to conceive for years [2, 15]. In such situations, the literature points to

the exceptionally high efficacy of active pharmacotherapy, based on stimulating medications used off-label but grounded in solid biochemical foundations.

4.2. hCG (Human Chorionic Gonadotropin) as the Cornerstone of Therapy

To initiate spermatogenesis in empty seminiferous tubules, we must achieve a massive concentration of intratesticular testosterone (ITT). Traditional exogenous testosterone replacement therapy (TRT) would be a malpractice here—it would suppress any residual LH and FSH secretion from the pituitary and act as a male contraceptive.

The drug of choice, a powerful ally to the andrologist, is human chorionic gonadotropin (hCG). Because its alpha subunit is identical to LH and its beta subunit is very similar, hCG binds directly to LH receptors on the Leydig cells. The effect is immediate—the testes are awakened from their slumber and forced into massive production of endogenous testosterone [2, 4, 15]. hCG monotherapy, typically administered in regimens of 1500–3000 IU intramuscularly or subcutaneously two to three times a week, incredibly rapidly and effectively alleviates the clinical symptoms of hypogonadism (fatigue, brain fog) and serves as the foundation for restoring fertility [2].

4.3. SERMs: Stimulating the Pituitary

hCG alone stimulates the testes, but it does not solve the problem of a dormant hypothalamus and the lack of FSH, without which Sertoli cells cannot nurture sperm. Therefore, comprehensive ASIH treatment protocols absolutely must incorporate Selective Estrogen Receptor Modulators (SERMs), the flagship example being clomiphene citrate [4].

The mechanism of action of clomiphene in these patients is brilliant in its simplicity. As we know, excess estrogens post-cycle suppress the hypothalamus. Clomiphene binds to estrogen receptors in the hypothalamus and pituitary, antagonizing them. The central nervous system is "tricked"—it interprets this as a drastic lack of blood estrogens. In a defensive response, the hypothalamus immediately generates powerful pulses of GnRH, which triggers a physiological surge of LH and, crucially, the invaluable FSH [2, 4]. It is this FSH surge induced by SERMs that is the key link in restoring full spermatogenesis [15].

4.4. Efficacy of Combination Therapy – History and Present

It is surprising how many doctors doubt the efficacy of such treatment, even though evidence of its effectiveness has existed for over a quarter of a century. As early as 1990 (Jarow) and 1995 (Turek), classic papers were published (cited in The BMJ [20]), proving that steroid-induced azoospermia is reversible.

Today, in the era of extreme doses used by amateurs, we achieve the best results through synergy. The literature review by McBride and Coward (2016) leaves no illusions: the simultaneous administration of hCG (which replaces LH and raises ITT) and clomiphene citrate (which generates an FSH surge) in men with profound azoospermia yields fantastic results [4]. Clinical observations prove that the appearance of the first motile sperm in the ejaculate of these patients is usually seen within a 3 to 6-month window. Parameters allowing for safe, natural conception are generally achieved within 12-18 months of treatment. Inspiring great optimism, the efficacy of such pharmacological restitution exceeds the 70% threshold in many studies [4, 15]. We can confidently tell our patients: if we act quickly and intelligently, we can save your fertility.

5. THE ROLE OF THE PRIMARY CARE PHYSICIAN: THE FRONTLINE AND HARM REDUCTION

The vast majority of these patients will never willingly see an endocrinologist or urologist until they start trying for a baby. The most important battle is being fought in the offices of general practitioners and internists (PCPs), which we unfortunately often fail to even notice.

5.1. The "Hidden" Patient in Our Waiting Room and Communication Barriers

Why does this happen? As researchers like Bates or Mullen so accurately note, the main barrier is a wall of silence and fear of stigmatization [10, 14]. The patient views us, doctors, as moralizers who have no idea about the "practical" application of steroids, and our only response is always: "throw that away immediately."

