

Ovary Targeted Drug Delivery for Treatment of Polycystic Ovary Syndrome: Current Advances and Future Perspectives - Review

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Abstract: Polycystic Ovary Syndrome (PCOS) is a complex heterogeneous endocrine and metabolic disorder that presents with hyperandrogenism, ovulatory dysfunction, insulin resistance, oxidative stress, chronic inflammation and 8-13 % of women with reproductive and metabolic disorders and is the most common cause of infertility. Treatment options currently available are primarily lifestyle modifications and conventional systemic therapies for individual clinical manifestations like hormonal control, metabolic regulation, androgen-related symptoms and restoring fertility. Conventional drug delivery methods have the limitations of non-specific systemic distribution, variable bioavailability, adverse effects, repeated dose administration and lesser drug accumulation at the ovarian site, thus giving an incentive for required strategies.

Ovary-targeted approaches seeking to localize, deliver and achieve therapeutic benefit within the ovarian tissue with minimal systemic impact are emerging. An array of receptor-mediated, ligand-assisted, molecular recognition, stimuli-responsive and biomaterial-based delivery systems and site-specific approaches provide exciting avenues to mitigate the constraints of conventional therapy. Local delivery approaches may even theoretically afford escalated regional drug delivery, despite the challenges of physiologic barriers, delivery specificity and formulation hurdles. Herein, we trace the development of PCOS management from traditional delivery modalities to the advent of ovary-targeted delivery, appraising the therapeutic modalities, recent advances, potential benefits, safety and limitations, and the future of ovary-specific delivery for PCOS.

Keywords: Polycystic ovary syndrome; Ovary; Ovarian disease; Ovary targeted drug delivery; Ovarian targeted drug delivery; Site-specific drug delivery; Precision medicine.

I. INTRODUCTION

Polycystic ovary syndrome (PCOS), which affects a substantial proportion of women of reproductive age population globally, with estimated prevalence varying between 6-20% in the recent systematic review depending on criteria used to define PCOS [1], is the most common women's health disorder. PCOS is a set of clinical and metabolic features defining the syndrome, according to the definition proposed in the Rotterdam criteria, whereby one or more clinical signs of hyperandrogenism (including hirsutism, and/or acnes that relates to androgen excess in women), Increased serum androgen concentrations, Ultrasound feature of multiple (10 or more) cysts larger than 2 mm in their long axis in at least one ovary and ovarian volume (OV) over 10 mL, occur alone or in combination, after the exclusion of all other known syndromes that lead to hyperandrogenism [2]. Polycystic ovary syndrome, has been recently indicated not solely as a reproductive disorder, but also as a systemic disorder, in which many women have hyperinsulinaemic insulin resistance which predisposes to T2DM, CVD and other metabolic disorders through a woman's lifespan [3].



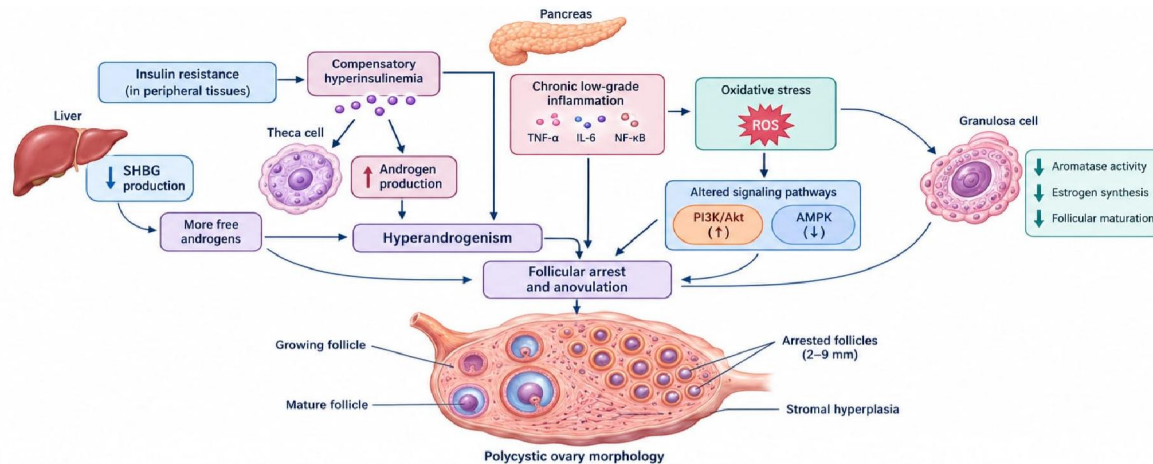


Figure: Schematic representation showing the possible effects of increased levels of circulating insulin levels and insulin resistance in women suffering from PCOS.

