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Impacts of Anabolic-androgenic steroid supplementation on female health and offspring: Mechanisms, side effects, and medical perspectives

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ABSTRACT

The increasing prevalence of Anabolic–androgenic steroids (AAS) among women, driven by the pursuit of improved body aesthetics, characterized by higher lean mass and reduced adipose tissue, raises significant health concerns, particularly due to the limited knowledge regarding their effects on the female organism. Prolonged use and/or high doses of AAS are linked to various harmful side effects, including mood changes, psychiatric disorders, voice deepening, clitoromegaly, menstrual irregularities, and cardiovascular complications, prompting medical societies to discourage their widespread use due to insufficient evidence supporting their safety and efficacy. Studies in female rodents have shown that AAS can lead to increased aggression, inflammation, reduced neuronal density, and negative impacts on the myocardium and blood vessels. Additionally, maternal administration of androgens during pregnancy can adversely affect offspring's reproductive, neuronal, and metabolic health, resulting in long-term impairments. The complexity of the mechanisms underlying AAS effects, and their potential genotoxicity remains poorly understood. This review aims to elucidate the various ways in which AAS can impact female physiology and that of their offspring, highlight commonly used anabolic substances, and discuss the positions of medical societies regarding AAS use.

1. Introduction

Androgens, synthesized in the testes, ovaries, adrenal and pineal glands, circulate in plasma, with about 2 % bioavailable (Kostic et al., 2011; Magoffin, 2005; Young and Mcneilly, 2010; Goldman et al., 2017; Raverot et al., 2010). They regulate male characteristics, reproduction, muscle mass, bone density, and erythropoiesis in men while influencing sexual desire, bone density, muscle strength, fat distribution, mood, energy, and psychological well-being in women (Lee et al., 2010; Sessa et al., 2018; Geyer et al., 2014; Khattab et al., 2020; Sherwin et al., 1985). In the central nervous system (CNS), they affect behavior, excitability, and motor neuron health (Khattab et al., 2020; Nguyen et al., 2017). Androgen receptors (ARs) are widely distributed in both males and females (Albano et al., 2021). Androgen signaling is mediated by AR activation, a transcription factor encoded by the NR3C4 gene (Mangelsdorf et al., 1995). Upon binding, the hormone-receptor complex translocates to the nucleus, where it interacts with androgen-responsive elements (AREs), promoting gene expression (Sanchez et al., 2019) or inducing intracellular signaling cascades (Hampl et al., 2016). Additionally, rapid and specific cellular responses have been linked to non-genomic mechanisms, including interactions with membrane-associated sex hormone-binding globulin (SHBG) receptors, G protein-coupled receptors, c-SRC activation, and ion channel modulation (Alemany, 2022; Kicman, 2008), as shown in Fig. 1.

Motivated by the desire for a more aesthetically attractive body with a high percentage of lean mass and low body fat, as well as by the desire to improve performance and increase strength, the population, in general, has resorted to using synthetic substances, specifically androgens analogues, indiscriminately. These drugs include the use of Anabolic-androgenic steroids (AAS) (Bordin et al., 2017). AAS constitute a set

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of molecules of endogenous origin, as in the case of testosterone metabolism in the liver, or are synthetic, resulting from artificial synthesis from testosterone or its precursors. These artificial molecules were developed to potentiate androgenic effects and optimize anabolic effects, favoring skeletal muscle growth and sports performance (Roman et al., 2018; Albano et al., 2021). Due to these properties, there has been an increase in the consumption of AAS in sports participants and the general population, driven by the desire to achieve a leaner and more muscular body condition (Ronde and Smit, 2020). However, the misuse of these substances for long periods and/or at large doses is associated with the development of deleterious effects on health, with the nervous, cardiac, reproductive, hepatic, and renal systems being the most affected (Bordin et al., 2017; Büttner and Thieme, 2010). Abusive use of AAS involves consuming these substances beyond medically recommended dosages or without a legitimate therapeutic purpose. This typically includes indiscriminate use, excessive dosage and compulsive behavior, The indiscriminate use of AAS by adolescents and young adults, without specialist recommendation for specific treatment, is alarming and can be considered a significant public health problem (Bordin et al., 2017; Kanayama et al., 2010).

The systematic doping program of the former German Democratic Republic (GDR) provided evidence of anabolic steroid and amphetamine use in female athletes (Karila, Kerlan, Christin-Maitre, 2024). In the 1970 s, GDR athletes were given anabolic steroids to enhance performance. Their dominance at the 1976 Montreal Olympics, winning 11 of 13 swimming events, raised suspicions due to atypical physical traits like deep voices and broad shoulders, typical signs of steroid-induced masculinization. This success led to increased steroid use among athletes in other countries, including the U.S. and Japan (Franke and Berendonk, 1997). The International Olympic Committee (IOC) banned AAS in 1975 (Hartgens and Kuipers, 2004). The use of anabolic steroids has gained popularity since the 1980 s, driven by the desire to enhance muscle mass and physical appearance (Pope et al., 2014). In response, the World Anti-Doping Agency (WADA) has annually updated its list of prohibited substances and methods since 2004, tailoring restrictions to the requirements of each sport and competition (Collomp et al., 2022; Albano et al., 2021). The list includes exogenous AAS, such as stanozolol, methandienone, and oxandrolone, and endogenous substances, such as testosterone, dehydroepiandrosterone, androstenedione, and selective androgen receptor modulators (SARMs), such as andarin, enobosarm (ostarine) and LGD-4033 (ligandrol) (*The 2023 prohibited list World anti-doping code*, 2023). Moreover, the prevalence of positive tests for banned substances in elite sports increased from 0.96 % to 2.45 % between 1987 and 2013 (Hon et al., 2015).

AAS use in the general population is linked to illicit drug use, prescription misuse, physical training, and lower education levels. Lifetime prevalence in the U.S. is estimated at 0.9 % for males and 0.1 % for females, higher among young males (1.5–6 %) and females (0–2.4 %). Additional correlates include adverse school experiences, unstable social environments, and criminal behavior (Hakansson et al., 2012). The male adult population with experience in strength training shows the highest prevalence of AAS use without a medical prescription (Arver et al., 2018). However, studies in Brazilian gyms revealed a growing trend among women to use such compounds for aesthetic purposes, with a significant proportion of participants reporting the use of these substances without medical supervision or recommendation (Abrahin et al., 2014). This trend is supported by studies conducted in Iran, Saudi Arabia, and Poland, which reported a notable incidence of women engaging in the indiscriminate administration of androgens (Albaker et al., 2021; Angoorani and Halabchi, 2015; Rachoń et al., 2006). However, the use of these substances without medical supervision carries significant risks to the organism.

