QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

Cite as: PAPUGA, Aleksandra, HEJDUK, Makary, MAKOWSKA, Joanna, DARMOŃ, Jerzy, PIEGZA, Natalia, DOMAŃSKA, Karolina, SIECZKA, Anna, WINDYGA, Maria and BURY, Justyna. Management of Hirsutism and Acne in Women with Polycystic Ovary Syndrome: A Narrative Review of Current Evidence and Emerging Therapies. Quality in Sport. 2026;58:72655. https://doi.org/10.12775/QS.2026.58.72655

ARTICLE TIMELINE

Received: 26.05.2026. Accepted: 06.06.2026.

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

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu.

Management of Hirsutism and Acne in Women with Polycystic Ovary Syndrome: A Narrative Review of Current Evidence and Emerging Therapies

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Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and is frequently associated with hyperandrogenic manifestations, including hirsutism and acne. These symptoms significantly impair quality of life and are closely linked to metabolic dysfunction, insulin resistance, and hormonal imbalance. The heterogeneous nature of PCOS contributes to variability in treatment response and complicates the development of optimal therapeutic strategies.

Aim: This narrative review aimed to evaluate current therapeutic approaches for hirsutism and acne in women with PCOS, focusing on clinical efficacy, mechanisms of action, and future therapeutic perspectives.

Materials and Methods: A narrative review of the literature was conducted using PubMed/MEDLINE and Google Scholar databases. Publications from 2015–2026 were analyzed, including randomized controlled trials, systematic reviews, meta-analyses and international clinical guidelines.

Results: Combined oral contraceptives remain the first-line treatment for hirsutism and acne due to their efficacy in reducing androgen excess and regulating menstrual cycles. Antiandrogens, particularly spironolactone, effectively reduce hirsutism, whereas metformin primarily improves metabolic abnormalities and insulin resistance. Emerging evidence suggests that GLP-1 receptor agonists may provide additional benefits through weight reduction, improved insulin sensitivity, and decreased androgen levels. However, current evidence is limited by heterogeneity of study populations, varying diagnostic criteria, short follow-up periods and lack of standardized outcome measures.

Conclusions: Management of hirsutism and acne in PCOS requires an individualized and multidimensional therapeutic approach. Further high-quality long-term studies are needed to optimize treatment strategies and improve clinical outcomes.

Keywords: polycystic ovary syndrome, PCOS, hirsutism, acne, hyperandrogenism

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine-metabolic disorder affecting approximately 6–13% of women of reproductive age and represents one of the most common causes of hyperandrogenism [1]. The diagnosis is currently most commonly based on the Rotterdam criteria, requiring the presence of at least two out of three features: hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology on ultrasound (PCOM) [1-5]. Depending on the combination of diagnostic criteria fulfilled, four phenotypes of PCOS are distinguished: phenotype A (HA + OD + PCOM), phenotype B (HA + OD), phenotype C (HA + PCOM), and phenotype D (OD + PCOM) [6-9].

PCOS is associated with numerous reproductive and gynecological complications, including infertility, obstetric complications, and an increased risk of endometrial cancer [10, 11]. Beyond gynecological abnormalities, PCOS is increasingly recognized as a systemic disorder associated with metabolic, cardiovascular, and psychological complications, all of which significantly contribute to long-term morbidity and underline the multifactorial nature of the disease [1-4, 6, 10, 12, 13].

Hyperandrogenism represents a key component of PCOS pathophysiology and is responsible for the development of dermatological manifestations such as hirsutism and acne, which are often the primary reasons for seeking medical attention. Cutaneous manifestations also include seborrhea, female-pattern hair loss, and acanthosis nigricans, and may persist throughout the patient's lifetime [3, 12, 14, 15]. The clinical and/or biochemical features of hyperandrogenism are observed in approximately 60–80% of women with PCOS, highlighting its major clinical relevance [8].

Hirsutism is the predominant clinical manifestation of hyperandrogenism and one of the most significant symptoms in women with PCOS. It is characterized by the presence of thick, dark, well-developed terminal hair in a typically male distribution pattern [12]. The prevalence of hirsutism among women with PCOS is estimated at approximately 65–75%, emphasizing the clinical importance of this condition [3]. Its pathogenesis is associated with elevated androgen levels acting on the pilosebaceous unit, particularly in androgen-sensitive areas such as the face, chest, and back. Increased androgen receptor expression and enhanced 5α-reductase activity also play crucial roles, contributing to excessive hair growth in these regions [3].

