Research Article ISSN 2768-6647

Medical and Clinical Case Reports

# Androgenic Activity of Progestins and Its Dermatological Implications: A Literature Review

**Agnes Belem Mega and Rodrigo Cé***

*Department of Biomedical Sciences, Centro Universitário Avantis, UNIAVAN, Av. Marginal Leste, Estados, Balneário Camboriú, Santa Catarina, Brazil.*

***Correspondence:**
Professor, Dr. Rodrigo Cé, Department of Biomedical Sciences, Centro Universitário Avantis, UNIAVAN, Av. Marginal Leste, Estados, Balneário Camboriú, Santa Catarina, Brazil.

**Received:** 06 Aug 2026; **Accepted:** 08 Sep 2026; **Published:** 19 Sep 2026

**Citation:** Agnes Belem Mega, Rodrigo Cé. Androgenic Activity of Progestins and Its Dermatological Implications: A Literature Review. Med Clin Case Rep. 2026; 6(3): 1-18.

## ABSTRACT

*Progestins are synthetic steroid hormones widely used in hormonal contraceptives, but their pharmacological effects vary according to molecular structure, receptor affinity, and androgenic or antiandrogenic activity. These differences may be clinically relevant in androgen-dependent dermatological conditions, particularly adult female acne and androgenetic alopecia. This literature review aimed to examine the relationship between the androgenic activity of progestins and their potential dermatological effects, with emphasis on the hormonal mechanisms underlying adult acne and androgenetic alopecia and on differences among individual progestin profiles. A qualitative literature review was conducted using PubMed/MEDLINE, Web of Science, SciELO, Google Scholar, and the Virtual Health Library. Publications addressing progestin pharmacology, androgenic activity, hormonal mechanisms, acne, androgenetic alopecia, and related dermatological effects were considered. The reviewed literature indicates that progestins differ substantially in their interactions with steroid receptors and consequently exhibit distinct androgenic, antiandrogenic, and tissue-specific effects. Progestins with greater androgenic activity may enhance androgen-dependent processes in susceptible individuals, including sebaceous gland activity and follicular responses, whereas compounds with antiandrogenic properties may exert different effects on androgen-sensitive tissues. In adult female acne, these mechanisms may interact with sebaceous activity, follicular keratinization, inflammation, and peripheral androgen sensitivity. In androgenetic alopecia, the potential influence of progestins appears to depend largely on genetic susceptibility, local androgen metabolism, androgen receptor activity, and follicular sensitivity. Therefore, the dermatological effects of progestins should be considered within the broader context of individual pharmacological profiles and patient characteristics. Further clinical studies are warranted to better define the magnitude and clinical relevance of these associations.*

## Keywords

Progestins, Androgenic Activity, Adult Female Acne, Androgenetic Alopecia, Hormonal Contraception.

## Introduction

Progestins are synthetic steroid hormones widely used in hormonal contraceptives and play an important role in the regulation of the hypothalamic–pituitary–ovarian axis and prevention of ovulation [1]. Their contraceptive effects are mainly mediated by suppression of the luteinizing hormone surge, increased cervical mucus viscosity, and changes in tubal motility, which together reduce the likelihood of fertilization [1,2]. However, progestins differ substantially in their pharmacological properties and receptor affinities, resulting in distinct systemic effects, including effects on the skin and hair follicles [3]. Those with androgenic properties may activate androgen receptors and consequently influence sebaceous gland activity and follicular function [3,4].

Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit characterized by comedones, papules, and pustules, with nodules and scarring occurring in more severe cases [5,6]. Its development involves several interrelated mechanisms,

including increased sebaceous gland activity, follicular hyperkeratinization, proliferation of *Cutibacterium acnes*, and local inflammatory responses [6,7]. Although commonly associated with adolescence, acne may persist or develop during adulthood, particularly among women, and may follow a prolonged or recurrent course [8]. Hormonal factors, together with genetic and environmental influences, contribute to its multifactorial pathogenesis [4].

Androgenetic alopecia (AGA) is the most common form of progressive hair loss and results from the gradual miniaturization of susceptible hair follicles [9]. Genetic predisposition and androgen signaling are central to its pathogenesis, with dihydrotestosterone (DHT) playing a major role through its interaction with androgen receptors in the hair follicle [9,10]. Increased androgen signaling promotes follicular miniaturization and progressively alters the hair cycle, resulting in shorter anagen phases and the production of increasingly thinner hair shafts [10,11]. The clinical course is gradual and varies according to genetic susceptibility and hormonal factors.

Acne and AGA share important pathogenic mechanisms related to androgen signaling in the pilosebaceous unit and hair follicle [4,10]. Consequently, the androgenic profile of progestins may be clinically relevant in individuals susceptible to these conditions. Progestins with androgenic activity may contribute to the development or worsening of acne and, in susceptible individuals, may influence androgen-dependent hair follicle changes [3,4]. Knowledge of the pharmacological characteristics and androgenic potential of individual progestins is therefore relevant when selecting hormonal contraceptive methods, particularly for patients with a history or predisposition to androgen-related dermatological conditions [1,2].

The androgenic properties of progestins may influence androgen-dependent tissues, particularly the skin and hair follicles, and their effects may vary according to molecular structure, receptor affinity, and tissue-specific sensitivity [3,4,8-10]. These pharmacological differences are clinically relevant because adult female acne and androgenetic alopecia are influenced by androgen signaling, although both conditions have multifactorial pathophysiology and may occur in the absence of systemic androgen abnormalities [3,4]. Therefore, understanding the androgenic profile of individual progestins may contribute to a more comprehensive assessment of their potential dermatological effects. Accordingly, this literature review aimed to synthesize the available evidence on the pharmacological and hormonal mechanisms underlying the androgenic activity of progestins and to discuss their potential implications for adult female acne and androgenetic alopecia, with particular emphasis on differences among progestin profiles and their clinical relevance.

## Methodology

This study consists of a qualitative literature review aimed at analyzing the association between progestins with androgenic activity and the development or exacerbation of acne and androgenetic alopecia. A bibliographic search was conducted in PubMed/MEDLINE, Web of Science, Scientific Electronic Library Online (SciELO), Google Scholar, and Virtual Health Library (BVS). Searches were performed using combinations of the following keywords and their corresponding terms in English: “progestins”, “androgenic activity”, “acne”, “adult female acne”, “androgenetic alopecia”, “androgens”, “hormonal contraceptives”, and “hormonal therapy”, combined using the Boolean operators AND and OR. Eligible publications included original research articles, clinical and observational studies, literature and systematic reviews, clinical guidelines, and relevant book chapters published in English or Portuguese. Studies were included when they addressed the hormonal mechanisms, androgenic activity, or dermatological effects of progestins, particularly in relation to acne and androgenetic alopecia. Duplicate studies, publications unrelated to the research topic, studies lacking sufficient scientific basis, and articles without full-text availability were excluded. The selected literature was qualitatively analyzed and thematically organized according to the androgenic profile of progestins, underlying hormonal mechanisms, and their dermatological implications.

## Theoretical Framework

### Androgens

#### Types of Androgens: Synthesis, Structure, and Biological Functions

Androgens comprise a group of steroid hormones involved in a broad range of physiological processes. The principal androgens include testosterone, DHT, androstenedione, and dehydroepiandrosterone (DHEA) [12,13]. They are produced predominantly by the gonads and adrenal glands, although their biological activity varies according to their receptor affinity, metabolic conversion, and tissue-specific actions [14]. Testosterone is the major circulating androgen, whereas DHT, which is generated through the enzymatic activity of 5α-reductase, exhibits greater androgenic potency at the receptor level [15]. In addition, DHEA and androstenedione function as important precursors within the androgen biosynthetic pathway and can subsequently be converted into more biologically active steroids in peripheral tissues [13].

Androgen biosynthesis begins with cholesterol, which is transported into the mitochondria and converted into pregnenolone, a process involving the steroidogenic acute regulatory protein (StAR) [16,17]. Pregnenolone subsequently serves as a precursor for the synthesis of DHEA and androstenedione through the coordinated activity of steroidogenic enzymes, including cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1) and 3β-hydroxysteroid dehydrogenase (3β-HSD), which are essential for the progression of steroidogenic pathways [18]. In peripheral tissues, these precursors can undergo further enzymatic conversion to testosterone, thereby contributing to the local generation of biologically active androgens [19]. The overall regulation of androgen biosynthesis depends on substrate availability, enzyme expression, and enzymatic activity, all of which influence the amount of hormone produced and its subsequent tissue availability [4].

Structurally, androgens share the characteristic steroid nucleus

composed of four interconnected carbon rings. This configuration contributes to their lipophilic properties, facilitating passage across cell membranes and interaction with intracellular steroid receptors [12,20]. Following androgen binding, the androgen receptor undergoes a conformational change and forms a hormone–receptor complex that can interact with specific DNA sequences and regulate the transcription of target genes [21]. Through this mechanism, androgens influence several cellular processes, including proliferation, differentiation, and metabolism [22]. In the skin, androgen signaling is particularly relevant to sebaceous gland activity, hair growth, and the regulation of the pilosebaceous unit [23].

## Mechanisms of Androgen Action

Androgens exert their biological effects through both genomic and non-genomic mechanisms, which interact to produce tissue-specific cellular responses [24]. The genomic pathway is primarily mediated by binding of the hormone to the intracellular androgen receptor, followed by receptor activation, nuclear translocation, and regulation of the transcription of androgen-responsive genes. This mechanism generally produces relatively slower but sustained cellular responses [25].

In contrast, non-genomic androgen signaling can elicit more rapid cellular responses without requiring direct changes in gene transcription [12]. These effects may involve membrane-associated receptors and the activation of intracellular signaling cascades, including the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways, as well as other protein kinase-dependent mechanisms [12,26,27]. Such signaling allows androgens to rapidly influence cellular functions, including enzyme activity, intracellular communication, and cellular responses to extracellular stimuli [12].

The interaction between genomic and non-genomic pathways contributes to the complexity of androgen signaling and enables the integration of rapid and sustained cellular responses [28]. This interplay is particularly relevant in the skin, where androgen activity regulates several components of the pilosebaceous unit and contributes to the control of sebaceous gland function and hair follicle biology ]8,29]. Therefore, androgen signaling should be regarded as an integrated network of molecular mechanisms rather than as an exclusively transcription-dependent process, helping to explain the diversity and tissue specificity of androgen-mediated effects [30].

## Regulation of Testosterone Synthesis and Bioavailability

Testosterone production is primarily regulated by the hypothalamic–pituitary–gonadal axis. Within this endocrine system, hypothalamic secretion of gonadotropin-releasing hormone (GnRH) stimulates the pituitary release of luteinizing hormone (LH), which subsequently regulates gonadal steroidogenesis. In females, LH acts on ovarian theca cells and contributes to androgen production, particularly androstenedione and testosterone precursors [31,32]. This axis is regulated through negative feedback mechanisms involving circulating sex steroids, which modulate hypothalamic and pituitary activity and thereby contribute to endocrine homeostasis [31,33]. Age, metabolic status, and other physiological factors can also modify the activity of this regulatory system, consequently influencing androgen production [32]. Testosterone homeostasis therefore results from a complex interaction between central neuroendocrine regulation, gonadal steroidogenesis, and peripheral hormone metabolism [31,34].

The tissue availability of testosterone is further determined by its association with plasma proteins, particularly sex hormone-binding globulin (SHBG), which plays an important role in regulating the circulating pool of biologically available hormone [35]. Most circulating testosterone is protein-bound, whereas only a relatively small proportion remains unbound and is readily available for diffusion into target tissues [35,36]. According to the free hormone hypothesis, the unbound fraction represents an important determinant of direct steroid action at the tissue level [35]. SHBG also contributes to the transport, distribution, and circulating half-life of testosterone, thereby influencing its overall bioavailability [37].

