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INSULIN RESISTANCE IN POLYCYSTIC OVARY SYNDROME — A NARRATIVE REVIEW OF MECHANISMS AND MANAGEMENT

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ABSTRACT

Polycystic ovary syndrome (PCOS) affects 11–13% of women of reproductive age worldwide and combines hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Once viewed as a purely reproductive disorder, PCOS is now also recognised as a metabolic one, with insulin resistance (IR) and compensatory hyperinsulinaemia linking its reproductive and metabolic features. In a 2026 international consensus published in The Lancet, the condition was formally renamed polyendocrine metabolic ovarian syndrome (PMOS); the term PCOS remains widely used during the announced three-year transition period. This narrative review synthesises current evidence on the role of insulin resistance in the pathophysiology of PCOS, with a focus on the 2023 International Evidence-based Guideline and recent pharmacological developments. We searched PubMed, Scopus and Google Scholar for peer-reviewed literature published in English between January 2004 and April 2026, prioritising original studies, systematic reviews, meta-analyses and current clinical guidelines. Hyperinsulinaemia stimulates ovarian theca-cell androgen production and lowers hepatic sex hormone-binding globulin synthesis, raising bioavailable androgens. A pathway-selective insulin signalling defect — impaired PI3K/Akt with relatively preserved MAPK signalling — has been proposed as a unifying molecular mechanism. Lifestyle modification remains first-line therapy; metformin and inositol improve metabolic and ovulatory parameters, and glucagon-like peptide-1 receptor agonists produce greater reductions in body weight and HOMA-IR than metformin in head-to-head studies. Insulin resistance is a key driver of both reproductive and metabolic outcomes, and early identification is essential for reducing long-term cardiometabolic morbidity.

KEYWORDS

Polycystic Ovary Syndrome; Insulin Resistance; Hyperandrogenism; Metformin; Inositol; GLP-1 Receptor Agonists

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1. Introduction

Polycystic ovary syndrome (PCOS) affects 11–13% of women of reproductive age worldwide (Stener-Victorin et al., 2024). It is a heterogeneous endocrine and metabolic disorder. Diagnostic criteria are hyperandrogenism, ovulatory dysfunction and either polycystic ovarian morphology or elevated anti-Müllerian hormone (AMH) (Teede et al., 2023). PCOS also has lifelong metabolic consequences: women with the syndrome are at higher risk of early-onset type 2 diabetes mellitus (T2DM), obesity and cardiovascular disease (Stener-Victorin et al., 2024; Teede et al., 2023).

The aetiology of PCOS remains incompletely understood, but insulin resistance (IR) is now recognised as a central mechanism present in most affected women, including those of normal weight (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997). Compensatory hyperinsulinaemia drives ovarian theca-cell androgen production, lowers hepatic synthesis of sex hormone-binding globulin (SHBG) and disrupts folliculogenesis (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011). The interaction between IR and hyperandrogenism creates a self-perpetuating cycle that ties together the metabolic and reproductive features of the syndrome (Barber et al., 2015; Stener-Victorin et al., 2024).

This narrative review summarises current evidence on the role of IR in PCOS. We integrate updated diagnostic frameworks from the 2023 International Evidence-based Guideline (Teede et al., 2023), recent insights into selective insulin signalling defects, and newer pharmacological options including inositol formulations and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (Fitz et al., 2024; Hoteit et al., 2025). The goal is a clinically oriented synthesis that can inform diagnostic and management strategies in women with PCOS.

Note on terminology. In May 2026, an international consensus process involving 56 academic, clinical, and patient organisations formally renamed the condition polyendocrine metabolic ovarian syndrome (PMOS),

citing the inaccuracy of 'polycystic ovary syndrome' as a descriptor and its contribution to diagnostic delay and stigma (Teede et al., 2026). A three-year transition period was announced. Throughout this review, the term PCOS is used, consistent with the terminology of the cited literature; however, all findings discussed apply equally to the condition under its new designation as PMOS.

2. Methodology

2.1. Search strategy

A structured literature search was performed in PubMed, Scopus and Google Scholar covering the period from January 2004 to April 2026. The search strategy combined the controlled terms and free-text keywords: ("polycystic ovary syndrome" OR "PCOS") AND ("insulin resistance" OR "hyperinsulinaemia" OR "insulin signalling") AND ("hyperandrogenism" OR "metformin" OR "inositol" OR "GLP-1 receptor agonist" OR "semaglutide" OR "liraglutide").

Eligible sources included peer-reviewed original research articles, systematic reviews, meta-analyses and international clinical practice guidelines published in English. The 2023 International Evidence-based Guideline for the Assessment and Management of PCOS (Teede et al., 2023) and the 2024 Nature Reviews Disease Primers article by Stener-Victorin et al. (Stener-Victorin et al., 2024) were used as anchor references for current consensus on diagnosis and pathophysiology. Studies were selected on the basis of methodological quality, relevance to insulin resistance in PCOS and clinical applicability.

Because this is a narrative rather than a systematic review, no PRISMA flow-diagram or formal risk-of-bias assessment was performed. The selection of cited works reflects the author's qualitative appraisal and is intended to provide a balanced clinical synthesis.

3. Results

3.1. Definition and diagnostic criteria of PCOS

According to the 2023 International Evidence-based Guideline (Teede et al., 2023), the diagnosis of PCOS in adults requires two of the following three criteria, after exclusion of other causes of hyperandrogenism: clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology on ultrasound or elevated serum AMH. The inclusion of AMH as an alternative to ultrasound is a key update from the 2018 recommendations (Teede et al., 2018) and reflects the desire to improve diagnostic accuracy where high-resolution imaging is not available (Stener-Victorin et al., 2024; Teede et al., 2023).

In adolescents, both hyperandrogenism and ovulatory dysfunction are required, and ovarian morphology and AMH are not used because of physiological overlap with normal pubertal changes (Teede et al., 2023). The 2023 guideline retains the framework of the Rotterdam consensus (Rotterdam Group, 2004) but tightens its application by introducing more specific cut-offs for hyperandrogenism and ultrasound criteria, especially with newer imaging technology (Teede et al., 2023).

