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Chapter 5: Beyond Treatment: Theranostic and Personalized Nanomedicine Approaches in (In-vitro, In-vivo and Ex-vivo) PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is a complex and multifactorial endocrine disorder that has a wide range of medical consequences all over the world, especially for women of reproductive age. The actual number of women suffering from PCOS is hard to determine since different studies give different estimates depending on the diagnostic criteria used, the population studied, and the methods applied. According to the NIH criteria, the syndrome is said to affect 5-10% of women in the world, but using Rotterdam and AE-PCOS criteria raises the percentages to 9-21% and 10-17%, respectively. A meta-analysis revealed a combined incidence of 6% (NIH), 10% (Rotterdam), and 10% (AE-PCOS) across 24 studies. Theranostics is a new multi-faceted discipline that fuses diagnosis and treatment course in sickness control thus making it more precise and personalized. The extraction of the PCOS drawing process involves combining a fine-tuned therapeutic approach with highly developed diagnostic technology to detect, monitor, and treat PCOS at the same time. Not only that, but also advanced gene editing technologies such as CRISPR, wearable device integration, and AI-empowered multi-omics platforms are together creating the reproductive nanomedicine future through their provision of unmatched accuracy and customization in the reproductive healthcare sector. With nanosensors, we now have such sensitive and specific outputs that they have made the early and more accurate diagnosis of infertility, PCOS, endometriosis, and reproductive cancer, to name just a few, possible. Moreover, we are not in the time where universal treatment strategies were the standard anymore; rather, we have come to the period of tailored nanotherapeutics that use AI and multi-omics to manage each patient's unique pathophysiology.

Keywords: *Theranostics, Personalized medicine, PCOS, CRISPR, Nanomaterials, Nanosensors.*

1. INTRODUCTION

Data show that the prevalence of PCOS is rising, showing a steady increase since 1990, reaching 867.7 per 100,000 women, corresponding to approximately 65.77 million women worldwide, suggesting possible underreporting of the prevalence. PCOS also contributes to anovulatory infertility, PCOS is associated with several long-term complications, including, namely: including metabolic syndrome, cardiovascular diseases, obesity, and psychological disorders, which adversely affect the quality of life[1].

Heterogeneity in populations, methodologies, and diagnostic capabilities. criteria lead to variations in the prevalence of polycystic ovary syndrome (PCOS). It is estimated to affect 5–10% of women globally when diagnosed according to the NIH criteria, which increases to 9–21% when using the Rotterdam criteria and 10–17% with AE-PCOS guidelines. A meta-analysis including 24 studies reported a pooled prevalence of 6% (NIH), 10% (Rotterdam), and 10% (AE-PCOS). Differences in ultrasound practice and the criteria used to define polycystic ovarian morphology also generate variability. In India, reported prevalence figures vary widely, ranging from 2% and 35% with West Bengal reporting 28% and Haryana 4.2%. A systematic review reported 11.3% overall prevalence; however, a more recent study in the Delhi NCR reported 17.4%, which has been attributed to higher rates due to lifestyle, education, and age[2,3].

The issue of PCOS diagnosis remains a controversial question at this time, and there are no universal diagnostic capabilities. standards. There are the Rotterdam, NIH, and Androgen Excess-PCOS Society criteria, which identify hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology as key factors. Also, these features, which may vary due to age, ethnicity, and issues such as those in the measurement process, which is particularly relevant in the case of teenage and perimenopausal women, share features with[4]. Significant differences in the standardization of laboratory tests for androgen levels further impede robust diagnosis confirmation. The cornerstones of modern therapy regimens, which focus more on symptom relief than underlying causes, include oral contraceptives, insulin sensitizers (such as metformin), and anti-androgens. However, there are certain risks associated with these drugs; insulin sensitizers sometimes cause gastrointestinal side effects, and contraceptives may raise the risk of thrombosis. Inadequate therapy and overall patient dissatisfaction result from many treatments' failure to consider the varied nature of PCOS and its metabolic and reproductive aftereffects.