Considering the current tendency to the context of aesthetic goals and the search for a perfect body and physical performance improvement in women (Havnes et al., 2021a; Havnes et al., 2021b; Ip et al., 2010) and the scarcity of literature about the clinical repercussions of the consumption of AAS by women (Börjesson et al., 2021; Huang and Basaria, 2018), it is imperative to systematically investigate the potential beneficial and adverse effects of AAS on the female organism. Thus, this review aimed to explore the most recent evidence on the

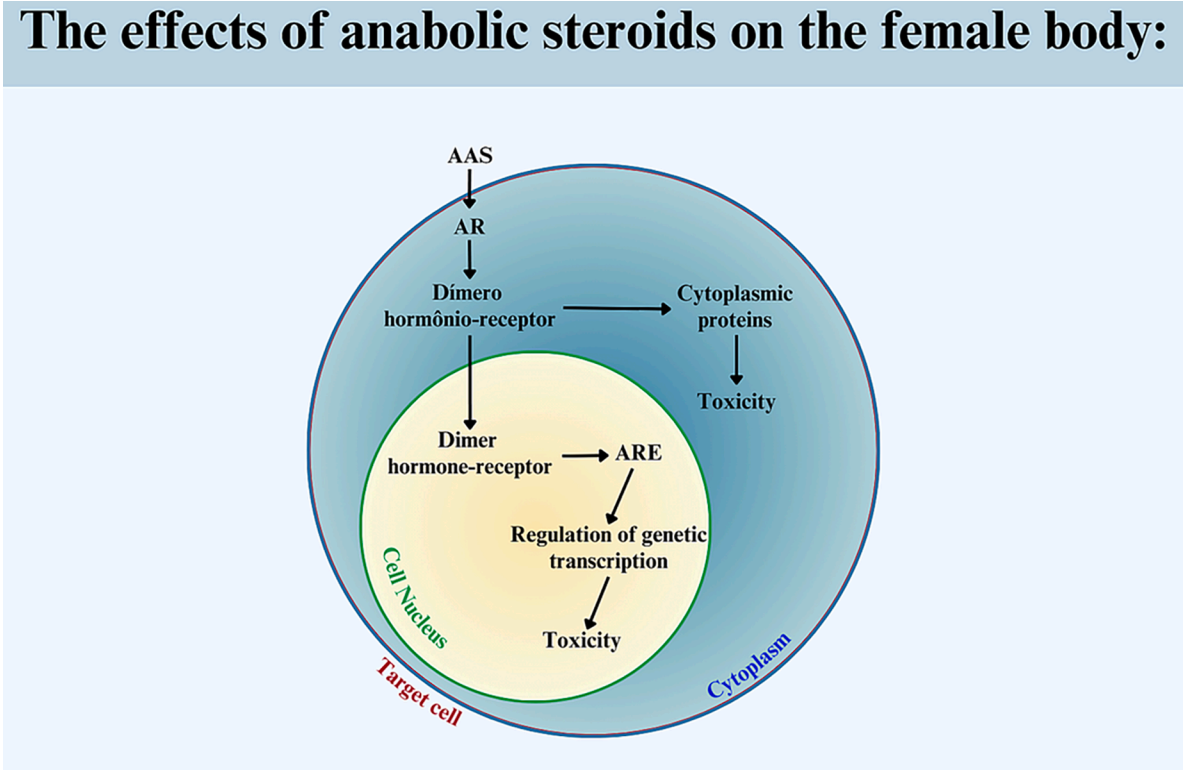

Fig. 1. Effects of anabolic steroids on different cells in the organism. AR: androgen receptor; ARE: androgen responsive element; AAS: Anabolic-androgenic steroids.

mechanisms of action, adverse effects, medical society guidelines, and the prevalence of abuse of anabolic substances among women.

2. The action of androgens in the female organism

The biologically active androgens in females include dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), androstenedione, testosterone, and dihydrotestosterone (DHT) (Smith and Batur, 2001), which are predominantly synthesized in the adrenal glands, ovaries and peripheral conversion of 4-androstenedione to testosterone (Bachmann et al., 2002; Basaria and Dobs, 2006). In target tissues, the 5-alpha-reductase enzyme transforms circulating testosterone into 5-α-DHT, which is predominantly aromatized by the aromatase enzyme into estradiol (Smith and Batur, 2001).

Hormones such as testosterone, 5-α-DHT, and estradiol substantially influence biochemical and physiological pathways, impacting cell structure and function (Berman et al., 2003; Sarrel, 2002; Bertin et al., 2014). Although androgens play a role in estrogen synthesis, their independent actions also contribute to physiological effects (Ceccarelli et al., 2022; Labrie et al., 2001; Smith and Batur, 2001).

The serum concentrations of testosterone and androstenedione vary throughout female reproductive life (Huang and Basaria, 2018). During the follicular phase, these concentrations gradually increase, culminating in a peak in testosterone and an increase in androstenedione in the preovulatory period. In the late luteal phase, androstenedione concentrations continue to increase, but testosterone levels remain stable (Judd and Yen, 1973; Sinha-Hikim et al., 1998). The interpretation of total testosterone measurements should be performed with caution (Smith and Batur, 2001) due to the lack of consensus on values indicative of female androgen deficiency and the absence of an internationally recognized standardized assay (Davis et al., 2019; Parish et al., 2021; Smith and Batur, 2001). Direct assays for testosterone measurement in women are highly uncertain, in contrast to liquid or gas chromatography and mass spectrometry, which demonstrate high precision and reproducibility (Bachmann et al., 2002; Davis et al., 2019).