3.1.1. Rotterdam phenotypes

Application of the Rotterdam criteria yields four clinically distinct phenotypes, defined by the combination of features present: phenotype A (hyperandrogenism + ovulatory dysfunction + polycystic ovarian morphology) — the "complete" or "classic" phenotype; phenotype B (hyperandrogenism + ovulatory dysfunction); phenotype C (hyperandrogenism + polycystic ovarian morphology) — sometimes called the "ovulatory" phenotype; and phenotype D (ovulatory dysfunction + polycystic ovarian morphology) — the non-hyperandrogenic phenotype (Rotterdam Group, 2004; Teede et al., 2023). The phenotypes differ in metabolic profile: insulin resistance is most prevalent and most severe in the hyperandrogenic phenotypes (A, B and C) and mildest in phenotype D (Stener-Victorin et al., 2024; Teede et al., 2023). This pattern fits the central role of hyperandrogenism in the IR–androgen feedback cycle described in section 3.3, and it has practical implications for risk assessment and individualised management (Stener-Victorin et al., 2024; Teede et al., 2023).

Table 1. *Rotterdam phenotypes of PCOS and their relative metabolic profiles.* PCOM, polycystic ovarian morphology; IR, insulin resistance.

Phenotype	Diagnostic features	Metabolic profile (relative to other PCOS phenotypes)
A ("classic")	Hyperandrogenism + ovulatory dysfunction + PCOM	Highest prevalence of IR and metabolic syndrome; greatest cardiometabolic risk (Stener-Victorin et al., 2024; Teede et al., 2023)
B	Hyperandrogenism + ovulatory dysfunction (no PCOM)	Metabolic risk comparable to phenotype A; classic NIH PCOS phenotype (Stener-Victorin et al., 2024; Teede et al., 2023)
C ("ovulatory")	Hyperandrogenism + PCOM (regular cycles)	Intermediate metabolic risk; lower than A/B but higher than D (Stener-Victorin et al., 2024; Teede et al., 2023)
D ("non-hyperandrogenic")	Ovulatory dysfunction + PCOM (normal androgens)	Mildest endocrine and metabolic disturbances; lowest prevalence of metabolic syndrome (Stener-Victorin et al., 2024; Teede et al., 2023)

3.2. Pathophysiology of polycystic ovary syndrome

PCOS arises from a mix of genetic predisposition, intrauterine programming and environmental factors — particularly excess adiposity (Goodarzi et al., 2011; Stener-Victorin et al., 2024). The central biochemical feature is hyperandrogenism, driven mainly by enhanced ovarian theca-cell androgen biosynthesis with a smaller adrenal contribution (Diamanti-Kandarakis & Dunaif, 2012; Ehrmann, 2005; Goodarzi et al., 2011).

The hypothalamic–pituitary–ovarian axis is also disturbed in PCOS. Pulsatile gonadotrophin-releasing hormone (GnRH) secretion increases and favours luteinising hormone (LH) over follicle-stimulating hormone (FSH) release; this promotes theca-cell androgen production and contributes to chronic anovulation (Goodarzi et al., 2011; Stener-Victorin et al., 2024). Metabolic factors — especially insulin resistance and hyperinsulinaemia — amplify these neuroendocrine changes, acting both centrally and at the level of the ovary (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012).

The clinical features of PCOS — menstrual irregularity, hirsutism, acne, infertility and metabolic morbidity — arise from this combined endocrine and metabolic dysregulation, dissected mechanistically in section 3.3.

3.3. Mechanisms of insulin resistance in PCOS

3.3.1. Definition and prevalence

Insulin resistance is defined as a reduced cellular response to physiological concentrations of insulin in its principal target tissues — skeletal muscle, liver and adipose tissue. To maintain normal blood glucose, the pancreatic β-cells must secrete more insulin, producing chronic compensatory hyperinsulinaemia (Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997). In women with PCOS, IR is observed across all body-mass index (BMI) categories. A meta-analysis of euglycaemic-hyperinsulinaemic clamp studies — the gold-standard method for measuring whole-body insulin sensitivity — reported a 27% reduction in insulin sensitivity in women with PCOS compared with weight-matched controls, an effect that was independent of BMI but exacerbated by obesity (Cassar et al., 2016). Direct clamp measurements show that 75–95% of women with PCOS meet the World Health Organization criteria for IR (Cassar et al., 2016; Stepto et al., 2019), confirming that the defect is intrinsic to the syndrome rather than secondary to adiposity alone. Skeletal muscle, which accounts for approximately 85% of insulin-stimulated glucose disposal in vivo, is the principal site of this defect (Stepto et al., 2019).

3.3.2. Direct effects of hyperinsulinaemia on ovarian and hepatic targets

Compensatory hyperinsulinaemia exerts direct ovarian effects by stimulating theca-cell androgen production. Insulin acts as a co-gonadotrophin — that is, it amplifies the normal action of luteinising hormone

(LH) — and increases the activity of the steroidogenic enzymes 17α-hydroxylase and 17,20-lyase, both encoded by the CYP17A1 gene (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011). Concurrently, insulin suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), the carrier protein that normally inactivates circulating testosterone. The result is a higher proportion of biologically active free androgens (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997). The combination of increased ovarian androgen synthesis and reduced SHBG explains the close clinical association between IR and the cardinal hyperandrogenic features of PCOS (Diamanti-Kandarakis & Dunaif, 2012; Stener-Victorin et al., 2024). Insulin also acts on granulosa cells of small antral follicles, contributing to premature differentiation and follicular arrest — one of the mechanisms underlying anovulation (Goodarzi et al., 2011).

3.3.3. Pathway-selective defect in insulin signalling

Women with PCOS show a pathway-selective defect in insulin signalling. When insulin binds its receptor, the signal passes to an adaptor protein known as insulin receptor substrate-1 (IRS-1), and from there splits into two parallel branches: a metabolic branch and a mitogenic branch (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012).

The metabolic branch runs through phosphatidylinositol-3-kinase (PI3K) and the kinase Akt (also known as protein kinase B). It mediates the metabolic actions of insulin — chiefly glucose uptake into muscle and adipose tissue, glycogen synthesis and suppression of hepatic glucose output. In PCOS, this branch is impaired (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997). The mitogenic branch runs through the Ras-Raf-MAPK kinase cascade and mediates cell-growth and steroidogenic effects. Unlike the metabolic branch, this branch remains intact or is even enhanced in PCOS, allowing insulin to keep stimulating ovarian androgen production even when peripheral tissues become resistant (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Stepto et al., 2019). This selective impairment explains the clinical paradox of PCOS: peripheral metabolic resistance alongside ovarian hypersensitivity to insulin.