Mechanisms in PCOS are better understood as a vicious circle rather than a single causative defect. Disordered gonadotrophin releasing hormone pulsatility increases the ratio of luteinising hormone to follicle-stimulating hormone and promotes excess theca-cell androgen production; in parallel, hyperinsulinaemia works synergistically with luteinising hormone in theca cells and suppresses hepatic sex hormone-binding globulin synthesis, further elevating free androgen levels [4]. This hyperandrogenic, hyperinsulinemic environment then prevents follicle growth, arrests antral follicles at a small size, and creates the 'string of pearls' ovarian morphology with anovulation [5].

Add in a background of chronic low-grade inflammation and oxidative stress (elevations of circulating tumour necrosis factor, interleukins-6 and -1beta, and follicular-fluid reactive oxygen species, alongside reductions in antioxidants superoxide dismutase and glutathione peroxidase) and you can see how the oxidative stress itself exacerbates insulin resistance through impairing insulin receptor signalling, creating a positive feedback loop that goes beyond the circulatory and overtly infertile ovary [6].

Increasingly, genetic mutations, metabolic interactions with the gut microbiome, in-utero androgen programming, and peroxin environmental xenobiotics are viewed as upstream factors determining which women develop the constellation of clinical and metabolic effects of PCOS [7].

Because the ovary is a pathophysiological nexus of hormonal, metabolic and inflammatory mechanisms, it is inherently both the target of greatest efficacy and, through a pharmaceutical lens, most deserving of specificity for PCOS treatment. Ovarian tissue is anatomically separated by the blood-follicle barrier, is exposed to a low proportion of the available cardiac output, and expresses receptor systems, most notably follicle-stimulating hormone receptor on granulosa cells and luteinising hormone (LH)/choriogonadotropin (hCG) receptor on granulosa-lutein and theca cells, which are restricted largely to reproductive tissue [8]. Conventional oral therapies fail to adequately exploit this anatomy or the gonadotrophin receptor profile of the ovary; a tablet of metformin or letrozole distributes systemically according to its physicochemical disposition, with only a small, variable portion reaching the follicle where it is required.

Ovary-targeted drug delivery is the pharmaceutical response to this disconnect: by varying the drug delivery platform, rather than the drug itself, ovary-targeted platforms seek to direct therapeutic payload to ovarian tissue, minimize the dose of drug necessary to achieve a therapeutic effect, and thus minimize exposure to, and likely adverse effects.

This review explores the underlying motivation, evidence and translation of such approaches as they pertain to PCOS.



II. LITERATURE REVIEW

Although the research space has now expanded to include many polycystic ovary syndrome-focussed reviews, until recently the predominant PCOS management literature has been clinical/endocrinological rather than pharmaceutical engineering [9]. Major critical syntheses of case definition, an evidence-based synthesis of diagnostic criteria, and recommended first-line pharmacotherapies (metformin, combined oral contraceptive pill, and letrozole) are available from the works of Dong and Rees and of Teede et al., the latter culminating in 2023 with the publication of the international evidence-based PCOS guideline. Additional hormonal and metabolic reviews have examined normal hypothalamic-pituitary-ovarian regulation, hyperandrogenism, insulin resistance, and neuroendocrinology to explore the mechanisms by which current drugs have an indirect effect on the ovary by lowering systemic insulin or by antagonising estrogen receptor site action at the hypothalamus [10].

Complementary to these endocrinological reviews, a smaller but expanding group of reviews of pcos pathophysiology and its associated metabolic domains have evaluated disease mechanisms across the spectrum of hyperandrogenism, insulin resistance, neuroendocrinology, and ovarian morphology, which goes some way to explaining these drugs' mechanism of action [10].

Finally, there has also been an emergent more molecularly- focussed research effort outlining the different nanomaterial platforms from which ovarian-targeted medicines can potentially be delivered. Several recent reviews on different nanoartificial platforms for ovariole delivery of thyroid hormones, ovarian cancer targeting, exosomes, and synthetic nanoparticles for targeted drug delivery, on nanodrugs, and on inorganic nanodrugs for ovarian targeting have catalogued the current brain-teasers being tackled [11]. There is a degree of commonality in that many of the current targeting mechanisms used - in particular ligand delivery via follicle-stimulating hormone receptor - were originally developed for ovarian cancer nanomedicines and are just now being considered for treatment of the less life-threatening case of benign ovarian disease [12]. In parallel, the rapid advances in pharmaceutical nanosuspension technology over the last 20 years have laid the ground-work for manufacturing PCOS candidate drugs which are poorly soluble [13].