Testosterone availability is additionally affected by metabolic and physiological factors that alter SHBG concentrations and, consequently, the proportion of circulating testosterone that remains free or bioavailable [38]. Obesity, aging, and hormonal alterations, for example, may modify SHBG levels and thereby influence androgen availability at target tissues [38,39]. Hepatic synthesis of SHBG and its interaction with circulating steroid hormones are therefore important components of the mechanisms governing systemic and tissue-specific androgen activity [39].

## Local Androgen Synthesis and Action in the Skin

The skin is an active endocrine and intracrine organ capable of locally metabolizing androgen precursors into biologically active steroids [40,41]. The pilosebaceous unit expresses several steroidogenic and steroid-metabolizing enzymes, including 5α-reductase and aromatase, which participate in the conversion of circulating precursors into locally active hormones, including DHT [40,42]. This enzymatic machinery enables cutaneous tissues to regulate androgen activation independently of circulating hormone concentrations, allowing local androgen signaling to be adapted to the specific requirements of individual tissues [13,43]. Consequently, peripheral steroid metabolism represents an important determinant of the biological effects of androgens in the skin [14,40].

Androgens play a central role in the regulation of sebaceous gland activity and pilosebaceous unit function, influencing both sebum production and hair follicle growth [44,45]. Androgen signaling promotes sebocyte proliferation and lipogenesis, thereby affecting the quantity and composition of sebum produced by the sebaceous glands [40,45]. In addition, androgens influence the hair follicle cycle and may affect the progression through its principal phases, including anagen, catagen, and telogen [46,47].

The magnitude of these effects depends not only on circulating androgen concentrations but also on local androgen receptor expression, receptor sensitivity, and the activity of steroid-metabolizing enzymes within cutaneous tissues [13,14]. Thus, androgen action in the skin reflects the combined effects of local intracrine steroid production, enzymatic metabolism, receptor-mediated signaling, and tissue-specific cellular responses. This integrated system is essential for normal cutaneous physiology but may also contribute to the development and persistence of androgen-dependent dermatological disorders [40,43,45].

## Role of Cutaneous Androgen Production in Acne Vulgaris

The contribution of cutaneous androgen metabolism to the pathophysiology of acne vulgaris is closely associated with the local responsiveness of the pilosebaceous unit [48]. Importantly, acne may develop or persist in individuals without clinically significant systemic androgen abnormalities, suggesting that local androgen sensitivity and metabolism may play a substantial role in disease expression [48,49]. Increased responsiveness of cutaneous tissues to androgens may result in enhanced biological effects even when circulating hormone concentrations remain within the physiological range [50,51]. Furthermore, interindividual differences in the expression and activity of steroidogenic enzymes may contribute to variations in clinical presentation and disease severity [40,42].

Androgen signaling is also linked to the regulation of inflammatory processes within the skin and may contribute to the initiation and persistence of the inflammatory response associated with acne vulgaris [50,52]. The interaction between androgen-mediated alterations in the pilosebaceous unit and local inflammatory pathways may therefore facilitate the progression of acne lesions and contribute to more persistent or severe clinical manifestations [48,53]. In addition, available evidence suggests that androgens can influence cutaneous immune responses and modify the interaction between the pilosebaceous environment and *Cutibacterium acnes* [44,51]. These findings support the concept that androgen activity in acne is not limited to sebaceous gland stimulation but involves a broader network of endocrine, intracrine, metabolic, and inflammatory mechanisms within the skin.

## Pathophysiology of Adult Acne

Adult acne is a multifactorial inflammatory disorder resulting from the interaction of hormonal influences, sebaceous gland dysfunction, follicular abnormalities, alterations in the cutaneous microbiota, and dysregulated inflammatory responses [5,54]. Its pathogenesis has traditionally been described in terms of four interrelated mechanisms: increased sebaceous gland activity, abnormal follicular keratinization leading to microcomedone formation, microbial dysbiosis, and subsequent activation of inflammatory pathways [54,55]. Although *Cutibacterium acnes* has historically been considered a major contributor to acne development, changes in the broader skin microbiota, including alterations involving *Malassezia* species, may also influence inflammatory signaling and disease expression [54,56].

The pilosebaceous unit functions as an important peripheral site of androgen metabolism. Within this compartment, 5α-reductase converts testosterone into DHT, a more potent androgen with high affinity for the androgen receptor [55,57]. Increased androgen signaling promotes sebocyte differentiation, lipogenesis, and sebaceous gland activity, thereby contributing to the development of an acne-prone microenvironment [57]. In parallel, alterations in cutaneous immune responses contribute to the initiation and persistence of inflammation, with increased production of pro-inflammatory cytokines and activation of innate immune pathways [5,55,58]. An exaggerated innate immune response may contribute to the persistence of inflammation even in the absence of marked systemic hormonal abnormalities [58].

The clinical course of adult acne may also be influenced by environmental and physiological factors, including psychological stress, metabolic alterations, and exposure to external stimuli that can modify sebaceous gland activity and cutaneous inflammatory responses [54,58]. Clinically, adult acne frequently differs from adolescent acne, with lesions often predominating in the lower face, particularly the mandibular and perioral regions, and with a tendency toward persistent inflammatory lesions [54]. Thus, adult acne reflects a complex interplay between endocrine, metabolic, microbial, follicular, and immune mechanisms, which may contribute to its chronicity and therapeutic complexity [5,54,58].

## Excessive and Altered Sebum Production

Sebaceous hypersecretion, or seborrhea, is one of the major components of acne pathogenesis and is strongly influenced by androgen signaling through receptors expressed by sebocytes [48]. Androgen stimulation promotes sebocyte differentiation, glandular growth, and lipid synthesis, increasing both the amount of sebum produced and its availability within the follicular canal [54]. However, acne is not solely associated with increased sebum production. Qualitative changes in sebum composition, often referred to as dysseborrhea, may also contribute substantially to disease development. These changes include increased squalene oxidation and alterations in essential fatty acids, particularly reduced levels of linoleic acid [53,59].

Changes in sebum composition can increase its comedogenic and pro-inflammatory potential, while also affecting the integrity and function of the follicular epithelium [59]. According to Deng, Wang, and He [60], alterations in sebaceous lipid metabolism may compromise the cutaneous barrier and contribute to abnormal follicular keratinization and microbial dysbiosis. In addition, dietary and environmental factors may influence sebaceous lipogenesis and acne severity through metabolic signaling pathways, including those involving insulin-like growth factor 1 (IGF-1) [60,61].

## Androgens, Sebum, and Inflammation

Alterations in sebaceous lipid composition can promote oxidative stress and inflammatory signaling, contributing to the generation of mediators that amplify the cutaneous inflammatory response associated with acne [62]. In this context, *C. acnes* can interact

with innate immune receptors, particularly Toll-like receptor 2 (TLR2), expressed by keratinocytes, sebocytes, and immune cells, thereby promoting local inflammatory signaling [63,64]. Several mediators, including cytokines, proteolytic enzymes, and antimicrobial peptides such as defensins, participate in this response and contribute to the progression of acne lesions [65].

Free fatty acids generated from sebaceous triglycerides may also contribute to the inflammatory environment by stimulating the expression of antimicrobial peptides, including β-defensin-2, and promoting the production of inflammatory mediators such as interleukin-1 (IL-1) [65,66]. These processes illustrate the close relationship between sebaceous lipid metabolism and cutaneous immune activation.

The effects of androgens on sebocyte differentiation and sebogenesis are also mediated, at least in part, through interactions with peroxisome proliferator-activated receptors (PPARs), particularly PPARγ [62,65]. PPARγ is an important regulator of lipid metabolism and sebocyte differentiation and may contribute to the integration of androgenic signaling with metabolic and inflammatory pathways within the pilosebaceous unit [62,63,65]. Crosstalk between the androgen receptor (AR) and PPARγ pathways may therefore represent an important component of acne pathophysiology and a potential therapeutic target. Modulation of these signaling pathways could theoretically reduce sebaceous activity and inflammatory responses, thereby limiting lesion development and supporting restoration of cutaneous homeostasis [63-65].

## Role of Androgen-Mediated Sebum Production in Acne

Androgen stimulation of the sebaceous glands represents a central component of acne pathogenesis because sebocytes are highly responsive to sex steroid signaling and possess extensive steroidogenic and metabolic activity [23]. Binding of DHT to the androgen receptor promotes androgen-responsive signaling within sebocytes and contributes to cellular differentiation and lipid synthesis, thereby increasing sebaceous output and facilitating lipid accumulation within the follicular infundibulum [65]. Excessive sebum production also contributes to microcomedone formation by interacting with abnormal follicular keratinization and retained corneocytes, promoting the development of a keratinous plug within the follicular canal [65]. Furthermore, changes in the lipid-rich follicular environment may influence microbial metabolism and inflammatory signaling, contributing to the persistence of acne-associated inflammation [66]. Importantly, the relationship between sebum and acne is not determined exclusively by its quantity. Changes in the composition and physicochemical properties of sebaceous lipids may alter follicular homeostasis and promote oxidative and inflammatory processes.

## Hormonal Regulation of Sebaceous Glands in Acne Vulgaris

Sebaceous glands are integral components of the pilosebaceous unit and consist predominantly of sebocytes specialized in the synthesis and secretion of sebum [67]. Sebum is a complex lipid mixture containing squalene, wax esters, cholesterol, cholesterol esters, triglycerides, and other lipid-derived compounds [68,69]. Within the skin, sebaceous triglycerides undergo enzymatic hydrolysis, generating free fatty acids that contribute to the physicochemical properties of the skin surface and may participate in antimicrobial defense mechanisms [67,69]. Sebaceous lipids also contribute to epidermal barrier function and may play roles in maintaining skin hydration, protecting against environmental stressors, and preserving cutaneous homeostasis [67,69].

Dysregulation of sebaceous gland activity is closely associated with the pathogenesis of acne vulgaris [62]. Sebum synthesis is strongly regulated by androgen signaling through interactions between circulating and locally produced androgens and androgen receptors expressed by sebocytes [67]. Activation of these receptors promotes cellular differentiation and lipid synthesis, thereby increasing sebaceous gland activity. Conversely, alterations in androgen signaling or androgen receptor activity can substantially modify sebaceous lipid production, highlighting the importance of this pathway in sebaceous gland physiology [67].

## Inflammation and Activation of the Innate Immune Response

Inflammation is a fundamental component of acne vulgaris pathogenesis and is closely associated with activation of the cutaneous innate immune system. *C. acnes* can be recognized by Toll-like receptors, particularly TLR2, expressed on keratinocytes, sebocytes, and immune cells [70,71]. Activation of these receptors initiates intracellular signaling cascades involving transcription factors such as nuclear factor kappa B (NF-κB), ultimately increasing the production of pro-inflammatory cytokines, including IL-1α, IL-1β, and tumor necrosis factor alpha (TNF-α) [70-73].

In addition to TLR-dependent signaling, activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome has been implicated in acne-associated inflammation [70-72]. Oxidized lipids and microbial-derived stimuli may contribute to inflammasome activation, promoting the maturation and secretion of inflammatory cytokines and reinforcing the local inflammatory response [70,72]. Increasing evidence suggests that inflammatory events can occur at very early stages of acne development and may precede the appearance of clinically apparent comedonal lesions [70,73].