The proximate molecular defect appears to lie downstream of the insulin receptor itself — receptor binding is normal, but the post-receptor signal is disrupted (Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997). A leading explanation is excessive serine phosphorylation of IRS-1, which inactivates IRS-1 and uncouples it from the PI3K branch, while leaving the mitogenic branch unaffected (Diamanti-Kandarakis & Dunaif, 2012). Several serine kinases have been implicated, including protein kinase C (PKC), mammalian target of rapamycin (mTOR) and c-Jun N-terminal kinase (JNK). Cultured skeletal-muscle cells (myotubes) from women with PCOS retain only part of this defect, indicating that both intrinsic genetic factors and the in vivo hormonal and metabolic environment contribute to the impairment (Stepto et al., 2019).

3.3.4. Mitochondrial dysfunction and intramyocellular lipid accumulation

A more recently characterised mechanism is dysfunction of mitochondria — the cellular organelles responsible for adenosine-triphosphate (ATP) production through oxidative phosphorylation — in the skeletal muscle of women with PCOS. Transcriptomic analyses of muscle biopsies have demonstrated reduced expression of nuclear-encoded genes that regulate mitochondrial biogenesis (notably PGC-1α and NRF1) and components of the electron transport chain, consistent with a reduced oxidative capacity (Stepto et al., 2019). The clinical consequence is impaired fatty-acid oxidation and accumulation of lipid intermediates — intramyocellular triglycerides and ceramides — within muscle fibres. Ceramides in particular interfere directly with IRS-1 signalling and provide an additional, lipid-mediated mechanism of insulin resistance (Cassar et al., 2016; Stepto et al., 2019). This pathway provides a mechanistic rationale for the well-documented benefits of structured exercise in PCOS, since aerobic and resistance training stimulate mitochondrial biogenesis and reduce intramyocellular lipid load even when weight loss is modest (Cassar et al., 2016; Stepto et al., 2019).

3.3.5. Adipose tissue dysfunction

Adipose tissue is not a passive lipid store but an active endocrine organ, and its dysfunction is central to the metabolic phenotype of PCOS. Visceral fat accumulation — present even in lean women with PCOS — is associated with adipocyte hypertrophy, chronic low-grade inflammation and altered secretion of adipokines (signalling molecules produced by fat tissue) (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011; Lim et al., 2012). Adiponectin, an adipokine that improves insulin sensitivity, is reduced; leptin and resistin are elevated. Pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) further impair insulin signalling at the receptor and post-receptor level (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011). The hypertrophied, dysfunctional adipocyte also releases excess free fatty acids into the circulation; these deposit ectopically in liver and skeletal muscle, amplifying systemic IR through the lipid mechanisms described above (Diamanti-Kandarakis & Dunaif, 2012; Lim et al., 2012). Within visceral adipose tissue, local cortisol regeneration via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) provides a further

link between adiposity, glucocorticoid action and androgen excess (Diamanti-Kandarakis & Dunaif, 2012). The result is a feedback loop: hyperandrogenism promotes central adiposity, central adiposity worsens IR, and IR-driven hyperinsulinaemia further amplifies hyperandrogenism (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Stener-Victorin et al., 2024).

3.3.6. Genetic susceptibility

PCOS is highly heritable. Twin and family studies estimate a heritability of approximately 70%, with first-degree relatives — including male relatives, who present with metabolic phenotypes such as IR and male-pattern balding — showing a markedly increased risk (Goodarzi et al., 2011; Stener-Victorin et al., 2024). The largest genome-wide association study (GWAS) meta-analysis to date combined data from 10,074 women with PCOS and 103,164 controls of European ancestry, and identified or replicated 14 risk loci (Day et al., 2018). Implicated genes span several biological themes relevant to PCOS pathophysiology: gonadotrophin signalling (FSHB, FSHR, LHCGR), steroidogenesis (DENND1A), thyroid- and metabolism-associated loci (THADA) and follicular dynamics (GATA4) (Day et al., 2018; Goodarzi et al., 2011). The genetic architecture is largely shared between cases diagnosed under the NIH and Rotterdam criteria, suggesting that these criteria capture the same underlying disease at different clinical thresholds rather than distinct disorders (Day et al., 2018). Mendelian-randomisation analyses, which use genetic variants as natural experiments to test causality, suggest that elevated fasting insulin and BMI play a causal role in PCOS — not merely an associative one — providing genetic support for IR as a primary aetiological factor (Day et al., 2018).

3.3.7. Developmental origins and epigenetic programming

Evidence increasingly supports the hypothesis that PCOS originates, at least in part, from intra-uterine programming. In animal models, prenatal androgen exposure in primates and sheep produces female offspring with adult phenotypes resembling human PCOS — including hyperandrogenism, ovulatory dysfunction, central adiposity and IR — even without postnatal androgen exposure (Goodarzi et al., 2011; Stener-Victorin et al., 2024). In humans, low birth weight followed by rapid postnatal weight gain (the so-called "adiposity rebound") is associated with adolescent IR and earlier onset of pubertal hyperandrogenism (Goodarzi et al., 2011). Daughters of women with PCOS show elevated AMH levels, larger ovarian volumes and reduced insulin sensitivity from puberty onwards, well before any clinical signs of the syndrome (Stener-Victorin et al., 2024). Altered DNA methylation patterns have been described in granulosa cells and adipose tissue from women with PCOS, and emerging data from animal models suggest that some of these epigenetic marks may be transmitted to offspring through the germ line, providing a possible mechanism for the familial clustering observed in clinical practice (Stener-Victorin et al., 2024). Together these findings support an integrated model in which genetic predisposition, intra-uterine androgen exposure and postnatal environmental factors (notably weight gain during adolescence) determine the timing and severity of PCOS expression.