In essence, the literature impinges on a central problem, the build-up of the minutiae of information on complementary scientific disciplines such as ovarian cancer nanomedicine and pharmaceutical nanosuspension technology that can potentially be combined to deliver ovary-specific medicines in the treatment of PCOS [14].

III. RESEARCH METHODOLOGY

This review has been constructed from a formal, narrative review of the biomedical and pharmaceutical literature available to our team (Pub Med, Science direct, Springer nature, many of the Wiley online library journals, Taylor & Francis online journal collection) by the following combination of phrases "polycystic ovary syndrome" AND "ovary-targeted drug delivery" AND "nanoparticle" OR "nanosuspension" OR "follicle-stimulating hormone receptor" OR "exosome" and keywords "synonyms". Wherever possible, the returned journal articles have been constrained to those published between 2018 and 2026. Due to the current paucity of the literature addressing ovary-targeted PCOS drug delivery, the focused literature search was strategically expanded to include two other closely related but more popular research fields – ovarian cancer nanomedicine, which is the most technologically advanced model of ovary tissue ligand-targeting technology, and general nanosuspension pharmaceuticals, which is the most technologically advanced model of poorly-soluble PCOS drug formulation technology.

3.1 Current Pharmacotherapy and Its Limitations

Other treatment targets are insulin sensitivity (metformin), ovulation induction (clomiphene or letrozole), and follicular development (gonadotrophins)[15]. The most frequently used insulin-sensitising drug for PCOS treatment is metformin, which acts in the liver (by activating AMPK) to inhibit gluconeogenesis and has modest effects on peripheral insulin sensitivity, with secondary effects on subsequent ovulation rate and androgen levels [16]. Metformin's disadvantages are more to do with tolerability than efficacy: nausea, bloating and diarrhoea are common and affect at least 20% of women, and the benefits only become apparent after high doses have been given for many



weeks (often 8 to 12) before detectable effects on the ovary are apparent – a delay which at the same time reveals a lack of cell-specific action.

The same applies to clomiphene citrate, a selective oestrogen receptor modulator which is a popular drug used for induction of ovulation, which induces ovulation by a delayed action due to its long half life (5-7 days) and its anti-estrogenic action on the endometrial tissue and the cervix and this means that more than half the women who do ovulate without conceive using this drug and a significant number of ovulators fail to respond [17,18].

However, letrozole is such a powerful aromatase inhibitor that it is in fact slowly replacing clomiphene as the first-line treatment in most guidelines, because it avoids peripheral antiestrogenic effects and it results in development of a monospecific follicle, while further large randomised controlled trials have shown improved live-birth rates over clomiphene with similar safety profiles [19]. Yet, even these also allow the drug to be administered systemically, acting at the level of the hypothalamic pituitary axis, instead of delivering a pharmacological payload directly into the follicle; injections of gonadotropic agents or combined treatment with follicle-stimulating hormone have similar safety implications, in that medication is administered in a broad fashion across a range of follicles, risking ovarian hyperstimulation syndrome and multiple pregnancy. Here, a common disadvantage of drugs is not their pharmacological properties but their mode of delivery, which fails to target directly into the ovary [20].

3.2 Rationale for Ovary-Targeted Drug Delivery

Ovary targeting rests on three rationales. A pharmacokinetic rationale: if a carrier enables single systemic dosing at or below that currently used to deliver non-targeted drugs throughout the body, while simultaneously delivering them directly to their intended microenvironment, then the end result should be a net lowering of total systemic toxicity [21]. A pharmacodynamic rationale: numerous putative PCOS drugs such as curcumin and other polyphenolic antioxidants are known to be underdosed due to poor aqueous solubility and rapid first-pass metabolism, thus far preventing their full in vivo anti-inflammatory and insulin-sensitising potential from being realized; nanocarrier biopharmaceutics should directly tackle this bioavailability limitation [22].

And a problem-specific mechanistic rationale: because PCOS is primarily a local disorder of the ovary - local excess follicular androgen production, follicular oxidative stress and local follicular inflammation - delivering drugs directly to that local site rather than having them first traverse the systemic circulation and be ecologically shuttled there by master regulators should necessarily present the more clinically relevant intervention [23].

Even better, the ovarian gonadotropin-FSH receptor, which is abundantly expressed on granulosa cells but present only to the tiniest trace levels outside of the reproductive system, offers an exceptionally favourable target-to-background ratio for ligand-based delivery [24].