Acne vulgaris is another common dermatological manifestation of PCOS - recent meta-analyses indicating that approximately half of affected women experience acne lesions [14]. The pathogenesis of acne in PCOS is associated not only with androgen excess but also with metabolic disturbances such as insulin resistance, which may enhance sebaceous gland activity and promote inflammatory processes within the skin [3, 16].

The management of hirsutism and acne in women with PCOS requires a multidimensional therapeutic approach involving both causal treatment targeting hyperandrogenism and symptomatic management. Current therapeutic strategies include combined oral contraceptives, anti-androgens, metformin, and dermatological therapies such as retinoids, antibiotics, and topical treatments, often used in combination regimens [3, 17]. Individualization of therapy according to PCOS phenotype and symptom severity is of key importance. In addition to pharmacotherapy, lifestyle modification, including regular physical activity and appropriate dietary interventions, plays a crucial role in improving insulin sensitivity and reducing androgen levels, thereby contributing to symptom improvement [15].

Although dermatological manifestations are often perceived primarily as cosmetic concerns, they substantially affect patients' quality of life, leading to reduced self-esteem, psychosocial difficulties, and an increased risk of mental health disorders. Contemporary clinical approaches therefore emphasize

the importance of addressing psychological and quality-of-life aspects during the therapeutic process [3, 15, 18].

Despite the availability of multiple therapeutic options, the management of dermatological symptoms in PCOS remains a clinical challenge, as treatment response is frequently delayed and incomplete. In recent years, increasing attention has been directed toward the development of personalized therapeutic approaches and strategies based on the underlying pathophysiological mechanisms of the disorder, which may improve treatment efficacy in the future [3]. Effective management also requires multidisciplinary collaboration among gynecologists, dermatologists, endocrinologists, psychologists, and psychiatrists. Such an integrated approach enables targeted treatment focused not only on symptom control but also on the underlying hormonal and metabolic disturbances contributing to disease development [3, 15].

2. Materials and Methods

This study constitutes a narrative review aimed at providing a comprehensive overview of current therapeutic strategies for the management of hirsutism and acne in patients with polycystic ovary syndrome (PCOS), with particular emphasis on their clinical efficacy and practical relevance.

The literature review was conducted using the PubMed/MEDLINE and Google Scholar databases. The search was performed between January 2025 and March 2026 and included publications published between 2015 and 2026. Combinations of keywords and Boolean operators (AND/OR) were applied, including: “polycystic ovary syndrome” OR “PCOS”, “hirsutism”, “acne”, “hyperandrogenism”, “treatment” OR “therapy”, “antiandrogens”, “oral contraceptives”, “metformin”, and “GLP-1 receptor agonists”. Additionally, the reference lists of selected articles were manually screened to identify relevant supplementary publications. The inclusion criteria comprised randomized controlled trials (RCTs), systematic reviews, meta-analyses, and current clinical guidelines published in English. Publications were initially screened based on titles and abstracts, followed by full-text evaluation for relevance to the aim of the study.

Data synthesis was qualitative in nature and focused on comparing the efficacy of therapeutic approaches, mechanisms of action, and their clinical and practical significance in the management of hyperandrogenic manifestations in PCOS.

3. Results

3.1 Pathophysiology of Hyperandrogenism in PCOS

Hyperandrogenism represents a central component of the pathophysiology of PCOS and is considered a multifactorial process involving hormonal disturbances, as well as genetic and environmental factors [7]. Excess androgen production primarily results from dysregulation of the hypothalamic–pituitary–ovarian axis and abnormal ovarian steroidogenesis within the theca cells [7]. In PCOS, increased

pulsatile secretion of gonadotropin-releasing hormone (GnRH) is observed, leading to excessive luteinizing hormone (LH) secretion accompanied by a relative deficiency of follicle-stimulating hormone (FSH) [7, 10]. Elevated LH levels stimulate ovarian theca cells to produce excessive amounts of androgens, whereas insufficient FSH limits the aromatization of androgens into estrogens within granulosa cells, resulting in androgen accumulation [7, 8, 10].