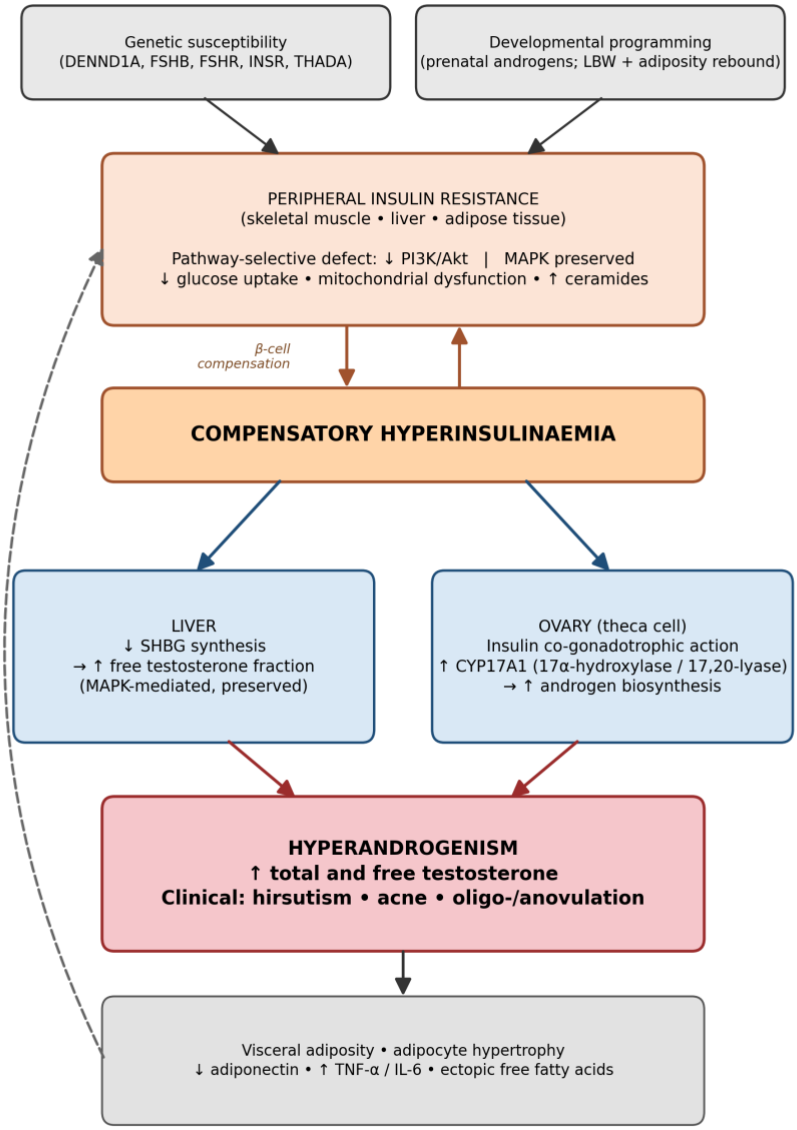
The principal mechanisms linking IR with PCOS, organised by biological level, are summarised in Table 2.

Table 2. Principal mechanisms linking insulin resistance with PCOS, organised by biological level.

Level	Mechanism	Key effect
Genetic	Risk loci *DENND1A*, *FSHB*, *FSHR*, *LHCGR*, *THADA* (GWAS)	Polygenic susceptibility; shared architecture across diagnostic criteria (Day et al., 2018)
Developmental	Prenatal androgen exposure; low birth weight + rapid postnatal weight gain	Programming of adult metabolic and reproductive phenotype (Goodarzi et al., 2011; Stener-Victorin et al., 2024)
Molecular	Excessive serine phosphorylation of IRS-1; impaired PI3K/Akt branch with preserved MAPK branch	Selective impairment of metabolic but not mitogenic insulin actions (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997)
Cellular	Mitochondrial dysfunction; intramyocellular triglyceride and ceramide accumulation	Reduced oxidative capacity; lipid-mediated inhibition of insulin signalling (Cassar et al., 2016; Stepto et al., 2019)

Tissue (ovary)	Insulin co-gonadotrophic action via *CYP17A1*; granulosa-cell dysfunction	Increased theca-cell androgen synthesis; follicular arrest (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011)
Tissue (liver)	Insulin-mediated suppression of SHBG synthesis	Higher fraction of biologically active free androgens (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Dunaif, 1997)
Tissue (adipose)	Adipocyte hypertrophy, ↓ adiponectin, ↑ leptin/resistin, low-grade inflammation, ectopic fat	Worsened systemic IR; cross-talk with cortisol via 11β-HSD1 (Diamanti-Kandarakis & Dunaif, 2012; Goodarzi et al., 2011; Lim et al., 2012)
Systemic	Compensatory hyperinsulinaemia; self-reinforcing IR–hyperandrogenism–adiposity cycle	Amplification and clinical manifestation of the syndrome (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Stener-Victorin et al., 2024)

The insulin resistance ↔ hyperandrogenism cycle in PCOS



Solid arrows: causal flows. Dashed arrow: self-perpetuating feedback loop. Colour key: orange = metabolic; blue = endocrine; pink = androgenic; grey = upstream/feedback.

Figure 1. Schematic of the insulin resistance ↔ hyperandrogenism cycle in polycystic ovary syndrome. Genetic susceptibility and developmental programming converge on peripheral insulin resistance, characterised by a pathway-selective post-receptor defect (impaired PI3K/Akt branch with preserved MAPK branch). Compensatory pancreatic β-cell hyperinsulinaemia stimulates ovarian theca-cell androgen biosynthesis via CYP17A1 and suppresses hepatic SHBG synthesis, raising the free testosterone fraction. The resulting hyperandrogenism — clinically expressed as hirsutism, acne and oligo-/anovulation — promotes visceral adiposity, which feeds back onto peripheral IR, completing a self-perpetuating cycle. Solid arrows indicate causal flows; the dashed arrow denotes the feedback loop. SHBG, sex hormone-binding globulin; LBW, low birth weight; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6.