The innate immune response in acne is not determined solely by the presence of *C. acnes*. Its magnitude and persistence are influenced by the composition of the cutaneous microbiota, sebaceous lipids, follicular conditions, and host immune responsiveness [72]. Persistent activation of innate immune pathways promotes the recruitment of inflammatory cells and the release of chemokines and cytokines, thereby sustaining local inflammation and contributing to lesion progression [72,74]. Interactions between the skin microbiota and the host immune system are therefore central to the pathophysiology of acne, particularly when alterations in microbial composition or host responsiveness favor prolonged inflammatory signaling [71,75].

### Alterations in Keratinocyte Differentiation and Proliferation

Abnormal keratinocyte proliferation and differentiation are considered important early events in acne development and contribute directly to follicular hyperkeratinization [76]. This process involves excessive accumulation and retention of keratinous material within the follicular canal, resulting in progressive obstruction and formation of the microcomedone, which represents an early precursor of clinically apparent acne lesions [48,77].

Increased keratinocyte proliferation, together with impaired desquamation, contributes to thickening of the follicular keratinous layer and retention of corneocytes within the follicular infundibulum [48,78]. Alterations in keratinocyte differentiation may further impair normal epidermal turnover and facilitate the formation of follicular plugs [79]. These changes are influenced by the local biochemical environment, including inflammatory mediators, sebaceous lipids, and microbial products, which can modify keratinocyte behavior and promote abnormal follicular differentiation.

Follicular hyperkeratinization should therefore be regarded not merely as a mechanical obstruction but as a biologically active process involving interactions among keratinocytes, sebaceous lipids, inflammatory mediators, and the local microbiota. Together, these mechanisms contribute to microcomedone formation and provide a structural and inflammatory environment that facilitates the subsequent development and persistence of acne lesions [76,77].

## Hyperandrogenism and Acne in Adult Women

### Epidemiology of Adult Female Acne

Adult female acne has become increasingly recognized over recent decades and may either persist from adolescence or develop after the age of 25 years, constituting a condition commonly referred to as adult female acne [80,81]. Its prevalence varies considerably across populations and study designs, with estimates ranging from approximately 40% to 55% among adult women [80]. Acne in women also tends to follow a more prolonged course than that observed in men, frequently persisting into the fourth or fifth decade of life [82]. These findings suggest that adult female acne has distinct epidemiological characteristics and should not be regarded solely as a continuation of adolescent acne [83]. Clinically, adult female acne exhibits characteristic patterns of distribution and disease course. Lesions predominantly affect the lower third of the face, particularly the mandibular and chin regions, and are often persistent or recurrent [81,82]. Beyond its dermatological manifestations, the condition can substantially impair quality of life and is frequently associated with psychosocial consequences, including anxiety and reduced self-esteem [81,82].

### Prevalence of Hyperandrogenism in Women with Adult Acne

A subset of women with persistent or late-onset acne presents with hormonal abnormalities, particularly those associated with increased androgen activity [81,82]. Clinical or biochemical manifestations of hyperandrogenism may include hirsutism, menstrual irregularities, and elevated circulating androgen concentrations [6,84]. However, a substantial proportion of women with adult acne have no detectable systemic hormonal abnormalities, suggesting that peripheral mechanisms, including increased cutaneous sensitivity to androgens, may contribute to disease pathogenesis [81,82].

The prevalence of hyperandrogenism appears to be higher among women with moderate-to-severe acne, particularly when acne occurs in association with other clinical manifestations of androgen excess [49]. In this context, polycystic ovary syndrome (PCOS) represents one of the most common causes of hyperandrogenism and is frequently associated with adult acne, with acne reported in approximately 30%–40% of women with PCOS [6,49]. Women presenting with acne together with clinical features suggestive of hyperandrogenism are more likely to have detectable hormonal abnormalities, underscoring the importance of a comprehensive clinical assessment [85]. Conversely, biochemical abnormalities are less frequently identified in women with mild or isolated acne, further supporting the multifactorial nature of the disorder [6].

### Diagnosis of Hyperandrogenism in Women with Adult Acne

The evaluation of hyperandrogenism in women with adult acne requires a systematic approach integrating clinical assessment with targeted laboratory investigation [49,86]. The medical history should include a detailed assessment of reproductive and menstrual characteristics, medication use, and the onset and progression of acne lesions, as these factors may provide important clues to underlying hormonal disturbances [49]. The presence of clinical manifestations associated with androgen excess, such as hirsutism, female pattern hair loss, and menstrual irregularities, increases the likelihood of hyperandrogenism and may raise suspicion of conditions such as PCOS [87]. In such cases, hormonal testing and, when clinically indicated, ovarian ultrasonography may assist in establishing the diagnosis and determining the underlying etiology [49].

Biochemical assessment generally includes measurement of circulating androgens, particularly total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S), and, in selected cases, androstenedione [49,88]. Free testosterone is generally more sensitive than total testosterone for detecting hyperandrogenism; however, its accurate measurement requires highly specific analytical methods, such as equilibrium dialysis, or may be estimated using total testosterone and sex hormone-binding globulin (SHBG) concentrations [49,89]. Measurement of DHEA-S is particularly useful when an adrenal source of androgen excess is suspected [49].

The differential diagnosis should include other disorders associated with hyperandrogenism, including non-classic congenital adrenal hyperplasia, Cushing syndrome, and androgen-secreting neoplasms, particularly in patients presenting with markedly elevated androgen concentrations or rapidly progressive and severe clinical manifestations [49,87]. Substantially elevated androgen levels may raise suspicion of an androgen-secreting

tumor, whereas additional testing, including measurement of 17-hydroxyprogesterone, may assist in the evaluation of adrenal disorders such as non-classic congenital adrenal hyperplasia [49,90].

## Alterations in Androgen Levels in Patients with Acne: Clinical Findings

Adult female acne frequently follows a persistent course and may represent either continuation of disease that began during adolescence or late-onset acne, with inflammatory and non-inflammatory lesions predominantly affecting the face [81,91]. In some patients, lesions show a preferential distribution over the lower face, particularly the mandibular and chin regions, although other facial areas may also be involved [91]. The disease may also exhibit a recurrent course and reduced responsiveness to conventional therapies, particularly when associated with hormonal abnormalities [51,81]. These clinical characteristics support a potential role for androgen-mediated mechanisms in the expression and persistence of adult female acne.

In this population, acne may occur alongside clinical features suggestive of hyperandrogenism, although not all affected women exhibit detectable biochemical abnormalities [49,81]. Evidence indicates that acne may represent a clinical manifestation of androgen excess, particularly in conditions such as PCOS, but it may also occur in women with androgen concentrations within the reference range, potentially reflecting increased peripheral sensitivity to androgens [49,91]. In addition, fluctuations in hormone concentrations throughout the menstrual cycle may influence acne severity, with premenstrual exacerbation commonly reported among affected women [91].

## Progestins and Androgenic Activity

### Mechanisms of Action of Progestins

Progestins exert their biological effects through interactions with several classes of cellular receptors, with the nuclear progesterone receptor (PR) representing the principal mediator of the classical signaling pathway [92]. The two major PR isoforms, PR-A and PR-B, function as ligand-activated transcription factors and regulate gene expression following hormone binding [92,93]. Upon interaction with a progestin, the receptor undergoes conformational changes and forms a hormone–receptor complex that translocates to the nucleus, where it binds to specific DNA sequences and regulates the transcription of target genes, ultimately producing functional changes in responsive cells [93]. This genomic mechanism is characterized by a relatively slow onset, with biological effects generally becoming apparent over several hours or days, and is responsible for sustained physiological responses in target tissues [94]. The magnitude and specificity of receptor-mediated signaling may also be influenced by the recruitment of transcriptional coactivators and corepressors, which contribute to tissue-specific responses to progestins [95].

In addition to classical nuclear signaling, progestins can activate non-genomic pathways mediated by membrane-associated receptors and related signaling proteins, resulting in more rapid cellular responses [96]. Membrane progesterone receptors (mPRs), in particular, have been implicated in the activation of intracellular signaling cascades occurring within a short period following hormone exposure [94]. These pathways may modulate second messengers, including cyclic adenosine monophosphate (cAMP), and activate protein kinases and other intracellular signaling systems, thereby producing cellular responses that do not require changes in gene transcription [92,94]. The coexistence of genomic and non-genomic mechanisms broadens the biological spectrum of progestin action and allows tissues to respond through both rapid signaling events and longer-term transcriptional regulation [93].

Evidence has also suggested a role for progesterone-related receptors localized to mitochondria in mediating some steroid hormone effects, raising the possibility of direct interactions between progestin signaling and cellular energy metabolism [97]. These mechanisms may influence mitochondrial function, energy production, and pathways involved in cell survival and proliferation [94]. Changes in mitochondrial activity can affect ATP production and signaling pathways associated with apoptosis, indicating that progestin action may extend beyond classical reproductive functions and contribute to cellular homeostasis [94,95]. Furthermore, some progestins exhibit measurable affinity for other steroid receptors, including androgen, glucocorticoid, and mineralocorticoid receptors. Consequently, their biological activity is determined not only by progesterone receptor activation but also by their chemical structure, receptor selectivity, and affinity for multiple molecular targets [92].

### Classification of Progestins

Progestins can be classified according to their structural origin and are traditionally divided into progesterone derivatives and 19-nortestosterone derivatives [98]. Progesterone derivatives include compounds such as medroxyprogesterone acetate and dydrogesterone, which share greater structural similarity with endogenous progesterone [4]. In contrast, 19-nortestosterone derivatives, including levonorgestrel and desogestrel, are structurally related to testosterone and have undergone modifications that confer high oral progestational potency and, in some cases, residual androgenic activity [92]. These structural differences contribute to clinically relevant variations in pharmacological properties, including potency, bioavailability, receptor affinity, and interaction with other steroid hormone receptors [4].

The 19-nortestosterone derivatives can be further subdivided into estranes and gonanes according to their chemical structure and degree of molecular modification [3]. Gonanes, such as levonorgestrel, exhibit potent progestational activity but may retain clinically relevant androgenic properties [99]. Later compounds, including desogestrel, were developed with the aim of maintaining effective progestational activity while reducing androgenic effects [97]. Progestins may also be characterized according to their interactions with steroid receptors, resulting in distinct androgenic, antiandrogenic, glucocorticoid, and mineralocorticoid profiles depending on their molecular structure and receptor selectivity [92].

Another commonly used classification is based on progestin generations, which broadly reflects the historical development of these compounds and differences in their pharmacological profiles, particularly their androgenic activity [3]. First-generation progestins, such as norethisterone, retain relatively greater androgenic activity because of their structural relationship to testosterone while maintaining agonist activity at the progesterone receptor [100]. Second-generation compounds, exemplified by levonorgestrel, possess high progestational potency but retain appreciable androgenic activity [98,99]. Third-generation progestins, such as desogestrel, were developed in an effort to reduce androgenic effects while preserving contraceptive efficacy [99]. Fourth-generation compounds, including drospirenone, exhibit antiandrogenic and antimineralocorticoid properties, resulting in a distinct pharmacological profile that may be advantageous in selected clinical settings [92].

The pharmacological differences among progestins, particularly their androgenic or antiandrogenic properties, may influence androgen signaling in susceptible tissues and consequently affect androgen-dependent cutaneous and follicular processes. The relationship between progestin pharmacological characteristics, androgen signaling, and the main dermatological conditions discussed in this review is summarized in Figure 1.

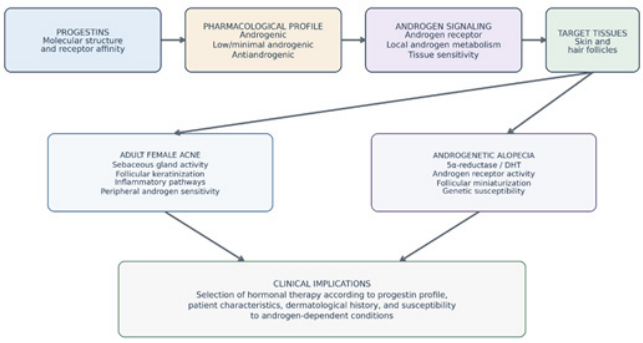


**Figure 1:** Relationship between progestin pharmacological profile, androgen signaling, and androgen-dependent dermatological conditions.