Chronological and ovarian aging are associated with a gradual decline in androgen synthesis (Davison et al., 2000; Guay et al., 2004; Santoro et al., 2021; Zumoff et al., 1995). Although estradiol synthesis decreases during the climacteric, ovarian stromal cells produce androgens (Dowsett et al., 1988; Santoro, 2005). Serum androgen levels remain stable throughout the menopausal transition (Davison et al., 2000), with evidence suggesting that ovarian cells may even enhance androgen production, mitigating a sharp decline in androgens (Judd and Yen, 1973; Longcope, 1986). However, around a decade postmenopause, androgen synthesis declines significantly, resulting in a 50 % reduction in serum testosterone levels in older women compared to younger adults (Sarrel et al., 1990; Cappola et al., 2007; Davison et al., 2005). Studies indicate that postmenopausal ovaries continue to produce hormones, contributing 40–50 % of total testosterone (Fogle et al., 2007; Laughlin et al., 2000). In addition to aging, factors such as estrogen use, glucocorticoid therapy, low body mass index (BMI), and bilateral oophorectomy are linked to decreased serum androgen levels at various stages of life (Cappola et al., 2007; Davison et al., 2005).

Symptoms such as sexual dysfunction, chronic fatigue, dysphoric mood, and decreased well-being have been associated with female androgen insufficiency (Sherwin et al., 1985; Smith and Batur, 2001). However, the Endocrine Society advises against diagnosing androgen deficiency in healthy women solely based on symptoms and plasma androgen levels. This approach is based on the absence of a well-defined female androgen deficiency syndrome and the lack of data correlating signs/symptoms with androgen concentrations. Furthermore, the Society opposes the widespread use of testosterone and DHEA in healthy women or those with adrenal insufficiency due to insufficient evidence regarding long-term efficacy and safety (Wierman et al., 2014). A global consensus, supported by several medical societies, indicates that the only evidence for prescribing testosterone in women is for the treatment of hypoactive sexual desire dysfunction (HSDD). There is inadequate scientific evidence to support androgen use for other symptoms, clinical conditions, or disease prevention (Davis et al., 2019).

An imbalance in androgen biosynthesis and metabolism significantly affects female health and well-being, impacting reproductive tissues, mood, cognition, skin, bones, vasculature, and muscles (Arlt et al., 1999; Labrie et al., 2001; Smith and Batur, 2001). Clinical conditions such as congenital adrenal hyperplasia (CAH), polycystic ovary syndrome (PCOS), androgen insensitivity syndrome (AIS), and deficiency of 5-alpha-reductase enzyme are linked to elevated endogenous androgens levels (Bachmann et al., 2002; Huang and Basaria, 2018). Hyperandrogenism increases the skiń sensitivity to androgens, leading to manifestations such as seborrhoea, acne, hirsutism, and androgenic alopecia (SAHA syndrome) (Makrantonaki and Zouboulis, 2020; Orfanos et al., 2000). Systemically, hyperandrogenaemia can cause menstrual irregularities, clitoral hypertrophy, virilization, deepened voice, and infertility (Makrantonaki and Zouboulis, 2020). These effects are like those observed in women who misuse AAS for non-clinical or recreational purposes, emphasizing that excess androgens in the female organism can compromise several tissues and systems.

3. Main anabolic agents used by women for non-clinical or recreational purposes

The use of AAS to elevate serum androgen levels is widespread and increasing (Mullen et al., 2020). Androgen concentration can rise via two primary mechanisms: (I) the administration of AAS; and (II) drugs that enhance endogenous androgen synthesis, such as peptide hormones (e.g., luteinizing hormone, corticotropins, human chorionic gonadotropin [hCG]), and their releasing factors (buserelin, corticorelin and lobopegsomatropin) (Anawalt, 2019; Albano et al., 2021). Although hCG is associated with increased testosterone levels in men, it does not produce a consistent or significant rise in testosterone in women (Handelsman, 2006). An analysis of anti-doping tests performed by the French Anti-Doping Agency (2013–2019) showed that stanozolol (ST) and oxandrolone (OXA) were the most commonly used anabolic steroids among female athletes (Collomp et al., 2022), corroborating with data from Brazilian women engaging in recreational resistance training (Abrahin et al., 2014). Female users typically prefer oral formulations of steroids, administered in cycles and at lower weekly doses compared to male users (Havnes et al., 2021; Piatkowski et al., 2023; Ip et al., 2010). However, women are more susceptible to the adverse effects of steroid supplementation (Havnes et al., 2021).

Stanozolol, a synthetic derivative of testosterone (Dodge and Hoagland, 2011), is a white crystalline substance soluble in water, alcohol, chloroform, and dimethylformamide (Lemma et al., 2017). Like 5-DHT, stanozolol does not aromatize to estrogen, resulting in low water and electrolyte retention (Osta et al., 2016). It is used by athletes and female resistance training practitioners (Abrahin et al., 2014; Collomp et al., 2022) and is clinically applied in treating conditions like aplastic anemia and hereditary angioedema (Vergallo et al., 2020). Commercially, it is available in oral and injectable formulations (Lemma et al., 2017; Mullen et al., 2020). The oral form, a 17α-esterified steroid, avoids first-pass hepatic metabolism via 17α-hydrogen by methyl or ethyl groups, potentially causing hepatotoxicity (Kanayama et al., 2010; Osta et al., 2016). With a half-life of 24 h, oral stanozolol requires daily dosing to maintain its ergogenic and therapeutic effects (Osta et al., 2016). The injectable form, esterified at the 17β position, has a longer half-life and less hepatic impact due to its slower absorption (Osta et al., 2016).

Oxandrolone is a synthetic derivative similar to 5-DHT. It does not aromatize to estrogen and has minimal water and electrolyte retention (Osta et al., 2016). Administered exclusively in oral form (Lemma et al., 2017; Mullen et al., 2020), it shares pharmacokinetic and pharmacodynamic characteristics with oral stanozolol (Osta et al., 2016). Its reduced androgenic activity makes it a preferred option by women and has led to its investigation for treating catabolic conditions in adults and

children (Karim et al., 1973; Ring et al., 2020).