In addition to ovarian androgen production, adrenal androgen excess may also contribute to hyperandrogenism in PCOS, although its role appears less prominent. Abnormal adrenal steroidogenesis is associated with increased activity of steroidogenic enzymes (e.g. CYP17A1), leading to enhanced synthesis of testosterone and androstenedione. Increased peripheral cortisol metabolism may further contribute to this process by stimulating adrenocorticotropic hormone (ACTH) secretion due to impaired negative feedback within the hypothalamic–pituitary–adrenal axis, thereby promoting adrenal steroidogenesis [7].

Insulin resistance is one of the most important pathophysiological mechanisms in PCOS and is present in up to approximately 75% of affected women [8]. It results in compensatory hyperinsulinemia, which plays a key role in exacerbating hyperandrogenism. Hyperinsulinemia has been shown to correlate positively with testosterone levels and negatively with sex hormone-binding globulin (SHBG) levels, highlighting its crucial role in the hormonal disturbances observed in PCOS [19, 20]. Insulin acts synergistically with LH, enhancing ovarian androgen production through stimulation of theca cells [10, 19]. Simultaneously, insulin suppresses hepatic SHBG synthesis, leading to increased levels of free biologically active androgens [7, 8, 10, 19, 21].

Reduced SHBG levels are a characteristic feature of PCOS and constitute an important mechanism increasing the bioavailability of circulating androgens. Elevated free androgen levels intensify the clinical manifestations of hyperandrogenism, including hirsutism and acne, and may further aggravate insulin resistance, thereby contributing to a self-perpetuating pathophysiological cycle [10].

Elevated anti-Müllerian hormone (AMH) levels may also contribute to the severity of hyperandrogenism in women with PCOS. In addition to directly stimulating androgen production, AMH may indirectly enhance androgen excess by inhibiting FSH-dependent aromatase activity [8].

Androgens exert significant effects on peripheral tissues, particularly the pilosebaceous unit and sebaceous glands. Increased local androgen activity promotes the conversion of fine vellus hairs into coarse terminal hairs, resulting in hirsutism, and simultaneously stimulates sebum production, thereby contributing to acne development. [3].

An increasing body of evidence also supports a substantial genetic contribution to PCOS pathogenesis, particularly through genes involved in insulin signaling pathways, such as INSR, IRS1, and PPAR-γ [22].

Metabolic disturbances, including obesity and chronic low-grade inflammation, further exacerbate insulin resistance and hyperandrogenism, emphasizing the multifactorial and systemic nature of PCOS [23].

3.2. Clinical Presentation

Hirsutism is a very common clinical manifestation of hyperandrogenism in women with PCOS and constitutes one of the principal diagnostic features of the syndrome. It is defined as excessive growth of terminal hair in androgen-dependent areas, such as the face, chest, and abdomen, and is most commonly assessed using the modified Ferriman–Gallwey (mFG) scoring system [3]. However, it should be emphasized that the recommended cutoff values for diagnosing hirsutism based on mFG scores continue to evolve. Current discussions suggest that these thresholds may need to differ between populations due to the potential influence of skin type, ethnicity, and age [12].

The severity of hirsutism does not always directly correlate with serum androgen levels, as peripheral factors such as local enzyme activity (particularly 5α-reductase) and androgen receptor sensitivity within the hair follicle play significant roles [3, 12]. This phenomenon may explain the considerable phenotypic variability observed among women with PCOS.

Acne is one of the most common cutaneous manifestations of PCOS and frequently coexists with other signs of hyperandrogenism. A recent meta-analysis indicated that acne affects approximately half of women with PCOS [14]. The pathogenesis of acne in PCOS is associated with excessive sebum production, abnormal follicular keratinization, and inflammatory processes, all of which are exacerbated by hyperandrogenism and insulin resistance [3, 16]. Similar to hirsutism, acne severity does not always correlate directly with systemic androgen levels, as local androgen activity appears to play a crucial role [3].

Compared with classic acne vulgaris, acne in women with PCOS more frequently presents with inflammatory papules, pustules, and nodules predominantly located on the lower face, chest, and upper back [3]. The presence of inflammatory, treatment-resistant, moderate-to-severe acne should prompt further evaluation for underlying endocrine disorders associated with hyperandrogenism, particularly PCOS [16].

In addition to hirsutism and acne, women with PCOS commonly present with other dermatological manifestations, including seborrhea, female-pattern androgenetic alopecia, and acanthosis nigricans [3, 12, 14, 15]. Together with hirsutism and acne, these manifestations reflect the systemic nature of endocrine disturbances associated with PCOS and highlight the close interplay between hormonal, metabolic, and inflammatory mechanisms. A comprehensive understanding of these interactions is essential for the development of effective therapeutic strategies targeting both local cutaneous symptoms and systemic consequences of PCOS [3].