## Biological Activities of Progestins

The interaction of progestins with intracellular steroid receptors represents a major mechanism underlying their biological effects, as these compounds can induce genomic responses and functionally counteract several estrogen-mediated effects [96]. Within the female reproductive system, progestins induce substantial endometrial changes, including secretory transformation and alterations in endometrial glandular activity. They also modify cervical gland secretion, increasing mucus viscosity and reducing its volume [101]. These changes alter cervical mucus characteristics, including its consistency and crystallization pattern, thereby creating a physical barrier that interferes with sperm penetration and upward migration through the reproductive tract and contributes substantially to contraceptive efficacy [102].

Beyond their effects on the endometrium, progestins influence cellular proliferation through functional antagonism of estradiol signaling [4]. One mechanism involves induction of 17β-hydroxysteroid dehydrogenase activity, which favors the conversion of estradiol to estrone and may consequently reduce local estrogen availability and estrogen receptor stimulation [103]. In breast tissue, progestational signaling also modulates estrogen-induced vascular permeability and tissue changes and contributes to glandular differentiation. During pregnancy, progesterone-mediated mechanisms further participate in the regulation of lactation by counteracting prolactin-dependent milk secretion until the hormonal environment changes following delivery [104].

At the endocrine level, progestins exert substantial antigonadotropic effects through modulation of the hypothalamic–pituitary–gonadal axis. Suppression of gonadotropin secretion, particularly inhibition of the LH surge, prevents ovulation and constitutes a central component of hormonal contraceptive action [2]. Certain progestins also interact with additional steroid-related pathways. Depending on their molecular characteristics, some compounds may influence androgen metabolism, including pathways involving 5α-reductase and DHT, whereas others, such as drospirenone, exhibit antagonistic activity at the mineralocorticoid receptor and may promote natriuresis, thereby counteracting aldosterone-mediated sodium and water retention [105]. Thus, the biological effects of progestins extend beyond reproductive physiology to include modulation of androgen-dependent processes and fluid and electrolyte homeostasis [4].

## Classification According to Interactions with Steroid Receptors

Although all progestins exert their principal pharmacological effects through the progesterone receptor, their activity is not restricted to this receptor. Depending on their molecular structure, individual compounds may also interact with androgen, glucocorticoid, and mineralocorticoid receptors [106]. Structural modifications introduced during the development of synthetic progestins influence receptor selectivity and affinity, resulting in substantial differences in pharmacodynamic profiles among compounds [92]. Accordingly, progestins may be categorized according to their activity at the androgen receptor as androgenic, antiandrogenic, or having relatively minimal androgenic activity [107].

Several 19-nortestosterone derivatives display greater affinity for the androgen receptor and may therefore produce biological effects that resemble those of endogenous androgens [92,108]. Other structurally distinct compounds exhibit antiandrogenic properties and can antagonize androgen receptor-mediated signaling, thereby attenuating androgen-dependent effects [92]. This distinction is clinically relevant in conditions influenced by androgen excess, as the choice of progestin may affect cutaneous and metabolic outcomes in susceptible individuals [108]. Even relatively minor structural modifications can substantially alter receptor affinity

and, consequently, the overall hormonal and pharmacological profile of a progestin [99].

Interactions with the glucocorticoid receptor may influence inflammatory and immune responses, whereas
activity at the mineralocorticoid receptor can affect fluid and electrolyte balance by modifying sodium and water retention or excretion [92,109]. Overall, the ability of individual progestins to interact with multiple steroid receptors contributes to the heterogeneity of their biological effects, which may include progestational, antigonadotropic, antiestrogenic, androgenic, or antiandrogenic actions depending on the specific compound and tissue context [4].

### Progestins in the Context of Drugs with Androgenic Activity

Progestins are widely used in hormonal contraceptives and hormone-based therapies, and their pharmacological properties vary considerably among individual compounds [99]. Formulations containing progestins with androgenic activity, such as levonorgestrel, may be associated with androgen-dependent cutaneous effects. Levonorgestrel is used in several contraceptive formulations, including combined oral contraceptives, subdermal etonogestrel implants, and levonorgestrel-releasing intrauterine systems [92,98,99]. In susceptible individuals, progestins with greater androgenic activity may contribute to increased sebaceous gland activity and skin oiliness, particularly when endogenous androgen signaling is also enhanced [98,99,110].

Conversely, contraceptive formulations containing progestins with low androgenic activity or antiandrogenic properties may exert different effects on androgen-sensitive tissues and may be preferable in specific clinical circumstances [92]. Drospirenone and dienogest are notable examples of compounds with antiandrogenic properties used in different hormonal contraceptive formulations [92,99]. Their pharmacological profiles may result in less stimulation of sebaceous gland activity and can be beneficial in the management of androgen-related cutaneous manifestations, including acne, in appropriately selected patients [111-113].

The selection of a progestin should therefore consider its individual receptor profile, androgenic potential, and the characteristics of the patient and target tissues [99]. In patients with acne or other androgen-dependent cutaneous manifestations, progestins with greater androgenic activity may be less desirable, whereas compounds with antiandrogenic properties may offer additional therapeutic advantages when incorporated into an appropriate hormonal regimen [110]. The clinical relevance of progestins consequently extends beyond their contraceptive or reproductive effects, as differences in molecular structure and receptor activity can influence their effects on androgen-sensitive tissues, including the skin [92,110].

## Androgenetic Alopecia (AGA)

### Etiology of Androgenetic Alopecia: Androgens and Androgen Receptors

Androgenetic alopecia (AGA) is characterized by progressive alterations in the hair follicle cycle and is consistently associated with androgen action in genetically susceptible individuals [114]. Among the androgens involved, DHT plays a central role by acting directly on susceptible hair follicles and promoting their progressive miniaturization [115,116]. This process results in a reduction in hair shaft diameter and length, accompanied by shortening of the anagen phase and relative prolongation of the telogen phase, ultimately contributing to gradual hair density reduction [117]. In female pattern hair loss, however, serum androgen concentrations are frequently within the normal range, indicating that the disorder cannot be explained solely by systemic androgen levels [118,119].

In this context, the density and functional sensitivity of androgen receptors are important determinants of the pathophysiology of AGA [114]. The follicular response to androgens varies according to the distribution and activity of these receptors, which are heterogeneously expressed across different regions of the scalp [116]. Scalp areas that are more susceptible to hair loss may exhibit greater androgen receptor expression or enhanced receptor-mediated activity, thereby amplifying the effects of DHT even when circulating androgen concentrations remain within the normal range [117,120]. Such differences in tissue responsiveness may contribute to the distinct clinical phenotypes observed among individuals with comparable circulating hormone levels, further supporting the concept that AGA is influenced by local, tissue-specific androgen sensitivity [115,121].

The interaction between androgens and androgen receptors induces progressive changes in hair follicle biology, characterized by the gradual replacement of terminal hairs with shorter and finer hairs [117]. This process develops slowly and continuously and, in female pattern hair loss, generally presents as diffuse thinning with relative preservation of the frontal hairline and predominant involvement of the central scalp [119]. Thus, the etiology of AGA involves not only the presence of androgens but also, and importantly, the increased follicular sensitivity to androgen signaling mediated by androgen receptors, which is a major determinant of disease progression [118,121].

### Role of 5α-Reductase

5α-Reductase plays a central role in AGA by converting testosterone into DHT, which has greater affinity for the androgen receptor and exerts more potent effects on susceptible scalp hair follicles [117,122,123]. This conversion occurs locally within the pilosebaceous unit, where increased intrafollicular DHT production promotes alterations in the hair cycle and progressive follicular miniaturization [118,119]. The main isoenzymes, types I and II, differ in tissue distribution, with type I predominantly expressed in the skin and sebaceous glands and type II more closely associated with hair follicles [121-123]. Increased activity of these enzymes in androgen-sensitive scalp regions may enhance local DHT production and contribute to follicular miniaturization, even in the presence of normal circulating testosterone levels, emphasizing the importance of peripheral androgen metabolism in AGA [116,117].

DHT generation through 5α-reductase activity is associated with structural and functional changes in the hair follicle, including progressive reduction in follicular size and shortening of the anagen phase [123,124]. These changes constitute key features of follicular miniaturization in AGA and are closely related to local androgen metabolism [124]. The clinical relevance of this pathway is supported by the effects of 5α-reductase inhibitors, particularly finasteride and dutasteride, which reduce the conversion of testosterone to DHT and may slow disease progression or produce partial clinical improvement in selected patients [116,122].

## Genetic Factors in Androgenetic Alopecia

AGA is considered a complex hereditary disorder in which multiple genetic factors influence the response of hair follicles to androgens and contribute to variations in disease susceptibility, clinical presentation, and progression [125,126]. Among the genes implicated in this process, the AR gene, located on the X chromosome, has received particular attention because genetic variation within or near this locus has been associated with differences in androgen sensitivity [127,128]. Such genetic variation may help explain the marked clinical heterogeneity observed among individuals with comparable circulating androgen concentrations and underscores the importance of inherited susceptibility in the pathogenesis of AGA [129].

Beyond the AR gene, genome-wide association studies have identified numerous additional loci associated with AGA, further supporting its polygenic and multifactorial nature [125]. The genes and genomic regions implicated in these studies are involved in biological pathways related to hair follicle cycling, cellular differentiation, androgen signaling, and tissue-specific responses to hormonal stimuli, all of which may contribute to follicular miniaturization [125,128]. A positive family history is one of the most consistent clinical indicators of genetic susceptibility and is frequently reported among affected individuals [130,131]. Therefore, hereditary factors influence not only the likelihood of developing AGA but may also contribute to variations in its pattern of distribution, severity, and age at onset [124].

Genetic susceptibility is also relevant in female pattern hair loss, although its clinical expression differs from the more characteristic pattern observed in men [120]. Women with a genetic predisposition may develop progressive hair thinning despite the absence of clinically significant elevations in circulating androgen concentrations, suggesting that follicular sensitivity to androgen signaling is an important component of disease development [120,127]. These observations support the concept that AGA results from a complex interaction between genetic predisposition and local hormonal signaling, with genetic factors modulating the tissue response to circulating and locally produced androgens [126,131].

## Androgenic Drugs Associated with Androgenetic Alopecia

Certain drugs with androgenic activity may influence the clinical course of AGA, particularly in genetically susceptible individuals, by increasing androgenic stimulation of susceptible hair follicles [126,127]. These agents may act through direct activation of androgen receptors or by altering peripheral androgen exposure and metabolism, potentially contributing to the acceleration or unmasking of hair loss [126,128]. Although such medications are not generally regarded as primary causes of AGA, they may act as contributing factors or aggravate an underlying predisposition to androgen-dependent follicular miniaturization [125].

Among the pharmacological agents of particular relevance are progestins with androgenic activity, especially derivatives of 19-nortestosterone [92]. Levonorgestrel, used in oral contraceptives and levonorgestrel-releasing intrauterine systems, exhibits androgen receptor activity and may produce androgenic effects in susceptible cutaneous tissues [98]. Similarly, norethisterone possesses androgenic properties and has been associated with potential changes in hair growth patterns in susceptible individuals [4].