Studies indicate that stanozolol and oxandrolone are the anabolic steroids most frequently used by women (Abrahin et al., 2014; Collomp et al., 2022). However, there has been an exponential increase in the use of hormonal implants containing gestrinone, raising concerns in medical societies. Gestrinone, derived from nandrolone, is a progestogen steroid that inhibits the release of gonadotropins and attenuates estrogen synthesis (Osta et al., 2016; Pinto et al., 2023). This hormone also has anabolic effects and is used to improve performance and for aesthetic purposes. For this reason, the World Anti-doping Agency prohibits the use of gestrinone (Albano et al., 2021). Gestrinone has been explored for clinical use in conditions such as endometriosis, uterine fibroids, and contraception (Pinto et al., 2023). However, a recent systematic review and *meta*-analysis showed limited evidence supporting its efficacy and safety for treating endometriosis (Ciou et al., 2022; Pinto et al., 2023). Although reports suggest its potential protective effect against gynecological cancers, the quality of the evidence remains insufficient for conclusions (Pinto et al., 2023). Moreover, the Brazilian Society of Endocrinology and Metabolism does not recognize gestrinone implants as a therapy for endometriosis and opposes their use as an anabolic agent.

Women undergoing AAS treatment often experience side effects such as mood changes, voice deepening, clitoral enlargement, and menstrual irregularities (Havnes et al., 2021; Ip et al., 2010). Preclinical studies in female rodents associate AAS administration with aggressive behaviors (Alrabadi et al., 2020), severe follicular degeneration (Camargo et al., 2014; Saddick, 2018), ovarian cyst formation (Camargo et al., 2014), endometrial hyperplasia, and increased myometrial thickness (Saddick, 2018). Excess androgens in both women and rodents lead to disruptions in the reproductive axis, including decreased luteinizing hormone, follicle-stimulating hormone, and estrogen (Anawalt, 2019; Saddick, 2018), which result in profound alterations to the menstrual cycle. Furthermore, approximately 50 % of women using AAS develop acne, attributed to androgenic effects on sebaceous glands, promoting secretion and increasing the risk of duct obstruction and inflammation (Ahmad et al., 2019; Anawalt, 2019), as shown in Fig. 2.

4. Adverse effects triggered by the use of AAS

The adverse effects of Anabolic-androgenic steroids are complex and multifaceted, impacting several organs and systems in both animals and humans (Albano et al., 2021). This section summarizes the primary adverse effects associated with AAS use:

4.1. Central nervous system (CNS)

Neuropsychiatric and behavioral effects associated with the use of AAS in humans include aggression, anxiety, irritability, and mood fluctuations in both males and females (Hauger et al., 2021; Havnes, et al, 2021; Ip et al., 2010; Onakomaiya and Henderson, 2016; Piacentino et al., 2015). In animal studies, similar aggressive behaviors and irritability have been demonstrated (Breuer et al., 2001). Furthermore, AAS increases inflammatory processes, reduces neuronal density (Pomara et al., 2015), and increases glutamate and aspartate levels in the amygdala (Kalinine et al., 2014). These effects may be linked to reduced glutamate reuptake and increased expression of glutamate receptors, resulting in glutamatergic hyperexcitability and increased emotional reactivity (Fischer et al., 2007; Kalinine et al., 2014; Kaufman et al., 2015).

The neurological effects of AAS are correlated with their ability to cross the blood–brain barrier (Lynch and Story, 2000) and interact with membrane-coupled ARs and G proteins (Caraci et al., 2011). Testosterone may exhibit both neuroprotective and neurotoxic effects, acting through mechanisms that involve both direct actions on ARs and indirect actions mediated by estrogen receptors after conversion to estradiol (Foradori et al., 2008; Scarth and Bjørnebekk, 2021). Low androgen levels result mainly in molecular changes in nuclear ARs, promoting neuronal and glial survival in males (Foradori et al., 2008). In contrast, high androgens concentrations predominantly activate membrane ARs, triggering rapid and potentially harmful changes in cell function and culminating in increased rates of apoptosis (Foradori et al., 2008). Although sample sizes limit human studies, AAS use has been associated with violence, aggression, and antisocial personality traits (Hauger et al., 2021). About 20 % of men using AAS report increased aggression,

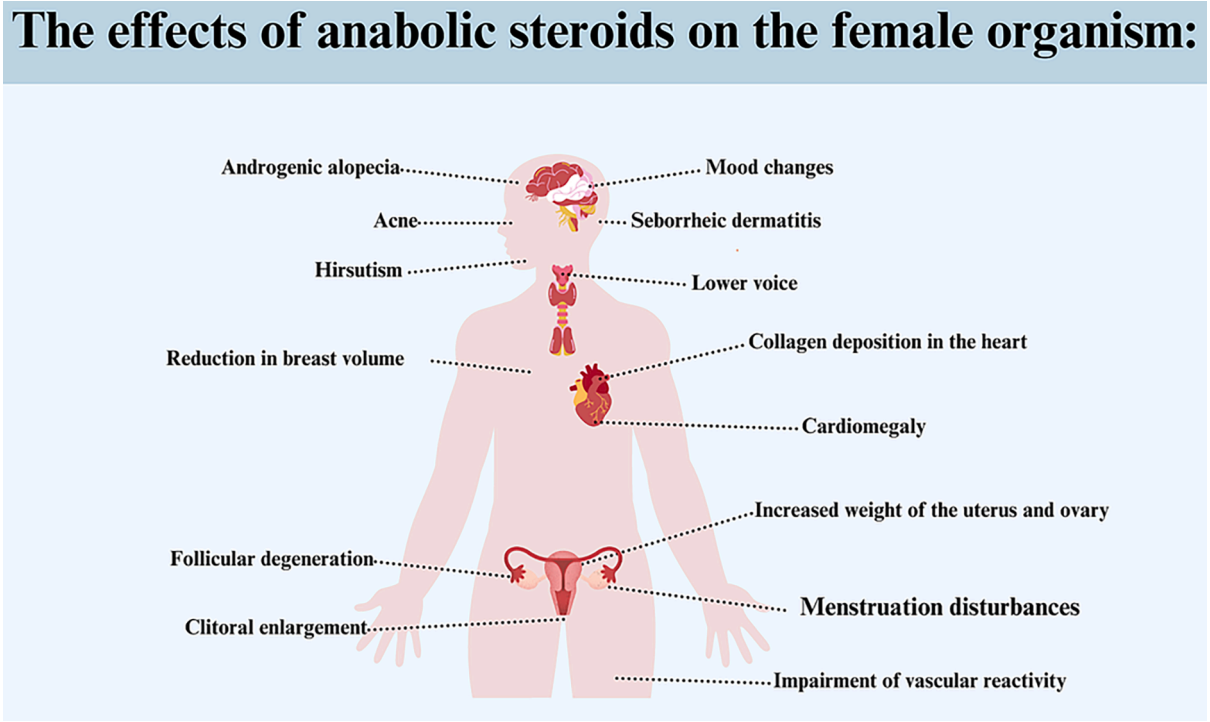

Fig. 2. Scheme summarizing the actions of Anabolic-androgenic steroids on the different systems of the female organism.

sexual dysfunction, fatigue, and depression (Nieschlag and Vorona, 2015).

