



**Metabolic Syndrome and Cardiovascular Risk in Women With
Polycystic Ovary Syndrome: An Integrative Review of Mechanisms,
Clinical Evidence, Real-World Data and Precision Prevention**

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder with consequences extending beyond ovulatory function and androgen excess. Metabolic syndrome, impaired glucose tolerance, type 2 diabetes, dyslipidemia, hypertension, and cardiovascular morbidity are important dimensions of long-term care. Objective: To critically integrate evidence linking PCOS to metabolic syndrome and cardiovascular risk, distinguish established associations from unresolved causal pathways, and assess opportunities for real-world evidence and artificial intelligence in prevention. Methods: This integrative narrative synthesis prioritizes the 2023 international evidence-based PCOS guideline, indexed systematic reviews and meta-analyses, and regulatory documents covering real-world evidence and responsible AI. No primary database search log, pooled effect estimate, or new trial analysis is claimed. Results: The international guideline recommends assessment of cardiometabolic risk in all women with PCOS, a lipid profile at diagnosis irrespective of body mass index, yearly blood pressure review reported increased composite cardiovascular events (odds ratio 1.68; 95% confidence interval 1.26–2.23) across 20 studies; between-study heterogeneity and residual confounding limit causal interpretation. Insulin resistance, visceral adiposity, androgen excess, sleep-disordered breathing, and psychosocial determinants create interacting but non-identical risk pathways. Metformin and weight-management strategies can improve intermediate metabolic endpoints, whereas definitive proof that any PCOS-specific treatment prevents myocardial infarction or stroke remains insufficient. Electronic health records and longitudinal registries could evaluate long-term effectiveness but demand rigorous confounding control and outcome validation. Conclusions: PCOS care should integrate reproductive goals with systematic, age-sensitive



cardiometabolic prevention. Research should use standardized phenotypes, prespecified causal questions, transparent prognostic validation and context-specific implementation. Cardiovascular risk signals must not be misconstrued as deterministic predictions for individual young women.

Keywords: polycystic ovary syndrome; metabolic syndrome; cardiovascular disease; insulin resistance; hyperandrogenism; dyslipidemia; glucose tolerance; type 2 diabetes; obesity; real-world evidence; artificial intelligence; preventive cardiology; clinical epidemiology.

1. INTRODUCTION

Clinical rationale

PCOS often enters medical care through menstrual disturbance, acne, hirsutism, or infertility. Yet the endocrine diagnosis can also flag longitudinal cardiometabolic vulnerability, creating a mismatch between the reason for consultation and conditions most consequential decades later. The clinician must avoid two symmetrical errors: overlooking diabetes and vascular risk because the patient is young, or telling every patient that a cardiovascular event is inevitable. Risk estimation demands baseline context, life-course assessment, and careful communication. [1,2]

Disease heterogeneity

PCOS is not one metabolic state. Different combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology produce phenotypes with variable adiposity, biochemical patterns and risk burden. Adolescents require additional diagnostic caution because normal pubertal physiology can mimic adult features. Comparing studies that use different definitions can manufacture between-study disagreement without any true biological contradiction. This diagnostic heterogeneity is relevant to transportability of risk models and interpretation of pooled cardiovascular associations. [1,2]

Metabolic syndrome versus individual components

Metabolic syndrome is an operational clustering of abdominal adiposity, blood-pressure elevation, dyslipidemia and abnormal glucose regulation. It is a useful clinical prompt, not a single molecular disease and not a substitute for identifying each modifiable component. Definitions and ethnicity-sensitive waist criteria vary across



studies. A patient who falls just below a component threshold can still have substantial risk, whereas a nominal syndrome label may conceal the magnitude of individual exposures. The article therefore examines categorical metabolic syndrome and continuous risk variables separately.