Exogenous androgens may also contribute to the progression or exacerbation of AGA [132]. Testosterone administration in therapeutic settings, as well as exposure to anabolic-androgenic steroids such as nandrolone, oxandrolone, and stanozolol, increases androgenic stimulation and may promote or accelerate follicular miniaturization in genetically predisposed individuals [124,126,133]. These compounds can alter the hair cycle, including shortening of the anagen phase and progressive reduction in hair shaft diameter, thereby contributing to the clinical expression and progression of androgen-dependent hair loss [130].

## Pharmacological Agents and Hormonal Influence

### Testosterone as a Pharmacological Agent with Androgenic Activity

Testosterone is the principal endogenous androgen and, when administered pharmacologically, acts through the androgen receptor and its active metabolites, including DHT and estradiol [134]. Testosterone replacement therapy aims to restore physiological androgen levels in individuals with hypogonadism, supporting sexual function, secondary sexual characteristics, and metabolic homeostasis. Available formulations include intramuscular, transdermal, subcutaneous, and buccal preparations, designed to provide sustained exposure and approximate physiological androgen availability [134-136]. Testosterone exerts genomic and non-genomic effects in androgen-sensitive tissues, modulating gene expression and cellular responses [137]. Increased local androgenic activity may contribute to sebaceous hyperactivity, acne, and worsening of androgenetic alopecia [138]. Although effective in treating androgen deficiency, testosterone therapy may cause adverse effects, particularly at supraphysiological doses or without appropriate clinical indications, emphasizing the need for clinical monitoring [139].

### Anabolic-Androgenic Steroids

Anabolic-androgenic steroids (AAS) are synthetic testosterone derivatives developed to enhance anabolic effects, particularly those associated with protein synthesis and skeletal muscle growth, while retaining varying degrees of androgenic activity [140,141]. These compounds exert their effects primarily through binding to

the androgen receptor, resulting in changes in gene transcription that affect multiple physiological systems, including skeletal muscle, the reproductive system, and the skin [142,143]. Although certain AAS have specific therapeutic applications, including the management of hypogonadism and catabolic conditions, their use outside medical indications, particularly at supraphysiological doses, substantially increases the risk of adverse effects [144]. Exogenous AAS also interfere with the hypothalamic–pituitary–gonadal axis, suppressing endogenous testosterone production and producing significant systemic hormonal alterations [145].

Among the principal compounds in this class are nandrolone, oxandrolone, and stanozolol, which differ in their relative anabolic and androgenic activities and in their pharmacokinetic properties and routes of administration [140]. Structural modifications of testosterone are intended to alter potency, bioavailability, and metabolic stability; however, these modifications may also contribute to clinically relevant adverse effects, including hepatotoxicity, dyslipidemia, and cardiovascular complications [142,146]. Prolonged exposure may result in persistent endocrine disturbances, including impaired fertility and hormonal dysfunction, particularly as a consequence of sustained suppression of the hypothalamic–pituitary–gonadal axis [147,148].

### Pharmacological Agents that Inhibit Estrogenic Activity

Anti-estrogenic agents primarily act by modulating or blocking estrogen receptors, thereby altering the biological effects of estradiol in target tissues [149,150]. Among these agents, selective estrogen receptor modulators (SERMs) are characterized by tissue-dependent agonist or antagonist activity. This selective behavior results from differences in receptor conformation and the recruitment of transcriptional coactivators and corepressors in specific tissues [151,152]. Tamoxifen, raloxifene, and clomiphene are representative members of this class. These agents exert anti-estrogenic effects in tissues such as the breast and hypothalamus while displaying partial or context-dependent estrogenic activity in other tissues, including bone [149,150]. Their tissue selectivity is largely attributable to ligand-induced conformational changes in the estrogen receptor, which modify interactions with transcriptional regulatory proteins and consequently alter the expression of estrogen-responsive genes [152,153].

Another important group of anti-estrogenic agents comprises selective estrogen receptor degraders (SERDs), which promote receptor degradation and thereby suppress estrogen receptor-mediated intracellular signaling more directly [150,153]. These agents are primarily used in hormone-dependent conditions, particularly estrogen receptor-positive breast cancer, in which inhibition of estrogen signaling represents an important therapeutic strategy for controlling tumor cell proliferation [149,151]. Modulation of estrogen signaling may also be relevant in specific endocrine contexts, including the management of reproductive disorders and interventions targeting the hypothalamic–pituitary–gonadal axis [152]. In contrast to aromatase inhibitors, which primarily reduce estrogen biosynthesis, SERMs and SERDs predominantly modify estrogen receptor activity or availability at the target-tissue level. Consequently, these agents represent distinct pharmacological approaches to controlling estrogen-dependent physiological and pathological processes [150,153].

### Aromatase Inhibitors

Aromatase inhibitors comprise a class of pharmacological agents that reduce estrogen biosynthesis by inhibiting aromatase (CYP19A1), the enzyme responsible for the peripheral conversion of androgens, including testosterone and androstenedione, into estradiol and estrone [154,155]. Aromatase is expressed in several peripheral tissues, including adipose tissue, the liver, and the skin, and contributes substantially to estrogen homeostasis. Its role becomes particularly relevant after menopause, when peripheral aromatization represents the principal source of endogenous estrogen production [156,157].

From a pharmacological perspective, aromatase inhibitors are classified as steroidal or nonsteroidal agents [158]. Steroidal inhibitors, such as exemestane, bind irreversibly to the aromatase enzyme and produce mechanism-based inhibition, whereas nonsteroidal agents, including anastrozole and letrozole, inhibit aromatase reversibly through competitive interaction with the enzyme's active site [154]. Inhibition of aromatase consequently decreases circulating estrogen concentrations and modifies physiological and pathological processes that depend on estrogenic signaling [155,159].

Clinically, aromatase inhibitors are widely used in the management of hormone-dependent malignancies, particularly hormone receptor-positive breast cancer in postmenopausal women, in whom suppression of peripheral estrogen production contributes to the inhibition of tumor cell proliferation [156,157]. Compared with other endocrine treatment strategies, these agents provide profound suppression of peripheral estrogen synthesis and are therefore frequently incorporated into first-line or sequential treatment regimens [158,159]. However, marked estrogen depletion may produce clinically relevant adverse effects, including reductions in bone mineral density, musculoskeletal symptoms, and metabolic alterations, reflecting the physiological importance of estrogen across multiple organ systems [154,155].

## Clinical Approach and Treatment

### Treatment of Female Adult Acne

The management of female adult acne should be tailored to clinical severity, with combination therapies often preferred to improve efficacy and reduce recurrence [81,160]. Topical retinoids remain first-line treatments and may be combined with benzoyl peroxide or topical antibiotics to enhance response and reduce antimicrobial resistance [53,160]. Systemic antibiotics may be used for limited periods in moderate disease, preferably alongside topical therapy rather than as monotherapy [81]. Oral isotretinoin is the most effective option for severe or refractory acne and requires individualized regimens and clinical monitoring, followed by topical retinoid maintenance to reduce relapse [81,91,112]. Hormonal therapies, including combined oral contraceptives and, in selected cases, spironolactone, are particularly useful for

persistent or inadequately controlled disease and may represent an alternative to isotretinoin in some patients [53,81,91,160]. Chemical peels and light-based therapies may also be used as adjunctive treatments to improve skin appearance and control inflammatory lesions [161].

### Treatment of Acne in Women with Hyperandrogenism

In women with hyperandrogenism, acne management should address the underlying endocrine disorder, making the investigation and treatment of associated conditions, particularly polycystic ovary syndrome, an important component of clinical care [81,162]. Therapeutic decisions should consider both the severity of the cutaneous manifestations and the individual hormonal profile, with interventions directed toward the underlying endocrine imbalance when appropriate [91]. Combined hormonal contraceptives are particularly useful in patients with ovulatory dysfunction, as they help regulate the menstrual cycle and reduce clinical manifestations associated with androgen excess [162]. Spironolactone may be used as an adjunctive treatment, particularly in patients with an inadequate response to conventional therapies, and can contribute to a progressive reduction in inflammatory lesions during treatment [163]. In more severe cases, isotretinoin may be used to control cutaneous disease; however, it does not directly address the hormonal etiology and primarily acts through effects on sebaceous gland activity and follicular inflammation [164].

### Diagnosis and Management of Androgenetic Alopecia

The diagnosis of AGA is primarily clinical and relies on the recognition of characteristic patterns of hair thinning. In women, the condition generally presents as diffuse reduction in hair density over the vertex, with relative preservation of the frontal hairline [116,126]. Dermoscopy can provide valuable complementary information by demonstrating findings such as follicular miniaturization, variation in hair shaft diameter, and an increased proportion of thin hairs, thereby improving diagnostic accuracy [120,125]. When an underlying endocrine disorder is suspected, laboratory evaluation may be warranted to investigate hormonal abnormalities and assist in treatment planning [119,129]. Differential diagnosis is also essential, particularly with conditions such as telogen effluvium and scarring alopecias, which may produce similar clinical findings but require different therapeutic approaches [120,126].

The primary goals of AGA treatment are to slow further hair loss and stimulate growth from follicles that remain functionally viable. Topical minoxidil is considered a first-line therapy and has demonstrated efficacy in improving hair density and shaft thickness [123,128]. In patients with an associated hormonal component, systemic therapies, including antiandrogenic agents, may be considered to modulate androgen-mediated effects on the hair follicle [116,119]. Adjunctive approaches, including injectable procedures and phototherapy, have also been investigated as complementary strategies for enhancing clinical outcomes [128]. Treatment generally needs to be continued over the long term because discontinuation may result in renewed disease progression. Long-term follow-up and adequate adherence are therefore important components of AGA management [125,129].

### Hormonal Therapies for the Treatment of Acne

Hormonal therapies represent an important option in the management of female acne, particularly in patients with recurrent disease or an inadequate response to conventional treatments. Their therapeutic effects are primarily related to modulation of peripheral androgen activity [165,166]. Combined oral contraceptives are among the principal hormonal therapies and have demonstrated consistent efficacy in reducing both inflammatory and non-inflammatory acne lesions. They may therefore be used as a long-term therapeutic strategy in appropriately selected patients [165,167].

Spironolactone is one of the principal systemic antiandrogenic therapies used for female acne. Its efficacy appears to be related, at least in part, to the administered dose, while clinical tolerability is generally favorable, with progressive reductions in acne lesion burden during treatment [168]. Other antiandrogenic agents and emerging approaches, including topical androgen receptor modulators, have further expanded the therapeutic options available for individualized management according to the clinical characteristics of each patient [165,169].

### Management of Androgen Supplementation in Patients with Alopecia

The management of AGA in patients receiving androgen supplementation requires careful assessment because exogenous androgens may enhance follicular miniaturization and accelerate disease progression [124,170]. In such circumstances, the risks and potential benefits of continuing hormonal therapy should be assessed on an individual basis, particularly when androgen supplementation is not essential for a clearly established clinical indication [170]. The clinical history should include a systematic assessment of factors that may contribute to disease progression, which should then be incorporated into the therapeutic plan, including consideration of dose adjustment or reassessment of the need for androgen supplementation [171].

Among pharmacological strategies, 5α-reductase inhibitors, including finasteride and dutasteride, are widely used to reduce the conversion of testosterone to dihydrotestosterone and thereby decrease androgen-mediated stimulation of susceptible hair follicles [172]. Conventional AGA therapies may also be continued when appropriate to preserve existing hair density and slow disease progression [171]. Consequently, management does not necessarily require immediate discontinuation of androgen supplementation. Instead, treatment should be individualized to balance the systemic effects of androgen therapy with the preservation of follicular integrity and long-term hair density [172, 173].