In animal models, AAS use has been shown to cause a significant increase in the formation of preapoptotic and apoptotic neurons, resulting in subsequent programming for cell death by apoptosis and cleavage of protective chaperone proteins, such as Hsp90 (Basile et al., 2013; Karimooy et al., 2019). Nandrolone supplementation increases neuroinflammatory markers, including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1B), indicating a neurotoxic response in the hippocampus (El-Shamarka et al., 2019). Puberty, a critical period for brain maturation, can be directly influenced by AAS, resulting in structural and brain development changes and potentially causing profound and lasting behavioral effects (Cunningham et al., 2013). Thus, these impacts may be more pronounced in young women, especially adolescents, than adults (Lumia and McGinnis, 2010).

Behavioral changes induced by AAS occur through both genomic and nongenomic pathways, affecting several neurotransmission systems, such as the glutamatergic, cholinergic, and opioid systems (Bueno et al., 2017; Damião et al., 2021; Kicman, 2008). Zelleroth and collaborators demonstrated, in vitro, that cortical neuronal cells from rats treated with anabolic steroids exhibited impaired mitochondrial function, reduced neurite outgrowth, and reduced expression in the Tubb3 gene which is associated with cognitive deficits and increased neuronal death (Zelleroth et al., 2021). These factors may be related to the development of psychiatric disorders (Huang and Song, 2019). Furthermore, long-term AAS use has also been linked to structural changes in brain regions like the prefrontal cortex, hippocampus, amygdala (Scarth and Bjørnebekk, 2021), and hypothalamus (Pozzi et al., 2021). These morphological changes are related to changes in executive function, emotional control (Scarth and Bjørnebekk, 2021), and the control of food intake (Friedman, 2016; Pozzi et al., 2021). Chronic use of nandrolone decanoate at supraphysiological doses in rats was associated with a decrease in food intake, a reduction in the plasma leptin levels, and an increase in orexin-A, causing changes in energy metabolism through changes in neuroendocrine responses (Pozzi et al., 2021).

The findings suggest that chronic high-dose use of anabolic steroids induces morphological brain changes, including cortical atrophy and amygdala hypertrophy (Bertozzi et al., 2019). These structural alterations are linked to anxiety-related behaviors, potentially mediated by mechanisms involving corticotropin-releasing factor and increased GABAergic inhibition in the central amygdala and bed nucleus of the stria terminalis (Bertozzi et al., 2018). Furthermore, prolonged use of anabolic steroids has been shown to modulate the expression of serotonin receptors, leading to a reduction in serotonin activity within the CNS (Seo et al., 2008). This alteration in serotonin signaling also affects the release of other neurotransmitters, including acetylcholine in the hippocampus and dopamine in the prefrontal cortex. These changes in neurotransmitter dynamics are implicated in the manifestation of aggressive behavior (Bertozzi et al., 2018).

In summary, AAS use can significantly impact females' brains, particularly during adolescence, and can lead to significant structural brain changes in females, resulting in increased aggression, anxiety, and mood alterations that may contribute to psychiatric disorders. Prolonged high-dose use can affect brain regions like the prefrontal cortex and amygdala, impairing emotional regulation, executive function, and neuroendocrine responses. Furthermore, concurrent use of AAS with CNS stimulants, such as amphetamines, or depressants, like benzodiazepines, can significantly intensify mood and behavioral side effects. AAS alone can increase aggression and irritability, effects that stimulants may further amplify. Conversely, depressants may exacerbate the depressive symptoms frequently associated with AAS withdrawal, compounding the psychological risks inherent to AAS use (Kanayama et al., 2018a).

4.2. Hepatic system

The effects of compounds derived from testosterone have been investigated in various contexts and organisms (Arver et al., 2018; Viega et al., 2020). These compounds are administered via intramuscular, sublingual, or transcutaneous methods (Anawalt, 2019). Specifically, 17α-alkylated anabolic steroids, that involve the addition of an alkyl group to the 17α-carbon position of testosterone, were developed to improve bioavailability and prolong action (Kicman, 2008). This modification results in an orally administered compound with a notable reduction in liver degradation, preventing inactivation of first-pass hepatic metabolism and increasing bioavailability (Albano et al., 2021; Neri et al., 2011; Solimini et al., 2017). While these modifications improve anabolic potency relative to androgenic effects, they are also associated with hepatotoxicity (Ramírez-Hernández et al., 2023; Solimini et al., 2017). In a case study, a 29-year-old male patient developed severe hepatocellular cholestasis after a five-month with a combination of mesterolone, testosterone undecanoate, nandrolone undecanoate, oxymetholone, stanozolol, and testosterone (Sánchez-Osorio et al., 2008).

Hepatotoxicity is a prevalent manifestation of severe effects resulting from synthetic compound abuse, particularly due to the active participation of the liver in metabolic reactions and the inhibition of excretion by exogenous substances (Bond et al., 2016; Schwingel et al., 2011). The overload of AAS impairs primary liver functions, leading to hepatotoxicity (Marocolo et al., 2018). AAS presence in liver tissue increases oxidative stress and mitochondrial oxidation, generating an imbalance between free radical production and the integrity of the cellular framework, ultimately causing liver damage (Arazi et al., 2017). Antioxidants have shown protective effects against AAS-induced hepatotoxicity (Frankenfeld et al., 2014).