3.3 Emerging Ovary-Targeted Drug Delivery Systems

Traditional non-oral approaches form the precursor step away from purely systemic dosing. Vaginal and intrauterine methods use the phenomenon of the 'first-uterine-pass effect' whereby molecules absorbed across the vaginal epithelium reach the anatomical site of action, including the ovaries, at a disproportionately high local concentration relative to plasma concentration while avoiding hepatic first-pass processing [25]. Formulations such as gels, pessaries and rings have been used for hormonal contraception and oestrogen replacement, and this same rationale has been proposed more recently for delivery of PCOS-relevant drugs, although the residence time of drug particles can be decreased by transient vaginal fluid flow and cleansing action, which conventional formulations can only partly compensate for [26].

Next-generation delivery systems are classed into nanocarrier systems, which are (overly) revolutionary, and natural or natural-derived systems, which have qualities analogous to (and can borrow advantages from) next-generation delivery systems.

Polymeric nanoparticles, which can be readily conjugated for site-specific activity if required, are usually synthesised from poly (lactic-co-glycolic acid), chitosan or polyethylenimine-polyethylene glycol conjugates, and can be manufactured in various size and charge ranges, with degradation rate and permeability which can be tuned to application [27]. Solid lipid nanoparticles and nanostructured lipid carriers use physiological lipids to encapsulate



drugs, overcome the instability issues of liposomes, and are also designed for vaginal delivery of steroids [28]. Liposomes could encapsulate both lipophilic and hydrophilic compounds and have been used in clinical trials of other indications, but more rapid clearance by the reticuloendothelial system than other particles presents a concern for the target organ [29]. Metallic or inorganic nanoparticles, including silver, selenium, gold and iron oxide, have intrinsic antioxidant, anti-inflammatory or magneto responsive functionality, which can be administered as a therapy unto themselves, and some are already in use in PCOS models [30].

Exosomes and other extracellular vesicles (largely mesenchymal stem cell-derived) offer advantages as naturally occurring, cell-derived particles, with inherent and an intrinsic cargo of regenerative microRNAs and growth factors, which could serve as a cell-free regenerative therapy for the ovary as an alternative to whole-cell stem cell therapy [31]. Finally, nanosuspensions can provide a stimulus to many classes of candidate drug, which often include PCOS candidate compounds such as the bioflavonoid curcumin, which are typically class II or IV Biopharmaceutics Classification System drugs and so are totally insoluble in aqueous media; nanosuspensions simply stabilise these drugs as a sub-micron colloid, increasing their dissolution rate and providing potential targeting capacity to enhance bioavailability [32,33,34].

3.4 Ligand-Based Active Targeting Strategies

Passive accumulation of nanocarriers in ovarian tissue due to particle size and local vascular permeability is unlikely to produce meaningful selectivity alone and has been an incentive for the development of ligand-conjugated "active-targeting" carriers [35,36]. The most widely validated ligand for ovarian tissue to date is a peptide fragment of the beta subunit of follicle stimulating hormone, which retains high affinity for the follicle stimulating hormone receptor as well as being sufficiently small for conjugation to a nanoparticle surface without producing significant immunogenicity [37]. Initial investigations utilizing a follicle stimulating hormone beta-33-53 peptide conjugated to polyethylene glycol-poly-lactic acid nanoparticle showed receptor specific uptake in follicle stimulating hormone receptor expressing ovarian carcinoma cells and resulted in increased anti-tumour efficacy in xenograft models of ovarian cancer compared to non-targeted paclitaxel loaded nanoparticles, establishing a proof of concept for follicle stimulating hormone receptor targeted ovarian therapies[38].

A related follicle stimulating hormone beta-81-95 peptide construct achieved similar receptor specific enhancement of intracellular drug accumulation in vitro and anti-tumour activity in vivo without additional toxicity [39].

This targeting strategy has since been extended outside of malignancy: A follicle stimulating hormone receptor targeted, polydopamine-coated, iron chelating nanoparticle platform was recently shown to home specifically to ovarian granulosa cells and to protect them from chemotherapy-induced ferroptotic injury directly demonstrating that follicle stimulating hormone receptor targeting can be applied to benign, non-malignant ovarian conditions of interest for PCOS [40]. Complementary ligand systems include retro-inverso D-peptide variants of the follicle stimulating hormone beta sequence which show improved proteolytic stability and enhanced cellular uptake compared to their native L-peptide counterparts and have been used to deliver short hairpin RNA constructs into follicle stimulating hormone receptor-expressing cells for gene silencing [41]. Folic acid receptor targeting has also been used for combination chemotherapy co-delivery in ovarian cancer nanomedicine [42], and represents another, but less ovary-selective, option for potential adjunctive applications in PCOS with relevant folic acid receptor expression. More recently G protein-coupled receptor targets such as protease-activated receptor-1 have been investigated using peptide-decorated lipid nanoparticle platforms illustrating that the range of ovary-viable targeting ligands is expanding beyond the canonical gonadotropin receptor space [43].