As a result, AAS users often present to us under a "cover story." This phenomenon is phenomenally illustrated by a recently published case study from daily general practice (de Carvalho Vilarinho et al., 2025). A 30-year-old man presented to the clinic with symptoms of... a mild cold. The doctor, maintaining exceptional vigilance, noticed during chest auscultation

an unnatural, disproportionate hypertrophy of the shoulder girdle musculature, obvious bilateral gynecomastia, and (upon expanding the examination) testicular atrophy. This was not a case of the flu; it was the tip of the iceberg of extensive systemic complications in an active steroid user [16]. We must learn to look at patients through the lens of these hidden signs: injection marks on the glutes or deltoids, sudden weight spikes, or unnaturally rapid male-pattern baldness.

5.2. Targeting High-Risk Organs: The Heart and Liver

Once we identify the patient, we cannot focus solely on the HPTA axis. Androgen abuse carries drastic systemic consequences, directly shortening lifespan, a fact definitively confirmed by Horwitz's epidemiological studies (showing significantly higher mortality among AAS users) [13].

In the GP's office, two organ systems should immediately trigger a red light in our heads:

1. Cardiovascular System: As Shankara-Narayana's team demonstrated, while the testes may regenerate over time, the heart is not so forgiving. Among AAS users, we observe massive left ventricular hypertrophy (often progressing to hypertrophic cardiomyopathy), diastolic dysfunction, and atherosclerosis driven by the complete destruction of the lipid profile (HDL drops frequently below 10 mg/dL!) [7]. These changes are often irreversible.

2. Liver: The second crucial flashpoint. Oral steroids (e.g., methandienone, stanozolol) are particularly popular among amateurs because they bypass the need for injections. They possess a 17-alpha alkyl group, which makes them resistant to breakdown in the liver (first-pass effect), rendering them extremely hepatotoxic. Toxicological analysis by Petrovic [18] indicates that they cause hepatocyte damage ranging from a seemingly harmless elevation of transaminases (ALT, AST), through severe cholestasis with jaundice, to directly life-threatening conditions: the formation of hepatic adenomas and *peliosis hepatis* (the formation of blood-filled, rupturing cysts in the liver parenchyma). It is worth noting that in weightlifters, AST and ALT can be elevated simply from muscle damage—therefore, our markers of choice for liver and biliary tract damage post-steroids should be GGT (gamma-glutamyl transferase) and bilirubin.

5.3. The Difficult Patient in Rehab – The Psychiatry of the Withdrawal Phase

The third, incredibly difficult area of care is the psyche. Reviews by Piacentino [17] and years of research by Harrison Pope and Kanayama [9, 12] make us realize the power of androgens' impact on the brain. During the use of supraphysiological doses, the patient often feels euphoria, is aggressive, and impulsive (the phenomenon of "roid rage" may be rare, but heightened irritability is the norm).

However, when the patient stops the drugs, they hit a wall. A catastrophic drop in dopamine and testosterone ensues. The ASIH phase is a time of profound depressive states. It is during this period that muscle dysmorphia (bigorexia) intensifies—the patient looks in the mirror and sees a skinny weakling, despite having an objectively good physique. The suicide risk during this period is alarming. Our psychological support, careful listening, and the potential implementation of antidepressants can be just as lifesaving as heart or liver medications [9, 17].

5.4. Harm Reduction in Practice – A Guide from the Gibbons Guidelines

We must be brutally honest with the patient, but professional. Categorical moralizing ends with the patient not coming back to us and seeking help from internet "gurus." The solution, extensively discussed by Bates [10], is the medicine of harm reduction.

The 2024 UK guidelines, published by Gibbons' team [3], hand us a ready-made algorithm. A PCP, when faced with a patient using AAS or struggling with withdrawal symptoms, should take the initiative to order an "essential blood testing" panel:

- Complete Blood Count (CBC): Elevated testosterone drastically stimulates erythropoiesis. Hematocrit often soars above 50-54%. This is a state of dangerous secondary polycythemia, which makes the blood thick as syrup, provoking thrombotic events, heart attacks, and ischemic strokes in 30-year-olds [2, 3].

- Lipid Panel: Objective proof for the patient of how they are destroying their blood vessels.

- Liver Function Tests (LFTs): (ALT, AST, ALP, GGT, bilirubin) for early diagnosis of DILI (drug-induced liver injury).

- Comprehensive Endocrine Panel: (Total testosterone, LH, FSH, SHBG, prolactin, estradiol) to assess the depth of HPTA blockade and prepare for a potential urology/endocrinology referral.