3.4. Clinical implications

The clinical features that bring women with PCOS to medical attention are heterogeneous but cluster into reproductive and dermatological manifestations of androgen excess and ovulatory dysfunction. Clinical hyperandrogenism — most commonly hirsutism, with acne and androgenic alopecia in a subset — is often the presenting complaint and a major source of psychosocial distress and quality-of-life impairment (Ehrmann, 2005; Escobar-Morreale, 2018). Menstrual irregularity (oligo- or amenorrhoea) reflects ovulatory dysfunction and may persist for years before evaluation, particularly when adolescent cycle irregularity is misattributed to physiological pubertal variation (Teede et al., 2023). Anovulation related to follicular arrest is the single most common cause of subfertility in women with PCOS, and many patients are first diagnosed during fertility evaluation (Escobar-Morreale, 2018; Goodarzi et al., 2011).

Metabolic abnormalities are frequently present at the time of diagnosis, even in women without overt obesity. Compared with weight-matched controls, women with PCOS show higher rates of central adiposity, impaired glucose tolerance, atherogenic dyslipidaemia (raised triglycerides, low HDL-cholesterol) and the full metabolic syndrome (Cassar et al., 2016; DeUgarte et al., 2005; Lim et al., 2012). Hypertension and obstructive sleep apnoea, while less prominent at presentation, are now recognised as additional metabolic comorbidities (Teede et al., 2023). During pregnancy, women with PCOS have higher rates of gestational diabetes, hypertensive disorders of pregnancy and preterm birth, the relative risks of which are mediated in large part by pre-existing IR and excess body weight (Stener-Victorin et al., 2024; Teede et al., 2023).

These reproductive and metabolic features are linked through the IR–hyperandrogenism axis described in section 3.3, and they typically coexist in the same patient. Clinically, this calls for an integrated initial assessment that captures both reproductive (cycle history, hirsutism scoring, fertility goals) and cardiometabolic (anthropometry, blood pressure, fasting lipids and glycaemic status) domains at the time of diagnosis (Teede et al., 2023). Recommendations for surveillance over the lifespan are set out in section 3.6.

3.5. Management of insulin resistance in PCOS

3.5.1. Therapeutic principles

Management of IR in PCOS combines lifestyle modification with pharmacological interventions, individualised to the patient's reproductive goals, BMI category and metabolic profile (Teede et al., 2018; Teede et al., 2023). The 2023 International Guideline reaffirms lifestyle therapy as first-line and provides a stepwise framework for adjunctive pharmacotherapy (Teede et al., 2023). A useful clinical distinction is between therapies that directly target IR — lifestyle modification, metformin, inositol, GLP-1 receptor agonists and bariatric surgery — and adjunctive therapies that address other clinical features of PCOS (hyperandrogenism, anovulation) without modifying insulin sensitivity. Both categories are commonly required in the same patient, and treatment selection must take into account both her current reproductive intentions and her long-term cardiometabolic risk (Teede et al., 2023).

3.5.2. Lifestyle modification

Structured dietary intervention combined with regular physical activity is the foundation of management and is recommended for all women with PCOS regardless of BMI (Moran et al., 2011; Teede et al., 2023). Even modest weight reduction — 5–10% of baseline body weight in women with overweight or obesity — improves insulin sensitivity, reduces the free androgen index, restores menstrual cyclicity in roughly half of women and increases the probability of spontaneous ovulation (Moran et al., 2011). The 2023 guideline does not endorse any single dietary pattern; instead, it emphasises sustainable energy reduction (typically a 500–750 kcal/day deficit) and cardiometabolic risk modification (Teede et al., 2023). Mediterranean and low-glycaemic-index dietary patterns are most consistently supported by available data, although adequately powered head-to-head superiority trials are lacking (Moran et al., 2011; Teede et al., 2023). Physical activity

recommendations follow general adult guidance: at least 150 minutes per week of moderate-intensity aerobic activity (or 75 minutes of vigorous activity) combined with resistance training on two or more days per week (Moran et al., 2011; Teede et al., 2023). Structured exercise improves insulin sensitivity and mitochondrial function in skeletal muscle independently of weight loss (Moran et al., 2011; Stepto et al., 2019), providing a mechanistic rationale for its role as a stand-alone intervention. Behavioural support, self-monitoring and long-term follow-up are essential, since adherence is the principal determinant of sustained benefit (Teede et al., 2023).

3.5.3. Metformin

Metformin is the most extensively studied insulin-sensitising agent in PCOS. By suppressing hepatic glucose production (chiefly through inhibition of mitochondrial complex I and activation of AMP-activated protein kinase, AMPK), enhancing peripheral glucose uptake and modestly reducing intestinal glucose absorption, metformin lowers compensatory hyperinsulinaemia and free androgen levels and improves menstrual cyclicity (Palomba et al., 2009; Teede et al., 2018). Therapeutic doses range from 500 to 2000 mg/day, typically initiated at 500 mg with food and titrated weekly to minimise gastrointestinal adverse effects (nausea, abdominal discomfort, diarrhoea), which are common but usually transient (Palomba et al., 2009). The 2023 guideline recommends metformin in addition to lifestyle modification for management of weight, hormonal and metabolic outcomes, particularly in women with overweight or obesity, with consideration also given in lean PCOS (Teede et al., 2023). Clinical effects on menstrual regularity and androgen levels are typically apparent within three to six months of treatment. Lactic acidosis is rare but contraindicates use in advanced renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2); annual renal monitoring is recommended in long-term users (Palomba et al., 2009). Vitamin B_{12} levels should be checked periodically, as long-term metformin therapy is associated with reduced B_{12} absorption (Palomba et al., 2009).