Real-world data and evidence

Real-world data (RWD) are routinely collected observations on patient health and care delivery, including electronic records, claims, registries and digital health technologies. Real-world evidence (RWE) is clinical evidence generated by analyzing such data with a defensible design and analysis. A database extract is not automatically evidence: the target population, exposure definition, validity of diagnosis codes, follow-up and missingness determine whether an analysis answers a meaningful question. FDA emphasizes fit-for-purpose RWD for regulatory evaluation; EMA uses regulator-led studies and DARWIN EU to complement trials. [5,6,7]

RCT efficacy versus practice effectiveness

Randomized controlled trials estimate treatment effects under explicit eligibility, allocation and follow-up rules, often measuring short-term metabolic surrogate outcomes. Routine-care cohorts can reveal adherence, discontinuation, switching, multimorbidity, access barriers and rare safety events. Efficacy refers to benefit in the trial-defined setting; effectiveness describes benefit in ordinary clinical conditions. They are related but not interchangeable, particularly when lifestyle support, pregnancy plans and medication persistence differ. Robust causal RWE should try to emulate a hypothetical target trial rather than compare loosely defined treated and untreated groups. [5,6]

AI and the risk of premature clinical adoption

Artificial intelligence (AI) may help assemble risk variables, identify unrecorded metabolic problems and predict downstream events. However, accurate prediction in a development dataset does not prove a change in clinical outcomes or clinical fairness. Models trained mostly on older patients with diabetes may misclassify younger women with PCOS. WHO guidance places transparency, human oversight, data governance and accountability at the centre of health-related AI. [8,9]



2. MATERIALS AND METHODS

Design. This is a critical integrative narrative review, not a PRISMA systematic review or a patient-level observational study. The authorship draft synthesized verifiable, explicitly identified high-priority guidelines, selected indexed meta-analyses and international policy documents. A reproducible database-by-database search history and exhaustive screening log were not available; no claim of having directly searched subscription Scopus, Web of Science or Embase is made. The evidence base is therefore purposive rather than exhaustive. Evidence cited in support of numerical estimates is linked to specific published reports. [1–9]

Eligibility and evidence hierarchy. Priority was placed on PCOS-specific international guidance; longitudinal studies reporting clinically defined diabetes or cardiovascular events; systematic reviews with extractable denominators and uncertainty intervals; and WHO, FDA, EMA policy documents. Publications discussing only surrogate cardiovascular outcomes were interpreted separately from adjudicated myocardial infarction, stroke or mortality. Studies involving non-PCOS diabetes or cancer were considered only as transportability comparisons, not as direct estimates of efficacy in PCOS. English-language evidence from 2020–2026 was emphasized while older foundational methods were included when indispensable.

Synthesis strategy. Clinical guidance is described as recommendation rather than newly observed effect; meta-analytic estimates are reproduced with their confidence intervals and design limitations; mechanistic pathways are described as biological plausibility rather than causal proof. No patient dataset was accessed, propensity score computed, Cox model fitted, Kaplan–Meier curve generated or AI model trained. The statistical methods below are a protocol for a future registry-based study, not completed analyses.

[Propensity-score matching and inverse probability weighting](#)

For a new-user active-comparator cohort, define baseline covariates before treatment initiation: age, PCOS phenotype, BMI, glycemic status, blood pressure, lipid variables, fertility intention, smoking, care setting and prior treatment. A propensity score models treatment probability conditional on measured covariates. Matching seeks comparable treatment groups; inverse probability weighting constructs a pseudopopulation in which treatment assignment is independent of measured



baseline variables. Evaluate overlap and standardized mean differences, trim extreme weights only with prespecification, and acknowledge unmeasured confounding.

[Cox regression, Kaplan–Meier and survival analysis](#)

Time-to-event research should specify time zero, incident event definitions, competing events, censoring and outcome ascertainment. Kaplan–Meier estimates an observed event-free survival function under independent censoring; it is not an adjusted causal effect. Cox proportional hazards regression models instantaneous hazards conditional on covariates and requires proportional-hazards checks. Cause-specific or competing-risk methods may be appropriate for cardiovascular death and noncardiovascular death, whereas restricted mean survival time can be more interpretable when hazards are nonproportional.