PCOS is characterized by a broad spectrum of clinical manifestations extending beyond dermatological symptoms and including menstrual irregularities, subfertility, and features of metabolic syndrome [3, 4, 11]. Many patients exhibit metabolic abnormalities such as obesity, insulin resistance, and dyslipidemia, which may coexist with dermatological manifestations and contribute to their severity [3, 11].

The clinical manifestations of PCOS, particularly visible skin lesions, have a substantial impact on patients' quality of life [3]. Women with PCOS, especially those affected by hirsutism and acne, demonstrate an increased risk of depression, anxiety, and other psychological disorders [5, 18, 24]. The psychological consequences and reduced quality of life indicate the need for a comprehensive clinical approach that also includes psychological interventions [18].

3.3. Treatment Strategies

The management of hyperandrogenic manifestations in PCOS, including hirsutism and acne, requires a multidimensional approach involving both interventions targeting the underlying pathophysiology of the disorder and symptomatic treatment [3]. Due to the heterogeneous clinical presentation of PCOS, current recommendations emphasize the importance of individualized therapy [1, 15]. Contemporary therapeutic strategies are largely based on combination treatment approaches, as single interventions rarely provide optimal control of clinical symptoms [3, 25].

Lifestyle modification, including maintenance of appropriate body weight, regular physical activity, and healthy dietary habits, represents the cornerstone of PCOS management [3, 8]. These interventions improve insulin sensitivity and reduce androgen levels, thereby contributing to the amelioration of clinical manifestations [3].

The treatment of acne in women with PCOS includes both topical and systemic therapies, with treatment selection depending on disease severity [3, 17]. Topical retinoids and antibacterial agents are commonly used to prevent comedones formation and reduce inflammatory lesions [3]. However, it is emphasized that dermatological treatment should be combined with hormonal or metabolic therapy, as symptomatic treatment alone does not address the underlying pathophysiological mechanisms of the disorder [3].

Several cosmetic and procedural methods may be used to reduce the visible manifestations of hirsutism, including waxing, hair bleaching, plucking, electrolysis, and laser hair removal. Although these interventions constitute an important adjunct to pharmacological therapy, they do not affect the underlying cause of the disorder and therefore should be combined with hormonal treatment [3].

Combined oral contraceptives (COCs) containing ethinylestradiol in combination with antiandrogenic progestins constitute the cornerstone of pharmacological treatment for hyperandrogenic symptoms in PCOS [3, 26]. Their mechanism of action involves suppression of LH secretion and increased hepatic

production of SHBG, leading to reduced levels of free circulating androgens [3, 27]. In addition to reducing hyperandrogenism, COCs are effective in regulating menstrual cycles [1].

Antiandrogen agents, including spironolactone, exert their effects through androgen receptor blockade, reduction of androgen production, or inhibition of 5α-reductase activity.

5α-reductase inhibitors, such as finasteride, represent a therapeutic option targeting peripheral androgen metabolism. Their mechanism of action involves inhibition of testosterone conversion to dihydrotestosterone (DHT), which exhibits substantially greater biological activity in target tissues, including the hair follicle [27].

A meta-analysis of randomized controlled trials demonstrated that spironolactone significantly reduces hirsutism severity as assessed by the Ferriman–Gallwey score, confirming its clinical efficacy [25]. Furthermore, spironolactone combined with COCs was shown to result in greater reductions in mFG scores compared with monotherapy [3]. Beyond improving hirsutism, combination therapy has also been associated with improved menstrual regularity and reduction in acne severity [3].

Clinical studies and comparative analyses indicate that spironolactone is more effective than metformin in reducing hirsutism due to its direct androgen receptor-blocking activity. In contrast, metformin demonstrates superior efficacy in improving insulin resistance and glucose metabolism, highlighting the distinct mechanisms of action of these agents [29]. Other studies suggest that antiandrogen therapy combined with metformin may improve hormonal parameters, including reductions in testosterone levels, and may also be associated with greater reductions in body mass index (BMI) [25].

However, the use of antiandrogen medications remains limited due to their potential teratogenic effects and the absence of unequivocal evidence demonstrating superiority over alternative therapeutic options. Nevertheless, they remain an important treatment option in patients with resistant forms of hyperandrogenism [27].