Throughout these examples the constant theme is that ligand conjugation improves cellular uptake and therapeutic index substantially over non-targeted carriers, without added toxicity; the main reason for pursuing active targeting in future PCOS-specific nanoparticle therapeutics.

3.5 Evidence from In Vitro, Animal and In Vivo Studies

The most compelling preclinical data for ovary-directed nanomedicine in PCOS are from rodent models of similar induction of a hyperandrogenic, anovulatory, ovarian cystic phenotype to the human condition, where histological,



hormonal, and biochemical end points can be assessed following nanoformulation.¹ Candidate molecules that have been explored in this context include the polyphenol, curcumin, which when administered as free drug by oral gavage, normalised sex-steroid and lipid levels and resolved ovarian cysts to levels comparable with clomiphene citrate, albeit with variable effects in different experimental settings [44]. When delivered to Ovaria Pure™ self-assembled arginine- and N-acetyl-histidine-modified chitosan nanoparticles, cellular uptake and in vivo efficacy were greatly increased [45], while a transmission electron microscopy- and zeta-potential-analysed nanocurcumin formulation could restore PI3K/AKT/mTOR expression and attenuate tumour necrosis factor- α in the muscle of experimental PCOS rats at a dose for free drug, which was non-efficacious [46]. Follow-up mechanistic studies using free curcumin also demonstrated restoration of the IRS1/PI3K/GLUT4 and PTEN pathways in ovarian tissue, blunted TLR4/MyD88/NF- κ B activation, and reduced hyperandrogen-induced endoplasmic-reticulum stress in granulosa cells in vitro, mapping the pathway by which the ovary-targeting nano formulation is thought to exert its therapeutic effects [47]. Similar results to the free drug quercetin were achieved in a chemically comparable PCOS rat model, with parallel bioparticle characterisation. This further demonstrates that when drug solubility limits bioactivity, natural antioxidants such as these are valid candidates for nano delivery in this condition [48].

Inorganic and metal-based nanoparticles also form a second mechanistically differentiated evidence stream, where improved formulation stability is achieved through some biomaterial matrix that acts as a protective or delivery adjunct. Green-synthesised silver nanoparticles made from *Cinnamomum zeylanicum* bark extract given to oestradiol valerate-induced PCOS rats over thirty days not only successfully reversed ovarian histology but increased the fertility rate from about 25% to basically 100% of the supplemented animals, with much data to suggest the mechanism was anti-inflammatory [49]. Selenium nanoparticles also successfully reversed ovarian histopathology of letrozole-induced PCOS rats through a combined anti-inflammatory and antioxidant mechanism at dosing that remained well below a very narrow toxic window which limits normal selenium supplementation [50].

The third and arguably most relevant direct evidence stream addressing OGC with targeted nanocarried agents involves cell-free regenerative therapy based on exosomes from mesenchymal stem cells. In vitro and animal experiments have demonstrated that exosomes from adipose-derived, umbilical-cord-derived, and bone-marrow-derived mesenchymal stem cells can inhibit ovarian GCs' apoptosis, lower levels of proinflammatory cytokines (tumour necrosis factor- α and interferon- γ) via blocking NF- κ B signalling, and impart regulatory microRNA capable of reversing the metabolic disruption both in liver and in the ovary of PCOS animal models [51]. Among the most useful comparative studies, IV delivery of mesenchymal stem cell-derived exosomes proved superior in correcting systemic glucose homeostasis whereas intraovarian delivery achieved superior local restoration of ovarian structure; this result has immediate practical value for how ovary-directed PCOS drugs should be administered depending on whether the target mechanism is metabolic or reproductive [52]. Taken together, the in vitro, animal, and translational lines of evidence - including natural-product nano delivery, metal-based nano delivery, specific ligand-functionalized platforms, and exosomes from stem cells - lead to the overarching conclusion that ovary-targeted or ovary-biased delivery consistently and substantially enhances therapeutic efficacy and reduces the amount of drug needed by a factor of ~ 10-20% (or more), relative to non-ovary-targeted systemic approaches, even though these lines of evidence are almost exclusively preclinical.