[Target trial emulation and causal inference](#)

Specify eligibility, strategies, assignment time, outcomes, follow-up, estimand and analysis before extracting observational comparisons. For metformin initiation versus a clinically plausible alternative, align drug initiation and entry to avoid immortal-time bias. Consider cloning, censoring and weighting for sustained-treatment strategies, and distinguish treatment-policy from per-protocol effects. Use directed acyclic graphs to map confounders and colliders, then conduct negative-control and quantitative bias analyses. Causal identification depends on exchangeability, consistency, positivity and correct measurement.

[Machine learning and deep learning](#)

Supervised learning may combine laboratory trends, medication trajectories and longitudinal anthropometry, but should be evaluated against simpler clinical scores. Nested tuning, grouped patient-level partitioning, temporal external validation, calibration intercept/slope, Brier score and decision-curve analysis are more useful than discrimination alone. Deep temporal models are data-hungry and vulnerable to care-process artifacts. SHAP or attribution plots can describe model behavior, not establish biological causation.

[Natural language processing and language models](#)

Clinical text may encode smoking status, menstrual symptoms, fertility goals, prior pregnancies and adverse-event narratives missing from structured fields. Natural language processing pipelines require manual error audits, temporal anchoring,

negation recognition and language-specific validation. Large language models may assist extraction or evidence navigation but can hallucinate diagnoses, citations and treatment advice; human adjudication remains mandatory.

Reinforcement learning and adaptive policies

Reinforcement learning optimizes sequential decisions using a specified reward and environment. For cardiometabolic prevention its reward must account for long horizons, adverse effects, equity and competing reproductive priorities; off-policy evaluation from routine data is vulnerable to confounding. It is a research method, not currently established standard-of-care for PCOS treatment selection.

3. RESULTS: INTEGRATED EVIDENCE

The following results summarize previously published evidence and clinically relevant methodological implications; they are not newly generated experimental or observational results.

3.1 Cardiovascular outcomes and evidence strength

A guideline-informing systematic review and meta-analysis of 20 studies involving approximately 1.06 million women reported an association between PCOS and composite clinical cardiovascular disease (OR 1.68, 95% CI 1.26–2.23), myocardial infarction (OR 2.50, 95% CI 1.43–4.38), and stroke (OR 1.71, 95% CI 1.20–2.44). Heterogeneity was substantial for several outcomes, and confidence bounds for cardiovascular mortality included no effect. These numbers characterize pooled observational associations and must not be relabeled as causal effects. [3]

A separate 2024 meta-analysis estimated an overall CVD relative risk of 1.51 (95% CI 1.36–1.69). The difference between a pooled risk ratio and an odds ratio is not just mathematical; populations, age and follow-up definitions differ. Absolute event probability can remain low in premenopausal women despite elevated relative risk. Such findings support prevention and surveillance but do not justify routine cardiac imaging in asymptomatic low-risk individuals. [4]

3.2 Insulin resistance and beta-cell dysfunction

Insulin resistance is a central PCOS mechanism but is neither necessary nor sufficient for the diagnosis. Compensatory hyperinsulinemia may amplify ovarian androgen production and alter hepatic sex-hormone binding globulin, while adipose tissue dysfunction and chronic low-grade inflammation interact with metabolic signaling.



The resultant physiology is bidirectional: excess androgen action may itself worsen visceral adiposity and metabolic flexibility. A simplistic linear chain from obesity to PCOS to diabetes obscures women who develop metabolic complications at lower BMI. [1,2]

The 2023 guideline recommends glycemic assessment at diagnosis, reassessment every one to three years according to risk, and the 75-g oral glucose tolerance test as the most accurate method for evaluating glycemic status in PCOS irrespective of BMI. Routine commercially available insulin assays are not recommended for routine clinical assessment because measurement and clinical interpretation are insufficiently reliable. Screening relies on glucose-based outcomes rather than diagnosing insulin resistance from a single fasting insulin result. [1,2]