## Conclusion

Progestins differ in their androgenic activity because of structural variations that affect their interaction with steroid receptors. These differences may influence androgen-sensitive tissues, particularly

the skin and hair follicles. Androgenic progestins may increase androgen-dependent effects in susceptible women, potentially influencing conditions such as adult female acne and androgenetic alopecia. However, these disorders are multifactorial and also depend on genetic predisposition, androgen receptor sensitivity, local androgen metabolism, 5α-reductase activity, sebaceous gland function, and follicular responses. Therefore, androgenic progestins should be considered potential contributing factors rather than direct causes. In clinical practice, their selection should take into account androgenic or antiandrogenic properties and the patient's dermatological history, although further studies are needed to determine the specific risks associated with individual progestins.

## References


1. Deborah J Anderson, Daniel S Johnston. A brief history and future prospects of contraception. Science. 2023; 380: 154-158.
2. Wen He, Xiaofeng Li, Daniel Adekunbi, et al. Hypothalamic effects of progesterone on regulation of the pulsatile and surge release of luteinising hormone in female rats. Sci Rep. 2017; 7: 8096.
3. Michael Edwards, Ahmet S Can. Progestins. StatPearls Publishing. 2024.
4. Mallmann Elaine S, Spritzer Poli Mara. Progestágenos: quando e por quê. Revista da AMRIGS, Porto Alegre. 1990; 34: 38-43.
5. Vasam Mallikarjun, Korutla Satyanarayana, Bohara Raghvendra Ashok. Acne vulgaris: A review of the pathophysiology, treatment, and recent nanotechnology based advances. Biochem Biophys Rep. 2023; 36: 101578.
6. Flavia Alvim Sant'Anna Addor, Sergio Schalka. Acne da mulher adulta: aspectos epidemiológicos, diagnósticos e terapêuticos. An Bras Dermatol. 2010; 85: 789-795.
7. Maria Júlia Toscano de Azevedo Santos, Sofia Leite Mitidieri, Victoria Natália Oliveira Artuzo, et al. Influência do eixo pele–intestino na eficácia do tratamento da acne vulgar. BJIHS. 2026; 8: 1011-1027.
8. Camila Mascarello. Acne da mulher adulta: aspectos clínicos, fisiopatológicos e abordagens terapêuticas na prática dermatológica. Research, Society and Development. 2026; 15: 1.
9. Medeiros Heveline da Silva. Alopecia androgenética padrão feminino: uma abordagem do processo e tratamento com base no uso de inibidores da 5-alfa redutase. 2021; 60.
10. Ribeiro Laís dos Santos, Miranda Luciana Teixeira Gomes. Alopecia androgenética feminina. Revista Estética em Movimento. 2018; 1: 1.
11. Houfar Sekhavat, Sara Bar Yehuda, Satish Asotra. Using the Mechanisms of Action Involved in the Pathogenesis of Androgenetic Alopecia to Treat Hair Loss. Int J Mol Sci. 2025; 26: 10712.
12. Alemany M. The Roles of Androgens in Humans: Biology, Metabolic Regulation and Health. Int J Mol Sci. 2022; 23: 11952.
13. Rawda Naamneh Elzenaty, Therina du Toit, Christa E Flück. Basics of androgen synthesis and action. Best Pract Res Clin Endocrinol Metab. 2022; 36: 1-17.
14. BURGER Henry G. Androgen production in women. Fertil Steril. 2002; 77: S3-S5.
15. Lakshman Kishore M, Bhasin Shalender, Araujo Andre B. Testosterone Therapy for Osteoporosis in Men. Osteoporosis in Men. Academic Press. 2010; 56: 691-712.
16. Stocco DM. StAR Protein and the Regulation of Steroid Hormone Biosynthesis. Annu Rev Physiol. 2001; 63: 193-213.
17. Adina F Turcu, Richard J Auchus. Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia. Endocrinol Metab Clin North Am. 2015; 44: 275-296.
18. Ida Emanuelsson, Mokhtar Almokhtar, Kjell Wikvall, et al. Expression and regulation of CYP17A1 and 3β-hydroxysteroid dehydrogenase in cells of the nervous system: Potential effects of vitamin D on brain steroidogenesis. Neurochem Int. 2018; 113: 46-55.
19. Walter L Miller, Richard J Auchus. The Molecular Biology, Biochemistry, and Physiology of Human Steroidogenesis and Its Disorders. Endocr Rev. 2011; 32: 81-151.
20. Yanqing Yang, Anna Krin, Xiaoli Cai, et al. Conformations of Steroid Hormones: Infrared and Vibrational Circular Dichroism Spectroscopy. Molecules. 2023; 28: 771.
21. Selçuk Yavuz, Hélène Kabbech, Jente van Staalduinen, et al. Compartmentalization of androgen receptors at endogenous genes in living cells. Nucleic Acids Res. 2023; 51: 10992-11009.
22. Shu Yang, Ming Jiang, Magdalena M Grabowska, et al. Androgen receptor differentially regulates prostate epithelial cell proliferation in vitro and in vivo. Oncotarget. 2016; 7: 43.
23. Jiann-Jyh Lai, Philip Chang, Kuo-Pao Lai, et al. The role of androgen and androgen receptor in skin-related disorders. Arch Dermatol Res. 2012; 304: 499-510.
24. Mohammad Asim. Decoding androgen receptor signalling: Genomic vs. non-genomic roles in prostate cancer. Neoplasia. 2024; 58.
25. Clarice KY Hong, Avinash Ramu, Siqi Zhao, et al. Effect of genomic and cellular environments on gene expression noise. Genome Biol. 2024; 25: 137.
26. Sandi R Wilkenfeld, Chenchu Lin, Daniel E Frigo. Communication between genomic and non-genomic signaling events coordinates steroid hormone action. Steroids. 2018; 133: 2-7.
27. Marie Cargnello, Philippe P Roux. Activation and Function of the MAPKs and Their Substrates, the MAPK-Activated Protein Kinases. Microbiol Mol Biol Rev. 2011; 75: 50-83.
28. James Q Del Rosso, Leon H Kircik, Linda Stein Gold, et al. Androgens, Androgen Receptors, and the Skin: From

the Laboratory to the Clinic With Emphasis on Clinical and Therapeutic Implications. J Drugs Dermatol. 2020; 19: 3.

29. Julieta María Ceruti, Gustavo José Leirós, María Eugenia Balañá. Androgens and androgen receptor action in skin and hair follicles. Mol Cell Endocrinol. 2018; 465: 122-133.
30. Angela K Lucas-Herald, Rheure Alves-Lopes, Augusto C Montezano, et al. Efeitos genômicos e não genômicos dos andrógenos no sistema cardiovascular: implicações clínicas. Clin Sci. 2017; 131: 1405-1418.
31. George N Nassar, Stephen W Leslie. Physiology, Testosterone. Ilha do Tesouro (FL): StatPearls Publishing. 2023.
32. Agnieszka Matuszewska, Krzysztof Kowalski, Paulina Jawień, et al. The Hypothalamic-Pituitary-Gonadal Axis in Men with Schizophrenia. Int J Mol Sci. 2023; 24: 6492.
33. Richard L Hauger, Ursula G Saelzler, Meghana S Pagadala, et al. The role of testosterone, the androgen receptor, and hypothalamic-pituitary-gonadal axis in depression in ageing Men. Rev Endocr Metab Disord. 2022; 23: 1259-1273.
34. Manpreet Kaur, Kiran Prakash, Shival Srivastav, et al. Crosstalk between brain and the endocrine system. In: Brain and Organ Communication. 2025; 155-176.
35. Michaël R Laurent, Geoffrey L Hammond, Marco Blokland, et al. Sex hormone-binding globulin regulation of androgen bioactivity in vivo: validation of the free hormone hypothesis. Scientific Reports. 2016; 6: 35539.
36. BIKLE Daniel D. The Free Hormone Hypothesis: When, Why, and How to Measure the Free Hormone Levels to Assess Vitamin D, Thyroid, Sex Hormone, and Cortisol Status. JBMR. 2021; 5: 1.
37. Nabila Bourebaba, ThuHa Ngo, Agnieszka Śmieszek, et al. Sex hormone binding globulin as a potential drug candidate for liver-related metabolic disorders treatment. Biomed Pharmacother. 2022; 153: 113261.
38. Frederico Gerlinger-Romero, Érico Chagas Caperuto, Adriano Fortes Maia, et al. Bases moleculares das ações da testosterona, hormônio do crescimento e IGF-I sobre a hipertrofia muscular esquelética e respostas ao treinamento de força. Revista Mackenzie de Educação Física e Esporte. 2013; 12: 187-208.
39. Rosa Luciana Abreu da. Papel da testosterona e da epitestosterona na regulação hormonal do processo de maturação testicular. 2020.
40. Zouboulis Christos C. A pele como órgão endócrino. Dermatoendocrinol. 2009; 5: 250-252.
41. Reprodução, Climatério. São Paulo: Ponto Comunicação & Editora. 2005; 20.
42. Megha Kataria Arora, Amita Yadav, Vandana Saini. Role of hormones in acne vulgaris. Clin Biochem. 2011; 44: 1035-1040.
43. José Antonio M Marcondes. Andrógenos e SHBG: Em Busca do Elo Desconhecido. Arq Bras Endocrinol Metab. 2002; 46: 493.
44. Maria Clara Neves Bulla, Natália de Sá Cortez, Márcia Freire dos Reis Gorny. A influência dos hormônios sexuais na pele feminina: um estudo para a prática da estética facial. RCMOS. 2005; 5.
45. Samira Yarak, Ediléia Bagatin, Karime Marques Hassun, et al. Hiperandrogenismo e pele: síndrome do ovário policístico e resistência periférica à insulina. An Bras Dermatol. 2005; 80: 395-410.
46. Shah MG, Maibach HI. Estrogen and skin: An overview. Am J Clin Dermatol. 2001; 2: 143-150.
47. Santana Luís Carlos Leal. Impacto de andrógenos sobre a proliferação e atividade de fibroblastos e células epiteliais em cultura celular. 2016.
48. Adilson Costa, Maurício Motta de Avelar Alchorne, Maria Cristina Bezzan Goldschmidt. Fatores etiopatogênicos da acne vulgar. An Bras Dermatol. 2008; 83: 451-459.
49. Enrico Carmina, Brigitte Dreno, W Anne Lucky, et al. Female Adult Acne and Androgen Excess: A Report From the Multidisciplinary Androgen Excess and PCOS Committee. J Endocr Soc. 2022; 6: 3.
50. Lakshmi Chembolli. Hormone therapy in acne. Indian J Dermatol Venereol Leprol. 2013; 79: 322-337.
51. Elsaie Mohamed L. Hormonal treatment of acne vulgaris: an update. Clin Cosmet Investig Dermatol. 2016; 9: 241-248.
52. Beatriz de Medeiros Ribeiro, Luiz Maurício Costa Almeida, Adilson Costa, et al. Etiopatogenia da acne vulgar: uma revisão prática para o dia a dia do consultório de dermatologia. Surg Cosmet Dermatol. 2015; 7: 20-26.
53. Augusto Ruiz do AMARAL, Gabriel Almeida VIANA, Silvia Messias BUENO. Acne: uma revisão bibliográfica. Revista Científica Unilago, São José do Rio Preto. 2023; 1: 1.
54. COSTA Inês Vieira da, VELHO Glória Maria Cardoso da Cunha. Acne Vulgar no Adulto. 2018; 76: 299-312.
55. Ewelina Firlej, Wioleta Kowalska, Karolina Szymaszek, et al. The Role of Skin Immune System in Acne. J Clin Med. 2022; 11: 1579.
56. Ditte M L Saunte, George Gaitanis, Roderick James Hay. Malassezia-Associated Skin Diseases, the Use of Diagnostics and Treatment. Front Cell Infect Microbiol. 2020; 10: 112.
57. Wen-Chieh Chen, Christos C Zouboulis. Hormones and the pilosebaceous unit. Dermatoendocrinol. 2009; 1: 81-86.
58. Lili J Rueda, Alexandra Porras, Alejandro Rico. Prevalence of adult female acne in Colombia: A population-based study. Int J Womens Dermatol. 2021; 7: 727-730.
59. Giorgia Condrò, Roberta Sciortino, Paola Perugini. Squalene Peroxidation and Biophysical Parameters in Acne-Prone Skin: A Pilot "In Vivo" Study. Pharmaceuticals. 2023; 16: 12.
60. Yuanyuan Deng, Feifei Wang, Li He. Skin Barrier Dysfunction in Acne Vulgaris: Pathogenesis and Therapeutic Approaches. Med Sci Monit. 2024; 30.
61. Rashmi Kumari, Devinder Mohan Thappa. Role of insulin resistance and diet in acne. Indian J Dermatol Venereol Leprol.