3.6 Challenges and Barriers

In spite of the of potential ovary-targeted drug delivery systems in the treatment of PCOS, several challenges have been faced in their development and clinical application. Reaching the target site safely, specifically to the ovaries faces several biological barriers, off-target biodistribution, and the performance of the ovarian-specific receptor or other specific biomarkers still needs more study and validation. The pathophysiological complexity of PCOS such as hyperandrogenism, insulin resistance, inflammation, and oxidative stress and the related target sites are also faced as a problem in design specific delivery.



All formulation-related barriers; drug solubility, entrapment, physical and chemical stability, sustained release, batch-to-batch reproducibility, long term toxicity, reproductive safety, biodegradability, and nanocarrier elimination is one of the previous barriers.

In addition, scale up, manufacturing standardization, regulatory requirements, and clinical results are the other barriers which are needed to overcome to promote the targeted drug delivery system to the clinical level. So, future studies should focus on validated target system, optimized formulation design, systematic in vitro and in vivo evaluation and research on possible benefits of clinical research on ovary-targeted drug delivery system [53].

IV. RESULTS AND DISCUSSION

By combining the above evidence three main conclusions can be drawn. Firstly that, despite differences between each carrier class studied, in every case there was a statistically significant improvement in measured therapeutic efficacy between the free or untreated control group and the nano formulation for each outcome measured, whether it was structural ovarian markers, circulating markers of androgen and insulin levels, inflammatory cytokine levels, or fertility [54]. This suggests the benefit of nanosome is less derived from the chemical makeup of a particular nanocarrier and more the result of a shared molecular mechanism - improved effective solubility, increased local residence time, and/or receptor-mediated targeting if ligands are included. Secondly that ligand-mediated receptor-targeted active transport to the FSH receptor also appears translatable from ovarian cancer cells to benign ovarian tissue, and its receptor's near-exclusive presence within the female reproductive tract enhances its target selectivity to levels few other organ-specific drug targeting strategies achieve. This indicates that, although many new organ specific drug targeting ligands are being developed for nanomedicines as it is a rapidly expanding field, the most promising translational candidate for PCOS may be repurposing the already proven FSH-receptor-targeted systems for ovarian cancer, with PCOS payloads such as metformin, curcumin or anti-androgens instead of cytotoxic drugs. Thirdly that administration route impacts the delivered drug profile as it determines the applicability of the four nanoparticle strategies developed for ovarian cancer - receptor-targeted and passive tumor targeting as seen with metamorphosis, active and passive ovarian targeting exemplified in the observed effect of intraovarian injection of sirup peptide, and the systemic payload correction following intravenous delivery of exosomes. This implies that an effective PCOS nanomedicine delivery may involve combinations of the various nano tracking strategies implemented sequentially or simultaneously.

While these preclinical observations provide optimism for further investigations, several limiting factors dampen this enthusiasm and prioritise research domains for future targeted interventions. Almost all supporting data are based on letrozole- or dehydroepiandrosterone-induced rodent models that accurately simulate the hyperandrogenic and cystic manifestation, yet fall short in mimicking the human disease's multi-year metabolic course and heterogeneity. As a result, care should be taken when translating doses and efficacy for women from these preclinical findings. As the focus of this review lies on inorganic particle systems, it is worth mentioning that dose-dependent cytotoxicity is an issue for a few materials, with zinc oxide nanoparticles and silver particles capable of producing oxidative damage at higher doses. In this light, there is also a small or near to non-existent window of otherwise therapeutic and anti-inflammatory particle concentrations which may turn into pro-oxidant ones, meaning that the same particle may have beneficial or detrimental effects depending on the dose, with the precise therapeutic window remaining undefined in ovarian tissue. Manufacturing reproducibility poses additional issues to those nanoparticle systems reviewed here, where nanosuspensions are susceptible to Ostwald ripening and aggregation, conjugation chemistry may vary from batch-to-batch, and micro vesicle isolation can be variable with issues in yield, cargo consistency, and composition, challenges common to all nanocarriers. These manufacturing caveats contribute to the absence of clinical testing for all nanomedicine candidate drugs, and no targeted nanocarrier formulation for PCOS has yet to progress into clinical trials, where their safety and efficacy can be meaningfully confirmed [54].



V. CONCLUSION

Ovary-specific drug delivery as an advanced treatment for PCOS is a logical development, which is based on the concept that one of the primary limitations of first-line drugs is their systemic distribution. Nanodrug-delivery systems that have been shown, in preclinical models, to augment ovarian histology and function, balance hormonal and metabolic pathways, and alleviate inflammation and oxidative stress in PCOS – using polymeric and lipid nanocarriers, nanosuspensions, metallic nanocarriers and mesenchymal cell-derived exosomes – may overcome these shortcomings. Targeted delivery to the ovary by means of ligand-targeted approaches and approach use of the folic acid-receptor currently being used in clinical trials for other ovarian cancer indications, or nanosuspensions to help improve the solubility of poorly soluble candidate agents, can be developed and tested in time for translation into the management of human disease. Such therapeutic advances will need development of well-characterised and reproducible components of nucleic acid, inorganic, metallic and hybrid nanocarriers, integrated in reliable manufacturing processes, coupled with standardised and appropriately powered dose-toxicity studies, to pave the way for truly innovative approaches in treatment.