This susceptibility appears to correlate with the dosage and potency of synthetic compounds (Socas et al., 2005). AAS induces intracellular androgenic actions that stimulate gene cascades essential for cellular homeostasis. However, the use of nandrolone decanoate (ND) in rats for five weeks found an increase in collagen deposition in the liver parenchyma, expression of markers of liver necrosis, production of inflammatory cytokines, and subsequent intensification of the immune response (Solimini et al., 2017). Additionally, AAS administration is linked to transient elevations in serum enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which indicate hepatocellular injury (Hartgens and Kuipers, 2004; Petrovic et al., 2022). The use of nandrolone decanoate in rats for six- and twelve weeks increased AST and ALT, regardless of the dose and duration of use (Salem and Alnahdi, 2020).

How women preferentially use AAS orally, these compounds, especially 17α-alkylated AAS, improve bioavailability but are linked to hepatotoxicity, leading to liver damage, oxidative stress, and, in severe cases, the development of liver tumors. These adverse effects are dose-dependent and worsen with prolonged use, highlighting the risks associated with AAS misuse in women.

4.3. Renal system

The renal system is essential for toxin excretion, fluid and electrolyte balance, blood pressure regulation, hormone secretion, and urine production (Hartgens and Kuipers, 2004). Prolonged androgen administration can lead to significant morphofunctional changes and nephrotoxicity (D'Errico et al., 2011; Filho et al., 2020). Morphologically, these changes predominantly affect the glomeruli, leading to mesangial matrix accumulation, podocyte attenuation, and structural adaptations (Brasil et al., 2015; D'Errico et al., 2011; Kahal and Allem, 2018; Riezzo et al., 2014). As a result, serum creatinine levels may rise, and conditions such as focal segmental glomerulosclerosis (FSGS), tubular atrophy, interstitial fibrosis, and chronic kidney disease (CKD) may develop (Davani-Davari et al., 2019; Luciano et al., 2014).

In male mice, intramuscular administration of nandrolone decanoate (ND) has been shown to induce significant histopathological alterations in the kidneys, including glomerular atrophy, severe rupture of the tubular walls, degeneration, hemorrhage, extensive necrosis, and bulky hyaline casts. Notably, renal histopathological changes were more pronounced six weeks after discontinuing androgens, indicating that complications may persist even after the use is discontinued (Kahal and Allem, 2018). Prolonged administration of ND in male rodents has been linked to increased oxidative stress, elevated levels of pro-inflammatory and pro-apoptotic markers (e.g., IL-1β, Hsp90, TNF), and a reduction in the activity of antioxidant enzymes, such as glutathione reductase and peroxidase. The increase in reactive oxidant species combined with an increase in proinflammatory and proapoptotic markers results in oxidative kidney injury and activation of intrinsic and extrinsic apoptotic pathways mediated by TNF-α, culminating in the development of focal segmental glomerulosclerosis (FSGS) (Riezzo et al., 2014).

These findings suggest that prolonged use of anabolic steroids is associated with nephrotoxic effects and kidney morphofunctional damage, potentially progressing to advanced chronic kidney disease (Davani-Davari et al., 2019). Oxidative stress, apoptosis, and inflammation are the main mechanisms involved in kidney damage (Albano et al., 2021). Well-designed experimental and clinical trials are needed, given the scarcity of relevant studies in the literature and the lack of comprehensive exploration of the underlying mechanisms involved (Davani-Davari et al., 2019).

Thus, prolonged use of AAS, particularly ND, is associated with nephrotoxic effects and morphofunctional changes in the renal system. Although oxidative stress, inflammation, and apoptosis are known mechanisms underlying kidney damage, the specific renal effects of AAS in women remain largely unexplored, highlighting the urgent need for well-designed experimental and clinical trials to investigate these effects.

4.4. Cardiovascular system

Studies in Wistar rats have demonstrated that the administration of high doses of AAS induces several cardiovascular alterations, including increased blood pressure (Ronchi et al., 2021), pathological cardiac hypertrophy, and left ventricular mass expansion (Dantas et al., 2021; Ronchi et al., 2021). AAS administration also leads to elevated triglycerides, decreased HDL-c, and maintained LDL-c levels (Rosca et al., 2019). In Wistar rats, unlike humans, LDL-c is not a major cholesterol transporter (Oschry and Eisenberg, 1982), potentially explaining the minimal changes in LDL-c observed (Rosca et al., 2019). Vascular reactivity to phenylephrine and acetylcholine showed no alterations in male Wistar rats treated with AAS (Seara et al., 2020). However, female Wistar rats treated with AAS found impairments in vascular reactivity to the vasodilator antagonist, acetylcholine, in mesenteric arteries (Caliman et al., 2017), suggesting possible sex-related differences in vascular response.

Cardiovascular side effects of AAS use, which vary due to individual differences, manifest with different signs and symptoms (Kindermann, 2006). AAS supplements may induce cardiovascular diseases, such as coronary artery disease (CAD) (Schrör et al., 1994), hypertension (Gheshlaghi et al., 2015), cardiac arrhythmias (Hernández-Guerra et al., 2019), cardiomyopathy (Montisci et al., 2012), thromboembolism (Freedman et al., 2015) and, notably, sudden death (Liu and Wu, 2019; Montisci et al., 2012). These risks are prevalent among athletes, bodybuilders, and long-term AAS users (Ahlgrim and Guglin, 2009).

Chronic exposure to AAS causes significant cardiovascular alterations due to androgen receptors in the myocardium and blood vessels (Bergink et al., 1985). High doses of AAS have been shown to cause severe cardiovascular effects, directly harming cardiomyocytes (Marsh et al., 1998), disrupting lipid metabolic disorders (Kuipers et al., 1991), reducing HDL-c and total cholesterol while increasing LDL-c levels (Nieschlag and Vorona, 2015), promoting atherogenesis and increasing the risk of myocardial infarction (Ference et al., 2017).

Prolonged AAS use also increases plasma homocysteine levels, contributing to coronary atherosclerosis (Peoples et al., 2014). Animal studies investigating nandrolone decanoate in rats demonstrate impaired cardiac protection induced by physical activity, suggesting that AAS may mediate cardiac ischaemic events via oxidative stress (Chaves et al., 2006). Similarly, primates supplemented with AAS exhibit accelerated development of coronary sclerotic changes (Obasanjo et al., 1996). Boldenone undecylenate use over four years promoted dilated cardiomyopathy with a 20 % ejection fraction (Jamal et al., 2022). Thus, cardiac dysfunction and tissue changes are associated with AAS abuse (Ahlgrim and Guglin, 2009; Garner et al., 2018; Han et al., 2015; Ilonze et al., 2022), a condition also associated with apoptosis and fibrosis in cardiac tissue (Ilonze et al., 2022). In vitro studies corroborate these findings, highlighting the role of AAS in promoting tissue fibrosis and apoptosis (Zaugg et al., 2001).