3.5.4. Inositol stereoisomers

Inositol stereoisomers — myo-inositol (MI) and D-chiro-inositol (DCI) — function as second messengers downstream of the insulin receptor and have been investigated extensively as insulin-sensitising supplements in PCOS (Fitz et al., 2024; Genazzani et al., 2008). The two isomers play distinct physiological roles: MI predominates in tissues responsible for glucose uptake (skeletal muscle, adipose tissue), while DCI is enriched in tissues that regulate glycogen storage and ovarian steroidogenesis. The plasma MI:DCI ratio in healthy individuals is approximately 40:1, and disturbances of this ratio have been hypothesised to contribute to PCOS pathophysiology, with relative MI deficiency in skeletal muscle and relative DCI excess in the ovary (Fitz et al., 2024; Genazzani et al., 2008). Most clinical trials have used either myo-inositol 4 g/day alone or a combination at the physiological 40:1 MI:DCI ratio (Fitz et al., 2024; Genazzani et al., 2008). The 2024 systematic review and meta-analysis informing the international guideline included data from randomised controlled trials and reported modest improvements in metabolic indices and ovulation rates with inositol supplementation, but the certainty of evidence was rated low and dosing protocols varied considerably between studies (Fitz et al., 2024). The 2023 guideline notes that inositol "could be considered" in women with PCOS based on individual preferences and values, given its limited harm and potential modest improvement in metabolic measures, but acknowledges that clinical benefits — including for ovulation, hirsutism and weight — remain limited; specific types, doses and combinations cannot currently be recommended (Fitz et al., 2024; Teede et al., 2023). In direct comparison with metformin, the guideline favours metformin for hirsutism and central adiposity (Teede et al., 2023). Despite this cautious recommendation, inositol remains widely used in clinical practice — particularly in Europe — owing to its favourable safety profile and over-the-counter availability.

3.5.5. GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally developed for type 2 diabetes and subsequently for obesity, are now an important therapeutic option for women with PCOS and obesity (Hoteit et al., 2025). By enhancing glucose-dependent insulin secretion, slowing gastric emptying, reducing appetite via central pathways and decreasing hepatic glucose production, GLP-1 RAs achieve clinically meaningful weight loss together with improvements in insulin sensitivity, lipid profile and reproductive outcomes (Hoteit et al., 2025). The agents most commonly studied in PCOS are liraglutide (1.2–3.0 mg subcutaneously daily), semaglutide (0.5–2.4 mg subcutaneously weekly) and exenatide (5–10 μg subcutaneously twice daily) (Hoteit et al., 2025). Meta-analyses comparing GLP-1 RAs with metformin have consistently shown greater reductions in body mass index, waist circumference and HOMA-IR with GLP-1 RAs, alongside parallel improvements in the free androgen index, hirsutism scores and menstrual cyclicity (Hoteit et al., 2025). The 2023 international guideline now explicitly includes anti-obesity pharmacotherapy, including GLP-1 RAs, as a recognised adjunct

in selected women with PCOS and obesity (Teede et al., 2023). Practical considerations include cost, predominantly subcutaneous administration, gastrointestinal adverse effects (nausea, vomiting, constipation), and the need for effective contraception during use given limited safety data on early-pregnancy exposure; current guidance recommends discontinuation at least two months before attempting conception (Hoteit et al., 2025).

3.5.6. Bariatric surgery

Bariatric (metabolic) surgery is an effective management option for women with PCOS and severe obesity who have not achieved sufficient weight loss with non-surgical interventions. The most commonly performed procedures are laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy, both of which produce sustained weight loss of approximately 25–35% of baseline body weight together with substantial improvements in insulin sensitivity, free androgen index and menstrual cyclicity (Teede et al., 2023). The 2023 guideline supports consideration of bariatric surgery in women with PCOS and a body mass index of 35 kg/m² or higher in the presence of obesity-related comorbidities, or 40 kg/m² without comorbidities, in line with general indications for surgical management of obesity (Teede et al., 2023). Beyond weight loss alone, bariatric surgery produces neuro-hormonal changes — including increases in endogenous GLP-1, peptide YY and bile-acid signalling — that contribute to early metabolic improvement, often before substantial weight loss has occurred. In the perinatal context, an interval of 12–24 months between surgery and conception is generally recommended to allow weight stabilisation and adequate micronutrient repletion; long-term postoperative supplementation (vitamin B_{12}, iron, calcium, vitamin D, folate) is essential, particularly during pregnancy (Teede et al., 2023).

3.5.7. Adjunctive therapies for hyperandrogenism and ovulation

Although this review focuses on IR, integrated management of women with PCOS frequently requires concurrent treatment of hyperandrogenic features and anovulatory infertility. The therapies summarised below do not directly target IR but are core components of clinical care.

Combined oral contraceptives (COC). COCs are first-line therapy for hyperandrogenism (hirsutism, acne) and menstrual cycle regulation in women who do not currently desire pregnancy (Teede et al., 2023). By suppressing pituitary gonadotrophin release — and thereby ovarian androgen production — and by increasing hepatic SHBG synthesis, COCs reduce both total and free androgen levels. Preparations containing low-androgenic or anti-androgenic progestogens (e.g. drospirenone, dienogest, cyproterone acetate) are generally preferred (Teede et al., 2023). COCs do not improve IR and may have small adverse effects on insulin sensitivity and lipid profile, particularly in women with pre-existing metabolic dysfunction; cardiometabolic risk should therefore be reassessed periodically during long-term use (Teede et al., 2023).

Antiandrogens. Spironolactone (25–100 mg/day, a dose range that according to the 2023 guideline "appears to have lower risks of adverse effects" (Teede et al., 2023)) and, in countries where available, cyproterone acetate are added to COCs when hirsutism remains inadequately controlled after at least six months of monotherapy (Teede et al., 2023). Effective contraception is mandatory throughout antiandrogen therapy because of the risk of feminisation in a male fetus.

Ovulation induction. Letrozole, an aromatase inhibitor, is the recommended first-line agent for ovulation induction in women with PCOS who seek pregnancy. The pivotal PPCOS-II randomised trial demonstrated that letrozole produced significantly higher cumulative live-birth rates than clomiphene citrate (27.5% vs 19.1%; rate ratio 1.44, 95% CI 1.10–1.87) and higher cumulative ovulation rates (61.7% vs 48.3%, $p<0.001$) in 750 women with PCOS (Legro et al., 2014). These results are reflected in the 2023 international guideline, which positions letrozole (typically 2.5–7.5 mg/day for five days) as first-line and clomiphene citrate (50–150 mg/day for five days) as a second-line option (Legro et al., 2014; Teede et al., 2023). Metformin co-administration may improve ovulation rates particularly in women with obesity, while gonadotrophin-based stimulation or in vitro fertilisation are reserved for women in whom oral agents have failed (Teede et al., 2023).