3.3 Dyslipidemia and vascular phenotype

Atherogenic lipid patterns can include raised triglycerides, reduced HDL cholesterol and altered LDL particle characteristics, but these patterns are not uniform across phenotypes. Diet, exercise, adiposity, thyroid status, family history and medication exposures must be evaluated before assigning lipid abnormalities to PCOS itself. Focusing only on total cholesterol may conceal risk-relevant non-HDL and triglyceride changes. The international guideline requests a full lipid profile at diagnosis regardless of BMI or age. [1,2]

An isolated lipid abnormality in a young adult does not automatically imply statin treatment. Therapeutic decisions require current general cardiovascular-prevention criteria, pregnancy potential, shared decision-making and avoidance of unnecessary extrapolation from older high-risk trial populations. Long-term registries should report drug indication and baseline absolute risk, not simply classify users versus nonusers.

3.4 Blood pressure, endothelial function and autonomic pathways

Blood-pressure elevation in PCOS may involve adipose distribution, renin–angiotensin system activity, sympathetic activation, insulin-related sodium handling and sleep apnea. Mechanistic plausibility does not determine which pathway dominates in a given patient. Hypertension should be confirmed with appropriate repeated measurements, and cardiovascular risk reduction should address established risk factors rather than biomarkers with uncertain clinical thresholds. The PCOS guideline

recommends annual blood-pressure measurement and assessment when planning pregnancy. [1,2]

Vascular surrogates such as pulse-wave velocity, carotid intima-media thickness and flow-mediated dilation help explore early pathophysiology. Nevertheless, improvements in these surrogate indices must not be presented as proof of fewer future myocardial infarctions. Device protocols, operator effects and age adjustment influence comparisons between case and control groups.

3.5 Obesity, visceral adiposity and metabolic syndrome classification

BMI has operational value but does not distinguish subcutaneous and visceral adiposity or capture adiposity-related insulin resistance in all ethnic groups. Waist circumference and longitudinal weight patterns add information. Metabolic syndrome prevalence is highly sensitive to component thresholds and sampling location; a fertility-clinic cohort will differ from a community cohort because care-seeking can select on obesity, reproductive symptoms and socioeconomic access. The appropriate denominator must accompany any reported prevalence.

The most informative intervention endpoints combine symptoms and patient priorities with anthropometry, blood pressure, glycemic tests and lipids. An endpoint such as change in waist circumference should not displace meaningful indicators of quality of life, treatment tolerability and eventual cardiovascular outcomes. Multiple risk determinants may improve without a patient crossing a categorical metabolic-syndrome threshold.

3.6 Sleep apnea, mental health and life-course risk

Obstructive sleep apnea is recognized at higher frequency in women with PCOS independently of BMI; guideline-informed symptom assessment includes snoring with nonrestorative sleep, fatigue and daytime sleepiness. Sleep disorders can reinforce glucose dysregulation and impair self-management. Mood symptoms, weight stigma and economic barriers also influence appointment attendance and medication persistence, creating prognostic differences that may be invisible in conventional laboratory datasets. [1,2]

Risk communication should treat mental health and sleep as intertwined components of whole-person care rather than blaming the patient for metabolic abnormalities.



Patient-reported outcomes and repeated symptom assessments in registries would help distinguish biologic treatment failure from lack of tolerable, sustained care.

3.7 Real-world data sources in PCOS prevention

Electronic health records contain diagnoses, anthropometry, clinician assessments and blood pressure; electronic prescribing systems document medications ordered rather than necessarily dispensed or consumed. Laboratory information systems provide OGTT, HbA1c and lipid trajectories. National registries may link pregnancy, diabetes and vascular events, whereas pharmacovigilance databases contain spontaneously reported adverse reactions. Insurance claims reveal reimbursed utilization but not all out-of-pocket care; wearables describe activity and sleep, and mobile apps may capture menstruation, diet or patient experience. [5,6]

Data linkage permits longitudinal follow-up but introduces governance, pseudonymization and interoperability challenges. Each source has characteristic bias: coded PCOS diagnoses have imperfect validity; missing OGTT may reflect selective testing; wearable users are not representative of all patients; and spontaneous adverse-event reports cannot yield straightforward incidence rates. A useful RWE platform must quantify these limitations before presenting associations.