The use of AAS is also associated with a significant increase in both systolic and diastolic blood pressure, which is proportional to the duration of use (Gheshlaghi et al., 2015). This hypertensive effect is suggested to be mediate by stimulation of the renal renin-angiotensin system, leading to elevated blood pressure (Kuipers et al., 1991). In addition, AAS use is associated with myocardial toxicity, potentially triggering defense mechanisms that increase collagen deposition in the heart (Montisci et al., 2012). While increased blood pressure has been observed in studies in male athletes (Gheshlaghi et al., 2015) and animals (Rämö, 1987; Trifunovic et al., 1995), there is a lack of research on these effects in females.

In women, AAS use has been linked to cardiovascular impairments, with studies in female rats showing reduced vascular reactivity, suggesting sex-specific vulnerabilities. Although the cardiovascular effects of AAS, such as hypertension and lipid imbalances, are well-documented in men, comparable studies in women remain scarce, highlighting the urgent need for further studies to fully assess the impact on women's cardiovascular health.

4.5. Reproduction and offspring

The influence of AAS on female fertility is a complex and underexplored topic. However, existing evidence suggests that the use of these substances can inhibit the pulsatile secretion of gonadotropin-releasing hormone in the hypothalamus, disrupting the release of ovarian hormones that are crucial for follicular development and ovulation (Karila et al., 2024). This hormonal disruption may lead to perturbations in the menstrual cycle, such as spaniomenorrhea and amenorrhea, anovulation, ultimately resulting in infertility (Karila et al., 2024; Saadedine et al., 2023).

Despite biotechnological advances, understanding the implications of maternal hormone supplementation during pregnancy for offspring remains limited. However, such supplementation can significantly impact the reproductive, neuronal, and metabolic development of the offspring (Auyeung et al., 2013; Chura et al., 2010; Marciniak et al., 2017; Steckler et al., 2007), as shown in Fig. 3. The intrauterine environment, through fetal programming, plays a crucial role in influencing fetal health, with long-term implications for disease predisposition and overall development (Marciniak et al., 2017). Changes in this environment directly affect fetal development and may increase susceptibility to various diseases later in life.

Experimental studies have shown that the administration of androgens to ewes during pregnancy leads to profound alterations in offspring development. These include a reduction in testicular weight, decreased Sertoli cell numbers, a marked reduction in spermatids, changes in seminiferous tubule dimensions, and an increase in anti-Müllerian hormone expression (Padmanabhan and Veiga-Lopez, 2014; Recabarren et al., 2017). These changes indicate a broad impairment of spermatogenesis, which can compromise the reproductive system in the long term. Prenatal exposure to testosterone has also been found to affect key

Effects on Offers of maternal hormone supplementation:

HUMAN	ANIMALS
Amniotic fluid (high concentrations of fetal testosterone)	**Androgens administration during the gestational period**
• Less visual contact and vocabulary extension. • Fewer social relationships. • Less vocabulary extension. • Asymmetry of the corpus callosum. • Higher scores on autism spectrum tests. • Masculinized behaviors.	• Reduction in testicular weight and spermatids. • Restricted intrauterine growth. • Altered ovulation patterns. • High expression of proinflammatory cytokines. • Increased expression of anti-Müllerian hormone. • Insulin resistance.

Fig. 3. Effects of high androgen levels in amniotic fluid or maternal androgen supplementation on offspring health in humans or animals.

reproductive parameters in adult offspring, including mating behavior, pregnancy rates, and the regulation of the hypothalamus-pituitary–gonadal axis (Cardoso et al., 2015; Steckler et al., 2007). Furthermore, this exposure disrupts the secretion of reproductive hormones in females, resulting in altered ovulation patterns and impaired follicular development (Padmanabhan and Veiga-Lopez, 2014).

Notably, the stage of embryonic development during which exposure occurs plays a critical role in the severity of outcomes. Early exposure to androgens tends to result in more pronounced changes and dysfunctions, underscoring the risks associated with hormonal imbalances at any stage of fetal development (Padmanabhan and Veiga-Lopez, 2014; Unsworth et al., 2005). Timing is particularly crucial, as exposure to testosterone during critical windows of neurodevelopment can lead to lasting damage to the developing nervous system. Studies in children have shown that increased fetal testosterone levels in amniotic fluid are associated with specific behavioral outcomes, such as reduced eye contact and language acquisition in toddlers, fewer social interactions in 4-year-olds, more masculinized behaviors, lower empathy, and higher autism spectrum disorder (ASD) scores in children aged 6 to 9 years (Auyeung et al., 2013; Chura et al., 2010; Knickmeyer and Baron-Cohen, 2006). Furthermore, fetal androgen excess has been linked to structural changes, such as asymmetry in the isthmus of the corpus callosum, although no significant asymmetries were observed in other regions or in the total corpus callosum area. The specific impact of this asymmetry on neurodevelopmental outcomes, particularly language development, warrants further investigation (Padmanabhan and Veiga-Lopez, 2014).

Understanding the broader implications of prenatal androgen exposure is particularly relevant given the rising prevalence of neurodevelopmental disorders, such as ASD and attention deficit hyperactivity disorder (ADHD), in contemporary populations. This underscores the necessity of investigating the effects of androgen exposure during critical windows of fetal development and elucidating the underlying pathophysiological mechanisms involved.

In addition to reproductive and neurodevelopmental impacts, metabolic alterations have also been observed. Studies involving ewe offspring exposed to testosterone concentrations equivalent to those found in males showed metabolic changes, including insulin resistance and high expression of pro-inflammatory cytokines such as interleukin 1β, interleukin 6, TNF-alpha and CCL2 (Cardoso et al., 2015). Moreover, restricted intrauterine growth, low birth weight, and placental dysfunction were frequently observed, potentially predisposing individuals to future metabolic and cardiovascular complications (Auyeung et al., 2013; Recabarren et al., 2005; Salam et al., 2014). These animals also exhibited significant alterations in plasma concentrations of aldosterone, epinephrine, glucose, sodium, and chloride ions, along with increased mean arterial pressure (King et al., 2007).