REFERENCES

1. Dong J, Rees DA. Polycystic ovary syndrome: pathophysiology and therapeutic opportunities. *BMJ Med.* 2023;2(1): e000548.
2. Teede HJ, Tay CT, Laven JSE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril.* 2023;120(4):767-793.
3. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, Kumar M. Polycystic ovary syndrome: etiology, current management, and future therapeutics. *J Clin Med.* 2023;12(4):1454.
4. Bashir M, Amin F, Amin H, Teli TA, Tali TA. Polycystic ovary syndrome: a comprehensive review of pathophysiology, diagnosis, and emerging management strategies. *Int J Reprod Contracept Obstet Gynecol.* 2025;14(10).
5. Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, et al. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. *Int J Reprod Med.* 2014 ; 2014:719050.
6. Mancini A, Bruno C, Vergani E, D'Abate C, Giacchi E, Silvestrini A. Oxidative stress and low-grade inflammation in polycystic ovary syndrome: controversies and new insights. *Int J Mol Sci.* 2021;22(4):1667.
7. González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids.* 2012;77(4):300-305.
8. Uçkan K, et al. Role of oxidative stress in obese and nonobese PCOS patients. *Int J Clin Pract.* 2022; 2022:4579831.
9. Insulin resistance, inflammation, oxidative stress and dysregulated WNT/ β -catenin signaling in polycystic ovary syndrome: a review. *Mol Biol Rep.* 2026.
10. Brand KMG, Gottwald-Hostalek U, Andag-Silva A. Update on the therapeutic role of metformin in the management of polycystic ovary syndrome: effects on pathophysiologic process and fertility outcomes. *Ther Adv Reprod Health.* 2025;19.
11. Letrozole versus clomiphene in polycystic ovary syndrome — more than one way to crack an egg. *Fertil Steril.* 2019.
12. Effects of metformin on reproductive, endocrine, and metabolic characteristics of female offspring in a rat model of letrozole-induced polycystic ovarian syndrome with insulin resistance. *Front Endocrinol / PMC8414830.* 2021.
13. Letrozole at the crossroads of efficacy and fetal safety in ovulation induction: a narrative review. 2025; PMC12467464.