3.8 Machine learning, deep learning and prediction

Machine learning may predict progression from normoglycemia to impaired glucose regulation using age, phenotype, baseline body size and metabolic trajectories. Deep learning can analyze complex longitudinal sequences and imaging inputs, although modeling sophistication cannot compensate for incomplete or biased labels. NLP can identify clinical histories from narrative notes. Large language models are suitable for supervised literature triage or text extraction but not autonomous cardiovascular decisions. Reinforcement learning remains an experimental approach for sequential prevention policies.

Model evaluation should report sensitivity, calibration, subgroup performance, clinical net benefit and workflow impact. A model that identifies many high-risk women but recommends testing already mandated by guidelines may add little value. External validation across geography, diagnostic phenotype, age and access to care is essential before deployment.



3.9 Metformin and metabolic treatment effectiveness

Metformin can be considered for anthropometric and metabolic outcomes in adults with PCOS, particularly when BMI is at least 25 kg/m², according to the 2023 guideline. Its rationale rests on metabolic outcomes rather than definitive proof of prevention of cardiovascular events in PCOS. Gastrointestinal intolerance, adherence and vitamin B12 risk influence real-world effectiveness. The comparison between metformin and combined oral contraceptives depends on whether the desired outcome is metabolic improvement or menstrual/hirsutism management. [1,2]

A rigorous effectiveness study would compare initiators under clearly specified indications and pregnancy intentions. Crude analyses risk confounding by indication because people with worse glycemic measures are more likely to receive metformin. Changes in OGTT, glycemic classification and patient-reported tolerability are closer to the evidence base than inferring unmeasured long-term stroke reduction.

3.10 Anti-obesity agents, GLP-1 therapies and individualized care

Guidance permits consideration of approved anti-obesity medications, including GLP-1 receptor agonists under general population indications alongside lifestyle intervention. Their ability to improve weight-related outcomes does not establish PCOS-specific cardiovascular event reduction. Pregnancy possibility and the need for effective contraception are critical, and patients should understand the limits of pregnancy safety data and potential weight regain when treatment stops. [1,2]

Future pragmatic comparisons should track dose escalation, discontinuation, pregnancy planning, gastrointestinal effects and affordability. Cardiometabolic gains achieved in narrow trials may be attenuated when access or persistence is limited. Reporting treatment exposure as a binary ever-used variable can create major bias.

3.11 Oral contraceptives, antiandrogens and reproductive tradeoffs

Combined hormonal contraceptives address cycle symptoms and androgen-related features but are not intended as cardiovascular prevention drugs. Decisions depend on smoking, personal thromboembolic risk, migraine characteristics, blood pressure and contraindications. Antiandrogen therapy requires pregnancy prevention and adverse-effect counseling. The correct therapeutic strategy depends on whether the immediate priority is menstrual symptom control, metabolic health or conception. [1,2]



Comparative studies must avoid assigning benefits or harms to PCOS-specific pathology when treatment selection tracks age, contraception preference or underlying cardiovascular risk. Physician choices are themselves part of the causal system, which explains why prescribing records should be linked to clinical indication.

3.12 Pharmacovigilance and adverse reaction surveillance

Adverse drug reactions (ADRs) in long-term PCOS management include gastrointestinal effects from metformin or GLP-1 agents, potential vitamin B12 deficiency during long-term metformin use, and safety considerations surrounding hormonal agents. Drug-safety signal detection uses disproportionality measures, temporal patterns and clinical review, but spontaneous-report databases lack reliable exposed-person denominators. The presence of a signal does not establish causality.

A PCOS-specific pharmacovigilance analytics program should include pregnancy exposure, formulation, dose, discontinuation, co-prescribing and event validation. Comparisons across reporting periods require caution because media attention and new drug launches alter reporting probability. Embedding medication safety within routine follow-up is more actionable than relying on an isolated automated flag.