2013; 79: 291-299.

62. Jie Li, Bingyong Mao, Xin Tang, et al. Endocrine and metabolic drivers of sebum dysregulation: Mechanisms and therapeutic strategies. Life Sci. 2025; 383.
63. Bodo C Melnik. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. Clin Cosmet Investig Dermatol. 2015; 8: 371-388.
64. James Q Del Rosso, Leon Kircik. The cutaneous effects of androgens and androgen-mediated sebum production and their pathophysiologic and therapeutic importance in acne vulgaris. J Dermatolog Treat. 2024; 35: 1.
65. Shuhui Wu, Xi Zhang, Yun Wang, et al. Lipid Metabolism Reprogramming of Immune Cells in Acne: An Update. Clin Cosmet Investig Dermatol. 2023; 16: 2391-2398.
66. Su-Kyung Kim, Minouk Lee, Yi Qing Lee, et al. Genome-scale metabolic modeling and in silico analysis of opportunistic skin pathogen Cutibacterium acnes. Front Cell Infect Microbiol. 2023; 13: 1-13.
67. James Q Del Rosso, Leon Kircik. The primary role of sebum in the pathophysiology of acne vulgaris and its therapeutic relevance in acne management. J Dermatolog Treat. 2024; 35: 1.
68. David R Drake, Kim A Brogden, Deborah V Dawson, et al. Thematic Review Series: Skin Lipids. Antimicrobial lipids at the skin surface. J Lipid Res. 2008; 49: 4-11.
69. Mauro Picardo, Monica Ottaviani, Emanuela Camera, et al. Sebaceous gland lipids. Dermatoendocrinol. 2009; 1: 68-71.
70. Kim Newton, Vishva M Dixit. Signaling in Innate Immunity and Inflammation. Cold Spring Harb Perspect Biol. 2012; 4: 3.
71. Cruvinel Wilson de Melo, Sistema imunitário Parte I. Fundamentos da imunidade inata com ênfase nos mecanismos moleculares e celulares da resposta inflamatória. Rev Bras Reumatol. 2010; 50: 434-447.
72. Maria Amélia da Cunha Vieira, Lilian de Abreu Ferreira. Potencial terapêutico dos probióticos na acne: uma revisão sistemática. Scientia Generalis. 2020; 3: 132-138.
73. Suelen Montagner, Adilson Costa. Diretrizes modernas no tratamento da acne vulgar: da abordagem inicial à manutenção dos benefícios clínicos. Surgical & Cosmetic Dermatology. 2010; 3: 205-213.
74. Sarah Vasconcelos Batista dos Santos, Werick Mendes Amorim. Exames laboratoriais na estética: avaliação da microbiota e impactos dermatológicos. Revista Ibero-Americana de Humanidades, Ciências e Educação. 2025; 11: 7785-7798.
75. NAVES Giovanna Rodrigues da Cunha. Evidências do uso de probióticos no tratamento da acne vulgar: uma revisão de revisões sistemáticas. Orientadora: Lilian Emiko Kato. 2026.
76. Thiboutot DM. The role of follicular hyperkeratinization in acne. Journal of Dermatological Treatment. 2000; 11: 5-8.
77. REI Madalena Celeiro. Desenvolvimento de um modelo de epiderme 3D inflamada, in vitro, para avaliar a eficácia de compostos anti-inflamatórios. Orientadores: Abel Oliva; Deodália Dias. 2022.
78. Ann M Hargis, Sherry Myers. The Integument. In: ZACHARY, James F. (ed.). Pathologic Basis of Veterinary Disease. 2017; 17: 1009-1173.
79. Eleni Zingkou, Georgios Pampalakis, Georgia Sotiropoulou. Keratinocyte differentiation and proteolytic pathways in skin (patho) physiology. Int J Dev Biol. 2022; 66: 269-275.
80. LANGE Eloana Pasqualin. Acne da mulher adulta: avaliação da prevalência e dos fatores de risco em uma amostra da população brasileira. 2023.
81. Edileia Bagatin, Thais Helena Proença de Freitas, Maria Cecilia Rivitti Machado, et al. Adult female acne: a guide to clinical practice. An Bras Dermatol. 2019; 94: 62-75.
82. Dréno B, Layton A, Zouboulis CC, et al. Adult female acne: a new paradigm. J Eur Acad Dermatol Venereol.2013; 27: 1063-1070.
83. Ömer Kutlu, Ayşe Serap Karadağ, Uwe Wollina. Acne no adulto versus acne no adolescente: revisão narrativa com foco na epidemiologia e no tratamento. An Bras Dermatol. 2023; 98: 75-83.
84. Alexis C Perkins, Jessica Maglione, Greg G Hillebrand, et al. Acne Vulgaris in Women: Prevalence Across the Life Span. J Womens Health. 2012; 21: 223-230.
85. Cemile Tuğba Altunel, Semih Tatlıcan. The clinical predictors of biochemical hyperandrogenemia and its relation to treatment resistance in women with acne. Postepy Dermatol Alergol. 2025; 42: 54-61.
86. Anu Sharma, Corrine K Welt. Practical Approach to Hyperandrogenism in Women. Med Clin North Am. 2021; 105: 1099-1116.
87. John Mihailidis, Racha Dermesropian, Pamela Taxel, et al. Endocrine evaluation of hirsutism. Int J Womens Dermatol. 2017; 3: S6-S10.
88. Erin Lanzo, Maria Monge, Maria Trent. Diagnosis and Management of Polycystic Ovary Syndrome in Adolescent Girls. Pediatr Ann. 2015; 44: e223-e230.
89. REHME Marta Francis Benevides. O hiperandrogenismo influencia no desenvolvimento de síndrome metabólica em pacientes com síndrome dos ovários policísticos? 2009.
90. NÓBREGA Lúcia Helena Coelho. Hiperplasia Adrenal Congênita: Dosagem da 17-Hidroxiprogesterona Basal para Seleção e Casos para Realização do Teste de Estímulo com ACTH Sintético. RBGO.2004; 26: 295-298.
91. Daciana Elena Branisteanu, Mihaela Paula Toader, Elena Andrese Porumb, et al. Adult female acne: Clinical and therapeutic particularities (Review). Exp Ther Med. 2022; 23: 1-7.
92. Manuel García-Sáenz, Raúl Ibarra-Salce, Francisco Javier Pozos-Varela, et al. Understanding Progestins: From Basics to Clinical Applicability. J Clin Med. 2023; 12: 1-15.

93. Christy R Hagan, Carol A Lange. Molecular determinants of context-dependent progesterone receptor action in breast cancer. BMC Med. 2014; 12: 1-15.

94. Fedotcheva TA. Clinical Use of Progestins and Their Mechanisms of Action: Present and Future (Review). Sovrem Tekhnologii Med. 2021; 13: 93-107.

95. Sandra L Grimm, Sean M Hartig, Dean P Edwards. Progesterone Receptor Signaling Mechanisms. J Mol Biol. 2016; 428: 3831-3849.

96. Lucie Kolatorova, Jana Vitku, Josef Suchopar, et al. Progesterone: A Steroid with Wide Range of Effects in Physiology as Well as Human Medicine. Int J Mol Sci. 2022; 23: 7989.

97. WOO, Qian Yee et al. Proteomics analysis reveals progesterone receptor induced mitochondria-mediated apoptosis in breast cancer cells. Scientific Reports, [S. l.], v. 15, p. 1-18, 2025. DOI:

98. Georg Griesinger, Herman Tournaye, Nick Macklon, et al. Dydrogesterone: pharmacological profile and mechanism of action as luteal phase support in assisted reproduction. Reprod Biomed Online. 2019; 38: 249-259.

99. Vigo Francieli, Lubianca Jaqueline Neves, CORLETA, Helena von Eye. Progestógenos: farmacologia e uso clínico. Femina. 2011; 39: 127-133.

100. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005; 8: 3-63.

101. Kun Yu, Zheng-Yuan Huang, Xue-Ling Xu, et al. et al. Estrogen Receptor Function: Impact on the Human Endometrium. Front Endocrinol. 2022; 13: 827724.

102. Leo Han, Mitchell D Creinin, Agnes Hemon, et al. Mechanism of action of a 0.075 mg norgestrel progestogen-only pill 2. Effect on cervical mucus and theoretical risk of conception. Contraception. 2022; 112: 43-47.

103. Mu Lv, Peiqin Chen, Mingzhu Bai, et al. Progestin Resistance and Corresponding Management of Abnormal Endometrial Hyperplasia and Endometrial Carcinoma. Cancers. 2022; 14: 1-19.

104. Isabelle E A Pontes, Antonio Braz de Araújo Júnior, Ana Gabriela Soares Vilas Boas, et al. Histologia mamária no ciclo gravídico-puerperal: das adaptações teiduais hormônio-dependentes às implicações clínicas. Revista Contribuciones a las Ciencias Sociales. 2025; 8: 1-19.

105. Laxmi Iyengar, Jane Li. Male and female pattern hair loss. Aust Prescr. 2025; 48: 93-97.

106. Waranya Chatuphonprasert, Kanokwan Jarukamjorn, Isabella Ellinger. Physiology and Pathophysiology of Steroid Biosynthesis, Transport and Metabolism in the Human Placenta. Front Pharmacol. 2018: 9: 1-20.

107. John C Stevenson, Serge Rozenberg, Silvia Maffei, et al. Progestogens as a component of menopausal hormone therapy: the right molecule makes the difference. Drugs Context. 2020; 9: 1-12.

108. Silva Filho, Agnaldo Lopes da. Reconhecimento e diagnóstico dos sintomas cutâneos do hiperandrogenismo em mulheres: proposta do Grupo Appropriate Care for Women with Androgen Excess (AWARE). Femina, Rio de Janeiro. 2018; 46: 252-258.

109. Derek W Cain, John A Cidlowski. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017; 17: 233-247.

110. Anna ABR, Anelise MP, Carolina AV, et al. Anticoncepcionais hormonais contendo apenas progestágenos e seus principais efeitos. BJSCR. 2016; 15: 75-81.

111. Radosław Słopień, Ewa Milewska, Piotr Rynio, et al. Use of oral contraceptives for management of acne vulgaris and hirsutism in women of reproductive and late reproductive age. Menopause Review. 2018; 17: 1-4.

112. Edilene Gadelha de Oliveira, Amanda Rodrigues Fernandes Silva, Stephany Osterno Silva Feitoza, et al. Uso do espironolactona no tratamento da acne vulgar na mulher adulta: uma revisão integrativa. Revista Saúde. 2025; 15.

113. Oliveira Katiulcy Carvalho, Sousa Geovanna Fernandes Lacerda, Maciel Josué Batista. Terapias hormonais: comprovação científica baseada em evidências e o uso indiscriminado. Revista ReGeo. 2025; 16: 1-32.