Metformin is the most widely used insulin-sensitizing agent in PCOS and remains the first-line therapy for metabolic abnormalities associated with the syndrome [30]. It has been shown to contribute to weight reduction, improved menstrual cycle regularity, and decreased hair growth rate [3]. Meta-analyses of randomized controlled trials demonstrated that metformin significantly reduces total testosterone levels and improves metabolic parameters, including body weight and insulin resistance [30, 31]. Metformin may also indirectly improve dermatological manifestations such as acne and hirsutism through reduction of hyperinsulinemia and secondary decreases in androgen production [3].

Nevertheless, systematic reviews of randomized controlled trials indicate that COCs are more effective than metformin in reducing hyperandrogenic symptoms and regulating menstrual cycles. Conversely, metformin demonstrates greater efficacy in improving metabolic outcomes, including insulin resistance, body composition, and ovulation, particularly when used in combination therapy. Available evidence also suggests that COCs may be associated with a less favorable metabolic profile, including potential worsening of insulin resistance, which may limit their use in patients at high metabolic risk [32].

Due to gastrointestinal adverse effects associated with metformin, many women with PCOS seek alternative approaches for the management of insulin resistance. One such option is inositol supplementation. Myo-inositol (MI) and D-chiro-inositol (DCI) participate in insulin signaling and glucose metabolism, including GLUT-4 transporter translocation and enhancement of insulin sensitivity. Myo-inositol also plays an important role in ovarian function through involvement in FSH-dependent pathways and potential enhancement of aromatase activity, which may contribute to reduced androgen production. In PCOS, hyperinsulinemia may disrupt the physiological ovarian MI/DCI ratio, adversely affecting follicular function and exacerbating hyperandrogenism [33].
Despite the biological rationale for inositol supplementation, recent systematic reviews and meta-analyses indicate that evidence supporting its efficacy in PCOS remains limited and inconclusive. Although inositol may improve selected metabolic parameters and ovulatory function, metformin continues to demonstrate greater clinical efficacy in improving several PCOS-related outcomes, including central obesity assessed by waist-to-hip ratio (WHR) and hirsutism [33].

Incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), represent a promising therapeutic group in PCOS management, especially among patients with obesity and insulin resistance. Their effects include weight reduction, improved insulin sensitivity, and modulation of metabolic parameters [26, 34]. Meta-analyses of randomized controlled trials demonstrated that GLP-1 RAs significantly reduce BMI, waist circumference, and testosterone levels, suggesting a potential beneficial effect on hyperandrogenism [26]. However, other systematic reviews emphasize that although these agents exert favorable metabolic effects, evidence regarding their efficacy in reducing clinical manifestations such as hirsutism remains limited and requires further high-quality studies [34, 35]. Current evidence suggests that GLP-1 receptor agonists may play a particularly important role in combination therapies targeting the core pathophysiological mechanisms of PCOS, including insulin resistance and obesity [35].

4. Discussion

The management of hirsutism and acne in women with PCOS remains a significant clinical challenge due to the heterogeneous nature of the disorder and the coexistence of hormonal, metabolic, and dermatological abnormalities. Current therapeutic strategies include hormonal, antiandrogenic, and metabolic interventions, as well as lifestyle modification. However, the efficacy of individual approaches varies depending on the predominant clinical manifestations and patient-specific characteristics.

Available evidence indicates that COCs remain the first-line treatment for hyperandrogenic symptoms in women not seeking pregnancy [36]. Their efficacy is primarily related to suppression of gonadotropin secretion and increased levels of SHBG, leading to reduced concentrations of free circulating androgens [3, 27].

Studies have demonstrated that COCs are more effective than metformin in reducing hirsutism and acne and in regulating menstrual cycles. In contrast, metformin exerts more favorable effects on metabolic parameters, including insulin resistance, body weight, and glycemic profile. These findings emphasize the complementary nature of both therapeutic strategies and highlight the importance of individualized treatment selection [32].

Inositol supplementation represents one of the alternative approaches to metformin for the management of insulin resistance in women with PCOS. Although inositol may improve selected metabolic parameters and ovulatory function, recent systematic reviews and meta-analyses indicate that evidence supporting its efficacy remains limited and inconclusive. Metformin continues to demonstrate superior clinical efficacy in improving several PCOS-related outcomes, including hirsutism [33].