3.13 Pharmacogenomics, phenotyping and precision medicine

Precision medicine aims to tailor risk evaluation to metabolic status, age, phenotype, family history, reproductive goals and treatment preference. Investigational pharmacogenomic markers may eventually inform drug response, but routine genetic selection of metformin or other PCOS therapies is not established practice. Biomarkers associated with insulin resistance or androgen excess should not be declared treatment-predictive without prospective interaction testing and external replication.

Practical personalization already exists without genomic panels: metabolic assessment and lifestyle counseling can be tailored to measured glucose, lipid and blood-pressure status. Research must distinguish prognostic markers predicting risk regardless of treatment from predictive markers identifying genuine differential treatment benefit.

3.14 Applicability of predictions from other diseases

Lessons from type 2 diabetes, cardiovascular medicine, oncology, infectious disease and neurology can inform time-series methods, drug-safety surveillance and



calibration, but effects estimated in these conditions do not automatically transport to PCOS. Baseline risk, competing outcomes, age distributions, pregnancy intentions and clinical interventions differ. A model predicting adverse cardiovascular events among older adults with established diabetes may appear discriminative while providing misleading absolute probabilities to women with PCOS.

Transportability analysis should examine effect modifiers and recalibrate baseline hazards when populations differ. In PCOS, risk prediction must also consider delayed diagnosis, phenotype drift and changes across pregnancy or menopause. Cross-disease AI is best treated as a methodological inspiration rather than direct clinical validation.

3.15 Uzbekistan: digital cardiometabolic pathway for women with PCOS

A potential Uzbekistan PCOS program could link gynecology, primary care, endocrinology, cardiology and laboratory services around a standardized encounter template. Core fields would include phenotype, waist/BMI, blood pressure, OGTT, lipid results, smoking, sleep symptoms, medications, fertility intentions and longitudinal outcomes. Electronic prescriptions and clinical registries may support medication reconciliation and follow-up where legally and technically implemented. No nationwide PCOS registry, comprehensive electronic prescription coverage or specific implementation outcome is assumed here without independent verification.

An incremental pilot should begin with anonymized data dictionaries, interoperable diagnostic coding, explicit consent or lawful processing grounds, audit trails, outcome validation, clinician education and patient involvement. Clinical pharmacology teams could assess treatment-related risk while digital-health teams assess completeness and representativeness. AI deployment should follow, not precede, evidence of acceptable data quality, external validation and an appealable human decision process.

3.16 Evidence integration and limitations

The clinical guideline and recent pooled observational evidence converge on a need for early cardiometabolic risk assessment. They do not, however, demonstrate that a specific medicine prevents major cardiovascular events in women with PCOS. Differences in PCOS definitions, ethnicity, age, confounder control and outcome

adjudication prevent a single universal risk multiplier from being used for bedside prediction. [1–4]

This review is deliberately critical rather than exhaustively systematic; it has no study-flow diagram, registered protocol or original pooled estimate. Its summary tables organize verified guidance and identified systematic evidence but cannot replace a full independently reproducible systematic review. Research conclusions are bounded by available data quality and exposure definitions.

Table 1. Selected quantitative clinical evidence

Source	Study / population	Reported association	Interpretation
Guideline-informing review (2024) [3]	20 studies; about 1.06 million women	Composite CVD OR 1.68 (95% CI 1.26–2.23)	Observational; heterogeneity and confounding
Same review [3]	Meta-analysis of clinical events	Myocardial infarction OR 2.50 (1.43–4.38); stroke OR 1.71 (1.20–2.44)	Not individual absolute risk
CVD burden synthesis (2024) [4]	17 articles	Overall pooled RR 1.51 (1.36–1.69)	Different design and estimand
2023 international guideline [1]	Evidence-based consensus	Annual BP; lipid testing at diagnosis; repeat glycemic testing every 1–3 years	Recommendations, not treatment-effect estimates

Table 2. Evidence-informed clinical risk assessment

Domain	Baseline approach	Interpretation / follow-up
Blood pressure	Measure at diagnosis and annually	Confirm hypertension and manage by usual criteria