3.5.8. Emerging therapies

Several therapeutic classes beyond GLP-1 RAs are being investigated for PCOS, motivated chiefly by the ongoing need for IR-targeting agents that combine metabolic and reproductive benefits. Dual GIP/GLP-1 receptor agonists — most notably tirzepatide — combine the actions of two incretin hormones and produce greater weight loss than GLP-1 RA monotherapy in trials of obesity and type 2 diabetes; however, PCOS-specific clinical data remain limited and inferences are largely extrapolated from non-PCOS obesity cohorts (Hoteit et al., 2025). Sodium-glucose co-transporter 2 (SGLT2) inhibitors improve insulin sensitivity and produce modest weight loss; small trials in women with PCOS have suggested favourable effects on body composition and HOMA-IR, but evidence remains preliminary and these agents are not yet incorporated into

PCOS-specific guidelines (Teede et al., 2023). Other approaches under investigation include selective androgen-receptor antagonists, kisspeptin/neurokinin pathway modulators and AMH-targeted therapies, all of which remain at early stages of clinical evaluation (Stener-Victorin et al., 2024).

Therapeutic approaches that directly target IR in PCOS are summarised in Table 3.

Table 3. Therapeutic approaches that directly target insulin resistance in PCOS.

Intervention	Mechanism of action	Clinical effect
Lifestyle modification (diet + exercise)	Caloric deficit; ↑ insulin-stimulated glucose uptake; mitochondrial improvements	5–10% weight loss → ↓IR, ↓FAI, restoration of ovulation (Moran et al., 2011; Stepto et al., 2019; Teede et al., 2023)
Metformin	↓ hepatic glucose production via AMPK; ↑ peripheral insulin sensitivity	↓ insulin and androgens; improved menstrual cyclicity (Palomba et al., 2009; Teede et al., 2018; Teede et al., 2023)
Inositol (myo + DCI 40:1)	Second messengers downstream of insulin receptor	Modest metabolic and ovulatory improvement; low certainty of evidence (Fitz et al., 2024; Genazzani et al., 2008; Teede et al., 2023)
GLP-1 receptor agonists	Glucose-dependent insulin secretion, ↓ appetite, weight loss	Greater BMI/HOMA-IR/FAI reduction than metformin in obese PCOS (Hoteit et al., 2025; Teede et al., 2023)
Bariatric surgery	Substantial weight loss + neuro-hormonal effects (↑ GLP-1, PYY)	~25–35% body weight loss; marked HOMA-IR reduction; restored ovulation (Teede et al., 2023)
Tirzepatide / dual GIP/GLP-1 (emerging)	Combined incretin signalling; greater weight loss than GLP-1 RA alone	Promising in obesity/T2DM trials; PCOS-specific data still limited (Hoteit et al., 2025)

3.6. Long-term complications and surveillance

PCOS is a lifelong condition: metabolic, cardiovascular and gynaecological risks persist and in some cases accelerate after the reproductive years (Stener-Victorin et al., 2024; Teede et al., 2023). The 2023 International Guideline therefore frames PCOS as a chronic disease that warrants structured, lifelong surveillance rather than episodic care, even in women whose reproductive symptoms have been managed (Teede et al., 2023).

For glucose homeostasis, the 2023 guideline recommends a 75-g oral glucose tolerance test (OGTT) at diagnosis as the most accurate test of glycaemic status, regardless of BMI, with reassessment every one to three years thereafter on the basis of individual risk factors (Teede et al., 2023). An OGTT should also be offered before pregnancy or fertility treatment, and again at 24–28 weeks gestation if not performed preconception (Teede et al., 2023). Long-term meta-analytic data place the relative risk of progression to type 2 diabetes mellitus in women with PCOS at approximately threefold that of the background population, with the absolute risk substantially modified by obesity and family history (Stener-Victorin et al., 2024; Teede et al., 2023).

For cardiovascular risk, the guideline recommends a baseline lipid profile at diagnosis in all women with PCOS regardless of age and BMI, with frequency of repeat testing determined by the presence of hyperlipidaemia and global cardiovascular risk; blood pressure should be measured at least annually and additionally before pregnancy or fertility treatment, given the elevated risk of hypertensive disorders of pregnancy (Teede et al., 2023). For endometrial protection, regular cycle regulation (with a combined oral contraceptive, cyclic progestogen or, where appropriate, a levonorgestrel-releasing intrauterine system) is the principal preventive strategy in women with prolonged anovulation, given the increased risk of endometrial hyperplasia and carcinoma associated with chronic unopposed oestrogen exposure (Ehrmann, 2005; Stener-Victorin et al., 2024; Teede et al., 2023). For mental health, screening for depression and anxiety is

recommended at diagnosis and at clinically relevant intervals thereafter, using regionally validated tools, with referral or treatment for those with moderate or severe symptoms (Teede et al., 2023). Together, these elements constitute a pragmatic surveillance framework that complements the IR-targeted treatments described in section 3.5.

4. Discussion

This narrative review confirms that IR is a core pathophysiological feature of PCOS and the main mechanistic link between the syndrome's reproductive and metabolic manifestations (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012; Stener-Victorin et al., 2024). Three updates compared with earlier reviews (Diamanti-Kandarakis & Dunaif, 2012; Teede et al., 2018) stand out: the introduction of AMH and revised ultrasound criteria in the 2023 guideline (Teede et al., 2023); the consolidation of evidence supporting pathway-selective insulin signalling defects as the molecular basis of metabolic IR with preserved ovarian steroidogenic responsiveness (Barber et al., 2015; Diamanti-Kandarakis & Dunaif, 2012); and the rise of GLP-1 RAs as a clinically relevant therapeutic class for women with PCOS and obesity (Hoteit et al., 2025).

PCOS is heterogeneous: not all women with the syndrome have IR, and not all women with IR have hyperandrogenism. Phenotype-based stratification — including the recognition of "lean PCOS" — is increasingly relevant to management (Stener-Victorin et al., 2024). In lean phenotypes, weight-loss-oriented interventions, including bariatric surgery and high-dose GLP-1 RAs, are not appropriate, and treatment should focus on hormonal and ovulatory support rather than on weight reduction (Hoteit et al., 2025; Stener-Victorin et al., 2024). Body composition assessment, rather than BMI alone, may better identify the women most likely to benefit from insulin-sensitising therapy (Stener-Victorin et al., 2024; Teede et al., 2023).