My experience and the literature [3, 10] are clear: showing the patient their results in black and white, making them realize that their blood is thick and on the verge of causing a stroke, is a powerful motivational impulse (motivational interviewing). Such objective clinical surveillance is the best method to protect these young men from premature death or permanent disability.

6. DISCUSSION: WAITING FOR A GLOBAL CONSENSUS

Subjecting the publications analyzed in this review to critical evaluation, I am struck by the discrepancy in how the same problem is perceived by different research teams, stemming from the limitations of our research tools.

On one hand, we have the highly rigorous, prospective HAARLEM study [1], which provides cautious optimism—"the axis will return to normal, give the patient a few to several months." On the other hand, we have the hard, long-term retrospective data from Rasmussen and Kanayama warning of irreversible endocrine disability and permanent damage to Leydig cells in nearly 30% of patients [5, 6]. How do we reconcile these two worlds? Most likely, the key, as emphasized by Anawalt and Shankara-Narayana [2, 7], is the long-term impact of the "cumulative dose" of toxins on testicular tissue and the phenomenon of polypharmacy [14]. Modern gym-goers rarely restrict themselves to testosterone alone; dozens of substances are used, undergoing strange interactions impossible to study in controlled conditions.

The lack of formal, unified global guidelines for withdrawal treatment from institutions like the Endocrine Society or the EAU is, in my opinion, a serious oversight [11]. Most effective therapies using hCG and clomiphene still rely on off-labeling [15, 20]. Consequently, many primary care physicians are afraid to provide supportive care to the patient, fearing accusations of "accepting and promoting addiction." I consider this a fundamentally flawed approach; refusing a patient routine blood work when they have a "hormonal soup" in their blood destroying their heart is a rejection of the basic principle of *Primum non nocere*. If we treat hypertension in an obese patient who smokes cigarettes without batting an eye, we cannot look away from the complications of doping.

7. SUMMARY AND CONCLUSIONS

The analysis of the medical consequences of amateur anabolic-androgenic steroid abuse paints a troubling picture of a new, massive chronic disease colliding with the healthcare system. Based on the cited evidence, I wish to formulate three primary conclusions:

1. ASIH is a chronic and incredibly burdensome pathology (Question 1): Recovery is a marathon, not a sprint. Complete regeneration, including the reawakening of spermatogenesis and the resolution of psychiatric symptoms, takes at least a year for most patients. We must loudly educate our patients that for about 30% of them, the damage to the HPTA axis will become irreversible, lowering their quality of life for many years after they stop injections.

2. The efficacy of pharmacological intervention is proven (Question 2): Early works by the classics of andrology [20] and the latest clinical protocols prove that post-steroid azoospermia is not a death sentence. Consistent, biochemically grounded, multi-month stimulation using hCG and SERM medications boasts excellent efficacy in restoring fertility. Watchful waiting in these patients is a mistake.

3. A new standard in Primary Care Clinics (Question 3): These are not patients we will cure with a scolding tone. They require empathy and a reliable, objective approach in the spirit of harm reduction. By systematically performing basic blood panels (CBC, liver tests, lipid profile), we protect their hearts, livers, and nervous systems from destruction. A non-stigmatizing conversation firmly rooted in medical ground is the most effective weapon the general practitioner has in the fight against the doping epidemic.

DISCLOSURE

AUTHORS'S CONTRIBUTION

Conceptualization: JR, WP, DG, NN, NR
Methodology: JR, WG, MK, AJ, KI
Software: JR, AK, WP, KI, DG
Check: JR, AJ, NN, MK, NR
Formal Analysis: JR, WG, AK, KI, AJ

Investigation: JR, MK, WG, NR, NN
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Writing-Rough Preparation: JR, NN, NR, WG, MK
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Visualization: JR, NN, AK, WP, DG
Supervision: JR, NN, NR, MK, AJ
Project Administration: JR, KI, AK, WP, NN

All authors have read and agreed with the published version of the manuscript.

Funding statement:
This review was not externally funded.

Statement of the institutional review board:
Not applicable.

Statement of informed consent:
Not applicable.

Statement of data availability:
Not applicable.

Conflict of interest:
The authors report no conflicts of interest

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