The development of theranostic and personalized nanomedicine approaches, which integrate targeted therapy with diagnosis to enable clinicians to better and more precisely tailor, is an emerging approach in PCOS management, which has a highly complex pathophysiology and heterogeneous symptoms. Also, in this field, the use of nanotechnology-based drug delivery systems such as nanoparticles and nanocarriers shows significant potential because they can specifically target the ovarian tissue, modify hormone and metabolic pathways with less impact on the rest of the body, and

also at the same time provide real-time diagnostic capabilities. feedback real-time results[5]. These nanosystems address the limitations of conventional therapies. to traditional therapy's flaws by improving drug absorption, reducing off-target effects, and enabling diagnostic capabilities. at the same time (theranostics). In the future, it may see highly personalized treatments tailored to each woman's molecular and clinical profile by use of nanomedicine and omics-based patient profiling, which in turn will improve results and reduce side effects[6].

2. PATHOPHYSIOLOGY OF PCOS

PCOS is caused by a failed regulation of the hypothalamic-pituitary-ovarian axis and is characterized by increased androgen secretion and elevated levels of luteinizing hormone (LH). Anovulation is accompanied by a failure of follicular maturation, resulting in polycystic ovarian morphology. Hyperinsulinemia and a low concentration of sex hormone-binding globulin aggravate the androgen excess. Other aspects of the intricate and convoluted pathophysiology, explaining the spectrum of clinical and metabolic manifestations in affected women, include low-grade inflammation, oxidative stress, and a genetic predisposition.

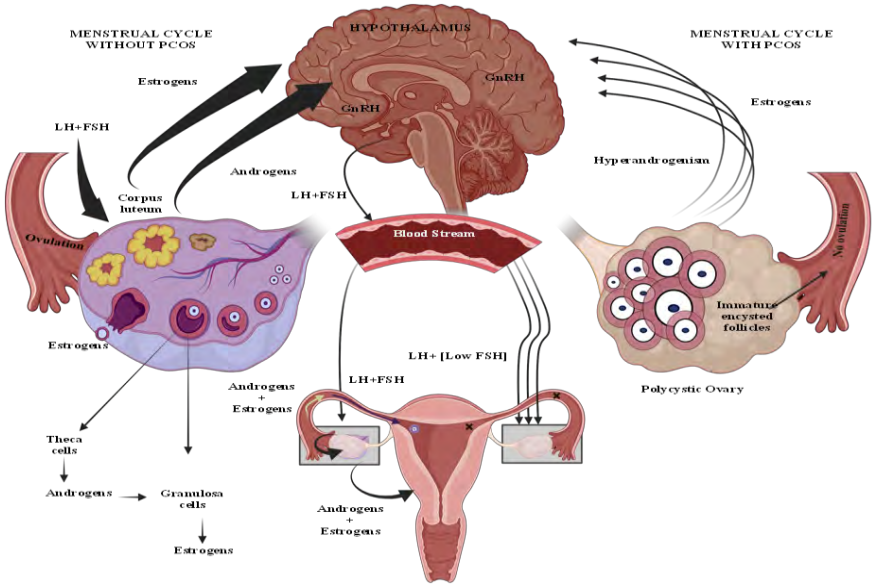

Figure 5.1: Pathophysiology of PCOS

2.1 Hormonal and metabolic dysfunction

Polycystic ovarian syndrome, better known as PCOS, is one of the major endocrine disorders that directly affect women of reproductive age. Alongside it is a whole range of hormonal and metabolic issues. The main culprit, however, is the dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis. One of the key features of PCOS is the abnormal elevation of luteinizing hormone compared to follicle-stimulating hormone,

which subsequently leads to the stimulation of ovaries' theca cells and overproduction of androgen. As a result, clinical presentations of hyperandrogenism like hair loss, breakout acne, and hirsutism [7]. Elevated levels of androgens disrupt normal follicle development, resulting in an accumulation of immature follicles. This leads to the ovaries displaying a polycystic appearance. These hormonal discrepancies cause a loss of ovulation and ovulatory infrequency, irregular menstruation, and, in some cases, infertility.

Metabolically dysfunctional insulin resistance is observed with PCOS and associated with compensatory hyperinsulinemia. The ovaries produce androgens, and the liver produces less SHBG in response to hyperinsulinemia. Low levels of SHBG increase the symptoms of hyperandrogenism. Insulin resistance is also associated with central obesity and weight gain, which may progress to cardiovascular disease and type 2 diabetes, and cause dyslipidemia, reduced glucose tolerance, and an increased risk of type 2 diabetes and cardiovascular diseases [8]. Hormone imbalance and metabolic dysfunction team up to create a negative cycle in which one condition makes the other worse. To break this cycle is the key to the development of better therapies, which in turn will address the reproductive and metabolic issues related to PCOS.