114. Mulinari-Brenner F, Seidel G, Hepp T. Entendendo a alopecia androgenética. Surg cosmet dermatol. 2011; 3: 329-337.

115. João Pedro Alencar Vieira M, Gabriela Macari dos S, et al. Alopecia androgenética feminina: uma revisão de literatura. Revista Científica Saúde e Tecnologia. 2022; 2: 1-13.

116. Ntshingila S, Khumalo NP, Engel M, et al. An appraisal of laboratory models of androgenetic alopecia: a systematic review. Skin Health Dis. 2021; 1: 1-11.

117. Starace M, Orlando G, Alessandrini A, et al. Female Androgenetic Alopecia: An Update on Diagnosis and Management. Am J Clin Dermatol. 2020; 21: 69-84.

118. Lucas Leandro Fustinoni L, Elenice S, Tratamento da alopecia androgenética em mulheres: revisão da literatura. Revista Eletrônica Biociências. 2018; 20: 43-57.

119. Nayara YMF, Valéria SFS, Eliane BL, et al. Alopecia androgenética feminina - o impacto na autoestima. Revista Científica Multidisciplinar. 2023; 4: 1-8.

120. Gabriel Lazzeri Corteza, Karime Hassunb, Verena Florenço, et al. Alopecia androgenética masculina. Anais Brasileiros de Dermatologia. 2025; 100: 2.

121. Rivera R, Guerra-Tapia A. Management of Androgenetic Alopecia in Postmenopausal Women. Actas Dermo-Sifiliográficas. 2008; 99: 257-261.

122. J Curtis Nickel. Comparison of Clinical Trials With Finasteride and Dutasteride. Rev Urol. 2004; 6: S31-S39.

123. Sinclair Rodney. Male pattern androgenetic alopecia. BMJ. 317: 865-869.

124. Vitor de Souza Ferreira H, Luíza Fricks C, Cristiane S, et al. Alopecia Androgenética: Fatores Hormonais, Genéticos e

Abordagens Terapêuticas Atuais. BJIHS. 2026; 8: 494-507.

125. Saskia P Hagenaars, W David Hill, Sarah E Harris, et al. Genetic prediction of male pattern baldness. PLoS Genet. 2017; 13: 1-16.

126. HO Queixo H, Sood Tanuj, Zito Patrick M. Androgenetic Alopecia. Treasure Island (FL): StatPearls Publishing. 2024.

127. Leila Asfour, William Cranwell, Rodney Sinclair. Male Androgenetic Alopecia. South Dartmouth (MA). 2023.

128. Vitor de Souza Ferreira H, Luíza Fricks C, Cristiane S, et al. The Biology and Genomics of Human Hair Follicles: A Focus on Androgenetic Alopecia. BJIHS. 2024; 25: 2542.

129. Mulinari-Brenner Fabiane, Soares Ivy Faigle. Alopecia androgenética masculina: uma atualização. Revista de Ciências Médicas. 2009; 18: 153-161.

130. Pedro Walisson Gomes F, Irving D, Izabela Pinho de A, et al. O aporte da genética na calvície masculina: uma revisão de literatura. Id on Line: Revista Multidisciplinar e de Psicologia. 2019; 44: 185-197.

131. Gabriella Ferreira H, José Chaia S, Ivana Picone Borges de A. O impacto da alopecia androgenética em homens e seus tratamentos: uma revisão de literatura. Revista Ibero-Americana de Humanidades, Ciências e Educação. 2023; 9: 514-526.

132. Weeratian T, Deesha D, Ambika N, et al. Hair loss in athletic testosterone use in males: a narrative review. Int J Dermatol. 2025; 64: 654-658.

133. Beatriz Menegate S, Alves de Souza JP, de Paula Goulart LR, et al. Impacts of Anabolic-androgenic steroid supplementation on female health and offspring: Mechanisms, side effects, and medical perspectives. Saudi Pharm J. 2024; 32: 102205.

134. Handelsman David J. Androgen Physiology, Pharmacology, Use and Misuse. Endotext ]. South Dartmouth (MA. 2020.

135. Srinivas-Shankar U, Frederick C. Drug Insight: testosterone preparations. Nat Clin Pract Urol. 2006; 3: 653-665.

136. Eduarda Feijó Belluco J, Queiroz Presot I, et al. Aplicações e segurança dos cremes de testosterona: revisão sistemática sobre formulações tópicas, eficácia clínica e riscos potenciais. Revista ReGeo, São José dos Pinhais. 2026; 17: 1-27.

137. Elia Abou C, Campos L, Savio L, et al. Dermatological adverse effects of testosterone replacement therapy: a scoping review of the literature. Sex Med Rev. 2026; 14: 1-6.

138. Eduardo Farraboti R, Luciana Lopes G, Valter Garcia S. Análise de afinidade da testosterona e seus derivados com os receptores androgênicos. Anais do Congresso Brasileiro de Iniciação Científica, Santos. 2024; 1: 106.

139. Eduardo Siqueira F, Pedro Raffael Farias. Uso de testosterona em mulheres com diminuição ou perda de interesse/excitação sexual. Revista Brasileira de Sexualidade Humana. 2019; 30: 66-72.

140. Kicman AT. Pharmacology of anabolic steroids. Br J Pharmacol. 2008; 154: 502-521.

141. Stephen W, Sajedur R, Kavitha G. Anabolic Steroids. Ilha do Tesouro (FL): StatPearls Publishing. 2025.

142. Anawalt Bradley D. Diagnosis and Management of Anabolic Androgenic Steroid Use. J Clin Endocrinol Metab. 2019; 104: 2490-2500.

143. Urival Magno Gomes F, Alan de Carvalho Dias, Andréa Maria Pires A, et al. Esteróides anabólicos androgênicos. Revista Brasileira em Promoção da Saúde. 2007; 20: 267-275.

144. Hugo Leonardo Pereira de S, Fellipe José Gomes Q. O uso dos esteroides anabolizantes androgênicos: uma revisão da literatura. Revista JRG de Estudos Acadêmicos. 2022; 11: 76-85.

145. Alisson Padilha de L, Fabrício Bruno C. Alterações fisiológicas e efeitos colaterais decorrentes da utilização de esteroides anabolizantes androgênicos. Revista Brasileira de Ciências da Saúde. 2011; 9: 39-44.

146. Rafael Ernesto A, Juan Pablo M. Los esteroides anabolizantes androgénicos, riesgos y consecuencias. Revista U.D.C.A Actualidad & Divulgación Científica. 2012; 15: 47-55.

147. Tiago Sousa V, Walter Neto Soares G, Luiza Gobira L, et al. Uso inadequado de esteroides anabolizantes androgênicos. Revista Saúde dos Vale. 2021; 1: 1-18.

148. Brígida Souza Cortês D, Mario Mecenas P, Millena Pancotti R. Esteróides anabolizantes: uma abordagem teórica. Revista Científica da Faculdade de Educação e Meio Ambiente. 2012; 2: 21-39.

149. Ozyurt Rumeysa, Ozpolat Bulent. Molecular Mechanisms of Anti-Estrogen Therapy Resistance and Novel Targeted Therapies. Cancers. 2022; 14: 5206.

150. Mary H, Farley S, Sparkman R, et al. Precautions for Patients Taking Aromatase Inhibitors. J Adv Pract Oncol. 2020; 11: 184-189.

151. Diez-Perez Adolfo. Selective Estrogen Receptor Modulators (SERMS). Arquivos Brasileiros de Endocrinologia & Metabologia São Paulo. 2006; 50: 720-734.

152. Joana Isabel Belo de S. Inibidores da aromatase e esteróide sulfatase no tratamento do cancro da mama. 2017.

153. Patel R, Klein P, Tiersten A, et al. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ Breast Cancer. 2023; 9: 1-13.

154. Mei Ka Fong, Preeti Patel. Aromatase Inhibitors. In: StatPearls [Internet]. Treasure Island. 2026.

155. Jennifer B, Fredrick N. Aromatase: Contributions to Physiology and Disease in Women and Men. Physiology. 2016; 31: 258-269.

156. Jean-Marc AN. Long-term safety of aromatase inhibitors in the treatment of breast cancer. Ther Clin Risk Manag. 2008; 4: 189-204.

157. Stefano G, Roberto P. Aromatase inhibitors, efficacy and metabolic risk in the treatment of postmenopausal women with early breast cancer. Clin Interv Aging. 2008; 4: 647-657.

158. John F Forbes. O Uso da Terapia Inibidora Adjuvante Precoce com Aromatase: Contribuições do Ensaio BIG 1-98 Letrozol.

Semin Oncol. 2006; 33: 2-7.

159. Saad Everardo D. Inibidores da aromatase no câncer de mama: da doença metastática ao tratamento adjuvante. Revista Brasileira de Cancerologia. 2002; 48: 555-567.

160. John K, Anatoli F. Management of acne. CMAJ. 2011; 183; 7: E430-E435.

161. Débora Rodrigues dos. Acne na mulher adulta e seus tratamentos. Estética em Movimento, Belo Horizonte. 2022; 1: 77-90.

162. Cristina Laguna B. Tratamento das manifestações androgênicas. In: Síndrome dos ovários policísticos. São Paulo: Federação Brasileira das Associações de Ginecologia e Obstetrícia (Febrasgo). 2018; 5: 56-67.

163. Grace K, James Q. Oral Spironolactone in Post-teenage Female Patients with Acne Vulgaris: Practical Considerations for the Clinician Based on Current Data and Clinical Experience. J Clin Aesthet Dermatol. 2012; 5: 37-50.

164. Carvalho Leite Júnior Ademir, Leite Alex Carvalho. Benefícios da isotretinoína no tratamento da acne nódulo-cística em pacientes hiperandrogênicas devido à síndrome dos ovários policísticos. Medicina Cutânea Ibero-Latino-Americana. 2005; 33: 211-218.

165. Courtney A Smith, Emily Gosnell, Turkan Banu Karatas, et al. Hormonal Therapies for Acne: A Comprehensive Update for Dermatologists. Dermatol Ther. 2025; 15: 45-59.

166. Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. Int J Womens Dermatol. 2017; 4: 56-71.

167. Trivedi MK, Shinkai K, Murase JE. A Review of hormone-based therapies to treat adult acne vulgaris in women. Int J Womens Dermatol. 2017; 3: 44-52.

168. Selvaraj Katina J, James William, Fallah Haady. Oral spironolactone for acne vulgaris in females: Evidence review and practical recommendations. JAAD Reviews. 2025; 5: 63-70.

169. Gao Jing, Mahto Anjali. Anti-Androgen Therapy in Female Adult Acne. J Dermatol Res Ther. 2016; 2: 23.

170. Sana Gupta, Jia Qi Adam Bai, Ryan S Q Geng, et al. The effect of androgen supplementation on hair loss: A systematic review. JAAD International. 2026; 26: 20-21.

171. Vañó-Galván S. Recommendations on the Clinical Management of Androgenetic Alopecia: A Consensus Statement From the Spanish Hair Disorders Group of the Spanish Academy of Dermatology and Venererology (AEDV). Actas Dermo-Sifiliográficas. 2024; 115: T347-T355.

172. Grijó Leonor, Cardoso Sofia, Beirão Liliana. Qual o papel dos inibidores da 5α-reductase no tratamento da alopecia androgenética? Uma revisão baseada na evidência. Revista Portuguesa de Medicina Geral e Familiar. 2020; 36: 135-143.

173. Arantes Anderson et al. A utilização de finasterida e minoxidil no tratamento da alopécia androgenética. Revista Vida et Salus, Trindade. 2017; 11: 72.