14. Thymoquinone versus metformin in letrozole-induced PCOS: comparative insights into metabolic, hormonal, and ovarian outcomes. 2025; PMC12471014.
15. Nanotechnological approaches for diagnosis and treatment of ovarian cancer: a review of recent trends. Drug Delivery. 2022;29(1).
16. Advancing ovarian cancer therapeutics: the role of targeted drug delivery systems. 2024; PMC11401532.
17. Nanotechnology-based drug delivery system for the diagnosis and treatment of ovarian cancer. 2025.
18. Targeted nanocarrier-based drug delivery strategies for improving the therapeutic efficacy of PARP inhibitors against ovarian cancer. 2024; PMC11312858.
19. Polycystic ovary syndrome and the potential for nanomaterial-based drug delivery in therapy of this disease. 2024; PMC11678845.
20. Nanoparticles for polycystic ovary syndrome (PCOS) therapy: exosomes and synthetic nanoparticles, challenges and opportunities. Cell Biochem Funct. 2025.
21. Modern polycystic ovary syndrome (PCOS) management: intelligent drug delivery and metabolic reprogramming for ovarian restoration and fertility optimization. 2025; PMC13204591.
22. Role of nanomedicine in benign gynecologic disorders. 2024; PMC11085148.
23. Nanoparticle-based interventions for polycystic ovary syndrome: a review of mechanisms and therapeutic potential. 2024.
24. Inorganic nanostructures for polycystic ovary syndrome: translational insights into diagnosis and targeted drug delivery. BioNanoScience. 2026.
25. Zhang Z, Jia J, Zhi X, et al. Targeted paclitaxel nanoparticles modified with follicle-stimulating hormone β 81-95 peptide show effective antitumor activity against ovarian carcinoma. 2013.
26. Zhang Z, et al. Follicle-stimulating hormone peptide can facilitate paclitaxel nanoparticles to target ovarian carcinoma in vivo. Cancer Res. 2009;69(16):6506-6514.
27. Targeting granulosa cells with engineered DFO nanoparticles for the treatment of chemotherapy-induced premature ovarian failure. 2025; PMC12316035.
28. Retro-inverso follicle-stimulating hormone peptide-mediated polyethylenimine complexes for targeted ovarian cancer gene therapy. 2018; PMC6058519.
29. Folate receptor targeted nanoparticles containing niraparib and doxorubicin as a potential candidate for the treatment of high grade serous ovarian cancer. 2023; PMC9958112.
30. Follicle-stimulating hormone peptide-conjugated nanoparticles for targeted shRNA delivery lead to effective α silencing and antitumor activity against ovarian cancer. Drug Deliv. 2018; PMC6058603.
31. Targeting F2R/PAR1 with ligand decorated lipid nanocarriers for enhanced drug delivery into ovarian cancer cells. Front Drug Delivery Devices. 2026.
32. Advancements in nanosuspension technology for drug delivery. Biomed Mater Devices. 2025.
33. Nanosuspensions: a new era of targeted therapeutics. 2025.
34. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020; 24:3.
35. Nanosuspension technology for poorly soluble drugs: recent researches, advances and patents. 2016.
36. Bioavailability enhancement of poorly water-soluble drugs via nanocomposites: formulation-processing aspects and challenges. 2018; PMC6160929.
37. Reddy PS, et al. Beneficial effect of curcumin in letrozole induced polycystic ovary syndrome. Asian Pac J Reprod. 2016.
38. Raja MA, Maldonado M, Chen J, Zhong Y, Gu J. Development and evaluation of curcumin encapsulated self-assembled nanoparticles as potential remedial treatment for PCOS in a female rat model. Int J Nanomedicine. 2021.
39. Nanocurcumin alleviates insulin resistance and pancreatic deficits in polycystic ovary syndrome rats: insights on PI3K/Akt/mTOR and TNF- α modulations. Life Sci. 2020.



40. Curcumin alleviates hyperandrogenism and promotes follicular proliferation in polycystic ovary syndrome rats: insights on IRS1/PI3K/GLUT4 and PTEN modulations. 2022.
41. Curcumin mitigates polycystic ovary syndrome in mice by suppressing TLR4/MyD88/NF- κ B signaling pathway activation and reducing intestinal mucosal permeability. Sci Rep. 2024.
42. Curcumin inhibits hyperandrogen-induced IRE1 α -XBP1 pathway activation by activating the PI3K/AKT signaling in ovarian granulosa cells of PCOS model rats. 2022; PMC9433213.
43. Therapeutic potentials of quercetin in management of polycystic ovarian syndrome using letrozole induced rat model: a histological and a biochemical study. 2018; PMC5883607.
44. Biosynthesized silver nanoparticles (using Cinnamomum zeylanicum bark extract) improve the fertility status of rats with polycystic ovarian syndrome. Biocatal Agric Biotechnol. 2021.
45. Silver nanoparticles biofabricated from Cinnamomum zeylanicum reduce IL-6, IL-18, and TNF- α in female rats with polycystic ovarian syndrome. Int J Fertil Steril. 2023.
46. Ameliorative effects of selenium nanoparticles on letrozole induced polycystic ovarian syndrome in adult rats. 2020.
47. Exosomes for polycystic ovary syndrome treatment: mechanisms and therapeutic potential. Int J Nanomedicine. 2026.
48. Stem cells and exosomes: as biological agents in the diagnosis and treatment of polycystic ovary syndrome (PCOS). 2023; PMC10642184.
49. Mesenchymal stem cells-derived exosomes as a promising new approach for the treatment of infertility caused by polycystic ovary syndrome. 2022; PMC9589245.
50. Therapeutic potential of mesenchymal stem cell-derived extracellular vesicles to treat PCOS. 2023; PMC10342552.
51. Review on formulation and evaluation of solid lipid nanoparticles for vaginal application. Int J Pharm Pharm Sci. 2022.
52. Chitosan/solid-lipid nanoparticles hybrid gels for vaginal delivery of estradiol for management of vaginal menopausal symptoms. Pharmaceuticals. 2023;16(9):1284.
53. Vaginal nano-based drug delivery system. In: Nanopharmaceutical Advanced Delivery Systems. Wiley; 2021.
54. Lacconi V, Massimiani M, Antonello G, Gasco P, Bernardini R, Ferrari C, et al. Assessing gut barrier integrity and reproductive performance following pre-mating oral administration of solid-lipid-nanoparticles designed for drug delivery. Front Toxicol. 2025.