5. Genotoxicity and carcinogenic mechanisms linked to AAS

In addition to the previously described adverse effects, the genotoxicity mechanism (Fig. 1) of AAS is not well understood. Still, it is believed to involve a combination of genetic and epigenetic factors, including DNA methylation, histone modifications, and chromatin condensation (Salerno et al., 2018). Moreover, AAS can be metabolized to 17β-estradiol, which has been linked to estrogen-dependent breast cancer and is considered a potential mutagenic and carcinogenic mediator (Liehr, 2000), mainly for women. Testosterone has been found to increase ovarian cancer cell viability via telomerase expression, activity, and phosphorylation, and by blocking phosphatidylinositol 3-kinase pathway inhibitors (Salerno et al., 2018). Alterations in telomerase activity are at the basis of stanozolol-induced DNA-damaging effects, and AAS effects are linked to dosage and frequency of administration (kara et al., 2017).

Prolonged AAS use can result in cholestatic liver lesions, peliosis hepatis (a vascular condition in which the sinusoids of the liver proliferate), and is associated with liver tumors, including adenomas and hepatocellular adenoma and/or carcinoma (Bond et al., 2016; Nieschlag and Vorona, 2015). The likely etiology of tumors and liver nodular regeneration may derive from the dysregulation of hepatocytic growth in response to exposure to AAS (Nakao et al., 2000; Petrovic et al., 2022). The specific types of AAS most frequently associated with the development of liver tumors include oxymetholone, testosterone, nandrolone, and stanozolol. Moreover, studies have highlighted the increased risk of liver tumors linked to AAS use, especially in the context of recreational consumption for bodybuilding purposes (Pinazo-Bandera et al., 2022).

Anabolic steroids can also alter the expression of microRNAs (miRNAs) (Sessa et al., 2020a). These small non-coding RNAs play a crucial role in gene regulation and may be associated with a molecular mechanism underlying the detrimental effects of anabolic steroids (Sessa et al., 2020a; Sessa et al., 2020b). Studies conducted in men have shown that the use of AAS modifies the expression profile of miRNAs in various organs, including the brain, kidneys, and Leydig cells. This alteration may contribute to the development of behavioral changes, chronic liver

diseases, and tumors (Salerno et al., 2018; Sessa et al., 2020a; Sessa et al., 2020b). Given these findings, future research should focus on several key areas. Longitudinal studies are necessary to assess the long-term effects of AAS on miRNA expression and their subsequent impact on health outcomes. Moreover, further investigations are needed to elucidate the mechanisms by which altered miRNA profiles contribute to specific adverse health effects associated with AAS use. Lastly, expanding research to include diverse populations, particularly women, is essential to understand the full spectrum of AAS-related health risks.

6. Discussion and conclusion

Although AAS are commonly used by both amateur and professional athletes to improve athletic performance and promote muscle growth, their use is not without significant risk (Albano et al., 2021). Improper use, particularly at high doses, leads to widespread adverse effects on several tissues and organs (Bordin et al., 2017). Mechanisms such as oxidative stress, apoptosis, and changes in protein synthesis have been associated with tissue damage and short-term side effects (Arver et al., 2018; Isenmann et al., 2019; Viega et al., 2020). Among the serious adverse effects is the development of non-alcoholic fatty liver disease (NAFLD), along with hepatotoxicity, renal dysfunction, immune system disturbances, increased risk of cardiovascular disease, genetic alterations, and the potential for sudden death (Bordin et al., 2017; Büttner and Thieme, 2010).

Psychological and behavioral consequences are also substantial, with manifestations including aggression, hostility, and mood disorders (Alrabadi et al., 2020). Moreover, AAS can lead to dependency, which has become an increasingly significant public health problem (Bordin et al., 2017; Kanayama et al., 2018b). Despite these well-documented risks, studies focusing on the effects of AAS in female organisms remain limited. While some evidence suggests potential therapeutic uses for conditions such as aplastic anemia, hereditary angioedema (Vergallo et al., 2020), catabolic conditions (Karim et al., 1973; Ring et al., 2020), endometriosis and uterine fibroids (Pinto et al., 2023), there is insufficient evidence to support the use of anabolic steroids in women for other clinical purposes due to the lack of comprehensive studies on safety and efficacy (Davis et al., 2019; Goldstein et al., 2017; Wierman et al., 2014). Furthermore, AAS supplementation in women can profoundly affect reproductive, neurological, and metabolic systems, with potential consequences for their offspring (Auyeung et al., 2013; Chura et al., 2010; Marciniak et al., 2017; Steckler et al., 2007). In Brazil, substances such as stanozolol, oxandrolone, and gestrinone are listed under Ordinance SVS/MS N° 344/1998, in category C5, and are subject to special control. Additionally, the use of anabolic–androgenic steroids for aesthetic purposes, muscle mass gain, and athletic performance enhancement is strictly prohibited (BRASIL, 2023). Moreover, emerging anabolic steroids available on the black market pose significant health risks due to their unregulated nature and potential for contamination. Substances such as methasterone, methylstenbolone, and Selective Androgen Receptor Modulators (SARMs) are examples of these compounds. The lack of oversight in their production can lead to variability in potency and purity, increasing the likelihood of adverse effects and complicating clinical outcomes (Mohideen et al., 2023).

Given this background, the present review underscores the urgent need for further investigation into the implications of AAS use in women across various clinical contexts and calls for informed discussions regarding the safety and long-term effects of these substances in female populations.

CRediT authorship contribution statement

Beatriz Menegate Santos: Writing – original draft, Investigation, Formal analysis, Data curation. **Jessica Peres Alves de Souza:** Writing – original draft, Methodology, Investigation. **Luísa Rodrigues de Paula Goulart:** Writing – original draft, Methodology, Investigation, Formal analysis. **Jéssica Castro Pereira Petrine:** Writing – original draft, Methodology, Investigation. **Fernando Henrique Ferrari Alves:** Writing – original draft, Methodology, Funding acquisition. **Bruno Del Bianco-Borges:** Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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