Antiandrogen therapies also play a substantial role in the treatment of hyperandrogenism, particularly spironolactone, which effectively reduces hirsutism through androgen receptor blockade. In recent years, increasing attention has also been directed toward 5α-reductase inhibitors, such as finasteride, which reduce the conversion of testosterone to DHT. Although these therapies appear promising, their use remains limited by insufficient long-term safety data and concerns regarding teratogenic potential [27].

Increasing importance has also been attributed to metabolic therapies, particularly
GLP-1 RAs. These agents exert beneficial effects on body weight reduction, insulin sensitivity, and androgen levels, suggesting a potential role in causal treatment of PCOS [26, 34]. Meta-analyses of randomized controlled trials indicate that GLP-1 receptor agonists may improve both metabolic and hormonal parameters. However, their effects on dermatological manifestations such as hirsutism and acne remain insufficiently investigated [26, 34, 35]. Therefore, additional high-quality long-term studies are required to determine their clinical utility in managing hyperandrogenic symptoms.

Current therapeutic strategies increasingly rely on combination treatment approaches integrating hormonal, antiandrogenic, and metabolic therapies. This concept reflects the multifactorial pathophysiology of PCOS and the need to simultaneously target both clinical manifestations and metabolic disturbances. Although several studies suggest potential benefits of combination therapy, the available evidence remains inconsistent. Some randomized controlled trials demonstrated no significant superiority of spironolactone combined with metformin over monotherapy in reducing hirsutism, whereas other analyses reported improvements in metabolic and reproductive outcomes with more comprehensive treatment regimens [25, 29].

Interpretation of currently available evidence is complicated by numerous methodological limitations. One of the major concerns is the substantial heterogeneity of study populations resulting from variations in PCOS phenotypes and differences in diagnostic criteria. This significantly limits the comparability of

studies and impairs the ability to establish definitive clinical conclusions. Meta-analyses involving large patient populations have highlighted that differences in age, BMI, and diagnostic methodologies significantly affect study outcomes and contribute to variability in therapeutic response [5]. Furthermore, many studies are limited by small sample sizes, short follow-up periods, and lack of standardized outcome measures, reducing their applicability to clinical practice [37]. Assessment of dermatological manifestations such as hirsutism and acne remains particularly problematic, as evaluation frequently relies on subjective clinical scoring systems. Moreover, many studies primarily focus on biochemical parameters, including testosterone levels, which do not always directly correlate with improvements in clinical symptoms and patient quality of life.

Another important limitation is the lack of long-term data regarding the safety and efficacy of PCOS treatment. Most available studies focus on short-term therapeutic outcomes, making it difficult to assess the long-term impact of treatment on disease progression and associated complications.

Limitations also apply to the evaluation of emerging therapeutic strategies. Despite growing interest in digital health interventions, current evidence remains limited and heterogeneous. Although some studies suggest beneficial effects on metabolic parameters and health-related behaviors, further multicenter high-quality studies with longer intervention periods are necessary to confirm their clinical value [38].

In response to these limitations, contemporary research increasingly focuses on the development of more comprehensive therapeutic strategies. Particular attention has been directed toward multi-target incretin-based therapies, including dual and triple receptor agonists, which may simultaneously improve body weight, glucose metabolism, and hormonal parameters [26, 34, 35].

Furthermore, increasing emphasis is being placed on personalized medicine and multidisciplinary care. Future therapeutic approaches will likely be based on the identification of dominant pathophysiological mechanisms in individual patients, such as hyperandrogenism, insulin resistance, or chronic low-grade inflammation. Such an approach may improve treatment efficacy while minimizing adverse effects through more precise therapy selection.

5. Conclusions

Hirsutism and acne in women with PCOS represent significant clinical challenges resulting from complex hormonal and metabolic disturbances. Management of these manifestations requires a multidirectional and individualized therapeutic approach. Available treatment strategies, including hormonal, antiandrogenic, and metabolic therapies, demonstrate variable efficacy and largely exert complementary effects. The absence of a clearly superior therapeutic strategy highlights the need for individualized treatment selection. Despite substantial advances in understanding the pathophysiology of PCOS and the development of novel therapeutic options, there remains a need for high-quality, long-term randomized controlled trials.

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

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Conflict of interest: None declared.

Declaration of AI Use: Artificial intelligence (AI) was used only for language enhancement purposes, such as grammar correction and stylistic refinement.

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