The therapeutic landscape has expanded beyond metformin and combined oral contraceptives. Inositol formulations remain widely used, particularly in Europe, but the 2023 meta-analysis informing the international guideline rated the evidence as low certainty and highlighted heterogeneity in dosing and outcome reporting (Fitz et al., 2024). By contrast, GLP-1 RAs are supported by stronger randomised data showing superiority over metformin for weight loss and improvements in HOMA-IR and the free androgen index (Hoteit et al., 2025). Their integration into PCOS management — together with lifestyle, metformin and, where indicated, combined oral contraceptives — is a meaningful clinical advance (Hoteit et al., 2025; Teede et al., 2023).

In practice, treatment choice in PCOS depends on three factors beyond IR itself: the woman's reproductive goals, her phenotype according to the Rotterdam stratification (section 3.1.1), and her BMI category. Lifestyle modification is the foundation across all categories (Moran et al., 2011; Teede et al., 2023). For hyperandrogenic phenotypes (A, B and C) with overweight or obesity, metformin and — in those not currently pursuing pregnancy — GLP-1 receptor agonists offer mutually compatible insulin-sensitising and weight-reducing benefits (Hoteit et al., 2025; Teede et al., 2023). In lean hyperandrogenic phenotypes, the rationale for weight-loss-oriented therapy is weaker and the focus shifts to metformin, inositol, combined oral contraceptives and antiandrogens for symptom control (Stener-Victorin et al., 2024; Teede et al., 2023). Phenotype D, with its milder metabolic profile (Stener-Victorin et al., 2024; Teede et al., 2023), may not require pharmacological IR targeting if no independent metabolic indications are present, although surveillance for emerging metabolic features is still warranted given the lifelong nature of PCOS (Teede et al., 2023). For women actively pursuing pregnancy, letrozole-based ovulation induction takes precedence, and metformin co-administration may improve ovulation rates particularly in those with obesity (Legro et al., 2014; Teede et al., 2023).

Adolescent presentation of PCOS calls for a different management approach. The 2023 guideline emphasises caution in adolescent diagnosis — neither ultrasound nor AMH is used in this age group — and stresses the importance of preventing weight gain rather than focusing on weight loss at this life stage (Teede et al., 2023). Lifestyle modification, combined oral contraceptives (where contraception is also desired or cycle regulation is needed) and metformin (with a lower maximum daily dose of 2 g) form the core therapeutic options; antiandrogens are deferred until response to first-line management has been assessed (Teede et al., 2023). Inositol and GLP-1 receptor agonists have very limited evidence in adolescents, and current guidelines do not recommend their routine use in this age group (Teede et al., 2023). Earlier identification of girls at risk — those with persistent post-menarcheal cycle irregularity, clinical hyperandrogenism or significant adolescent weight gain — might change the long-term trajectory of metabolic disease, although prospective evidence to support this is still limited (Stener-Victorin et al., 2024; Teede et al., 2023).

4.1. Limitations of this review

This is a narrative review, not a systematic one, and is therefore open to selection bias. No formal risk-of-bias assessment, PRISMA flow diagram or quantitative synthesis was performed. The literature on PCOS is extensive and rapidly evolving; some relevant primary studies and emerging therapies (e.g. dual GIP/GLP-1 agonists such as tirzepatide) may not have been fully captured. The evidence base for several interventions, particularly inositol, is heterogeneous and of low certainty (Fitz et al., 2024). Cited prevalence figures and treatment effect estimates are summarised from contemporary guidelines and consensus reviews (Hoteit et al., 2025; Stener-Victorin et al., 2024; Teede et al., 2023), and individual estimates may vary by population, diagnostic criteria and study design. The treatment framework discussed above reflects the author's synthesis of guideline recommendations and individual treatment decisions should be made through shared decision-making with each woman and her clinical team (Teede et al., 2023).

4.2. Future directions

Several priorities remain. Standardised definitions of IR in PCOS — including consistent use of HOMA-IR thresholds, OGTT-based indices and direct measures such as the hyperinsulinaemic-euglycaemic clamp — would improve comparability across studies (Barber et al., 2015; Teede et al., 2023). Equally, large randomised trials should explicitly stratify enrolment by Rotterdam phenotype rather than treating PCOS as a single entity, and should incorporate reproductive outcomes (ovulation, pregnancy, live birth) as primary endpoints alongside metabolic endpoints (Hoteit et al., 2025; Stener-Victorin et al., 2024). Prospective long-term safety data on GLP-1 RAs in the periconceptional window are also needed, given the increasing use of these agents in women of reproductive age (Hoteit et al., 2025). The evidence base in adolescents — currently very limited for both metformin extended use and for inositol — requires dedicated trials with developmentally appropriate endpoints (Teede et al., 2023). Mechanistic work on phenotype-specific signalling defects and on the role of adipose tissue, gut microbiome and AMH in early life (Stener-Victorin et al., 2024) may permit precision-medicine approaches in the future. Finally, early identification of IR — particularly in adolescents and lean women with PCOS — could reduce the long-term cardiometabolic burden of the syndrome (Stener-Victorin et al., 2024; Teede et al., 2023). Beyond the mechanistic agenda, the 2026 renaming of PCOS to PMOS reflects the recognition of this condition as a complex multisystem endocrine and metabolic disorder, not a primarily gynaecological one. Future research and clinical guidelines will increasingly adopt the PMOS terminology over the announced three-year transition period.

5. Conclusion

Insulin resistance is a central feature of PCOS and the main link between its reproductive and metabolic manifestations. Compensatory hyperinsulinaemia drives ovarian androgen excess and SHBG suppression, while a pathway-selective signalling defect explains the coexistence of peripheral metabolic IR with preserved insulin-driven ovarian steroidogenesis. The 2023 International Evidence-based Guideline provides an updated framework for diagnosis and management, including the use of AMH as a diagnostic option and a tiered approach to pharmacotherapy. Lifestyle modification is the foundation of treatment; metformin remains a key option; inositol may offer modest additional benefit but with low-certainty evidence; GLP-1 receptor agonists are now an important option in women with PCOS and obesity. Early recognition of insulin resistance and individualised, phenotype-aware management are essential to improve both short-term symptoms and long-term cardiometabolic outcomes.

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