Lipids

Full lipid profile at diagnosis regardless of BMI
Frequency depends on dyslipidemia and total risk

Glycemia

75-g OGTT preferred

Repeat at 1–3 years according to risk

Adiposity

BMI, waist circumference, longitudinal trajectory

Avoid substituting BMI for individualized risk

Sleep and well-being

Screen for OSA symptoms, distress and access barriers

Refer or investigate as clinically indicated

4. DISCUSSION

Clinical interpretation and causal caution

The most reproducible message is that PCOS creates a clinically meaningful opportunity for preventive assessment, not an automatic diagnosis of future heart disease. Differences between younger and older cohorts, limited events at younger ages and imperfect phenotype capture complicate causal interpretation. A guideline recommendation can be justified by convergent harms and feasibility even when an intervention-specific cardiovascular endpoint trial is absent. [1–4]

Selection bias and confounding

Patients attending specialty reproductive clinics may be enriched for infertility, obesity or higher socioeconomic access. Adjusting for measured BMI does not necessarily control lifetime adiposity, and conditioning on a care-seeking variable can open collider bias. Registry analyses require a prespecified causal graph, valid index date, robust comparator and quantitative sensitivity analyses. Inappropriate adjustment for a mediator such as post-treatment weight may obscure a genuine total effect.

Data quality and missingness

Missing OGTT is often informative: clinicians preferentially test patients perceived as higher risk. Complete-case analysis can systematically distort both prevalence and model performance. Multiple imputation assumes a defensible missingness mechanism and must preserve longitudinal structure. EHR migration, incompatible

laboratory units and inconsistent PCOS coding also require provenance checks. Apparent precision from large sample size cannot compensate for systematic bias.

Explainable, ethical and regulatory AI

Explainable AI can support clinician review with feature summaries, calibration plots, uncertainty communication and subgroup audits, but explanation tools do not eliminate model leakage or erroneous labels. WHO emphasizes ethics, governance and oversight, including more recent concerns about equity and research review. FDA has published RWE frameworks and AI-related regulatory pathways; EMA coordinates DARWIN EU for regulator-led RWE generation. These are cross-cutting governance models, not approvals of any PCOS-specific AI prediction product. [5–9]

Clinical decision support

A useful clinical decision-support system should remind clinicians of evidence-based BP, lipid and glycemic assessment rather than replace judgement. It should log why recommendations were made, allow clinicians to override them, and monitor missed disease, unnecessary testing and patient burden. Implementation evaluation should test whether reminders improve completion and timely management without amplifying disparities across rural clinics, languages or digital access levels.

Research agenda and global trends

A prospective multi-center registry with standardized PCOS phenotypes, reliable medication exposures and validated diabetes/CVD endpoints would support meaningful RWE. A nested pragmatic trial could assess reminder systems or follow-up strategies. For drug comparisons, target-trial emulation should define strategies and harms in advance. International networks are increasingly linking data sources under federated governance, but local clinical definitions, privacy regulation and community trust remain essential for generalizability.

5. CONCLUSION

Women with PCOS require integrated reproductive and cardiometabolic care. International guidance supports assessment of lipids at diagnosis, annual blood-pressure measurement and risk-based glycemic reassessment; the 75-g OGTT is the preferred glycemic test. Pooled cohort studies indicate increased clinical cardiovascular event risk, but association should not be mistaken for deterministic individual prognosis or proof of a particular drug's cardiovascular protection. Lifestyle



and indicated metabolic treatments should be evaluated using outcomes relevant to each patient. Reliable PCOS registries, causal RWE and externally validated, ethically governed decision support offer a route toward more equitable prevention. [1–9]

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Reference transparency: The list contains 12 traceable source records, including two journal presentations and a guideline resource addressing the same international PCOS guideline. It does NOT meet the requested threshold of 30–50 independent references. Bibliographic items without verified complete metadata are identified by PMID or source URL rather than inventing author strings or DOI values.