2.2 Role of insulin resistance, oxidative stress, and inflammation

A hallmark of Polycystic Ovary Syndrome is insulin resistance, which in plays a role in both metabolic and reproductive issues. In women with PCOS reduced insulin sensitivity in the periphery, which includes muscle and fat tissue. That leads to hyperinsulinemia, which in turn is a response. High insulin levels directly stimulate androgen production in theca cells of the ovary and also suppress SHBG synthesis, which in turn increases free testosterone and causes more hyperandrogenism. Anovulation, irregular menses, and clinical signs like acne and hirsutism are maintained by this hormone imbalance.

Oxidative stress, which is an imbalance between what is produced of reactive oxygen species (ROS) and what the body has in place for antioxidant defence, is a common feature of PCOS. Overproduction of ROS may damage ovarian tissue, stop follicle development in its tracks and reduce oocyte quality. Also, it plays a role in worsening endothelial function and insulin resistance, which in turn puts affected women at risk for cardiovascular disease [9]. Chronic low-grade inflammation is yet another etiological factor of PCOS. Among patients with PCOS, inflammation factors such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are elevated.

These inflammatory factors impair insulin action and ovarian function, worsening the cycle of hyperandrogenism with insulin- and glucose- metabolic disorders. Chronic oxidative stress, inflammation, and insulin resistance interrelate to amplify the metabolic and endocrine PCOS dysregulations. Insights here are pivotal to inform the

development of anti-reproductive complications therapies that also address the metabolic and cardiovascular risks associated with the disorder [10].

2.3 Genetic and epigenetic contributors

Twin and family studies report that PCOS has a very strong genetic basis. Many a genes related to steroid production, control of gonadotropins, insulin response and metabolic pathways, which play a role in the physiopathology of PCOS. Hyperandrogenism, insulin resistance and impaired ovarian function are associated with variants in genes like CYP11A1, CYP17, DENND1A, LHCGR, FSHR, and INSR. In terms of the many forms of PCOS in affected women are a result of these genetic predispositions.

In also to genetic elements, epigenetic changes play a large role in the development of PCOS. Epigenetic mechanisms such as DNA methylation, histone modification and microRNA regulation, which do not change the DNA sequence, can alter gene expression. As for environmental factors which play a role in insulin signalling, ovarian folliculogenesis, and the hypothalamic-pituitary-ovarian axis in obesity, metabolic stress, and in utero androgen exposure [11]. The disorders arising from these epigenetic changes may end up being metabolic and reproductive issues for the offspring and initiate the onset of disease for the individual. Genetic predisposition and epigenetic changes play a complex role in PCOS, explaining the variable metabolic presentations and clinical diversity. As developed greater insight into these molecular changes and also increased the chance to put in place individualized treatments that improve upon metabolic and reproductive issues in PCOS. This is the direction precision medicine is going for PCOS.

3. CONVENTIONAL APPROACHES: DIAGNOSIS &THERAPY

Nanotechnology has helped with disease prevention, diagnosis, and treatment, and it has given rise to a new hope for resolving today's human problems. Nanotechnology uses str uctures and
materials with novel features and applications in biology and medicine because of their s mall sizes (1 and 100 nm) at the supramolecular, molecular, and atomic levels.

3.1 Clinical diagnostic criteria (Rotterdam, NIH)

In 2003, during a joint session of the American Society for Reproductive Medicine (ASRM) and the European Society for Human Reproduction (ESHRE), a breakthrough in the diagnosis of PCOS was suggested. The new guidelines acknowledged that the polycystic ovary syndrome (PCOS) is characterized by two or more of the following conditions: hyperandrogenism, chronic anovulation, and polycystic ovaries (Rotterdam criteria) [12]. While the NIH criteria are no longer used, the Rotterdam criteria have emerged as a compelling alternative. A couple of PCO (polycystic ovary) phenotypes have been included in the list of new diagnostic criteria. The first one is PCO with androgen excess and no ovulatory dysfunction, while the second one is PCO with

ovulatory dysfunction and no androgen excess. Still, 91% of patients with Rotterdam criteria and 85% of patients with NIH criteria had PCO, so it could be considered as the most common symptom of PCOS in patients.

3.2 Standard treatment (OCPS, Metformin, Clomiphene)

1. OCPS: OCPS are accepted as the most widespread initial treatment for women having PCOS who are not expecting a child. They function by decreasing the secretion of luteinizing hormones (LH), thereby diminishing the production of ovarian androgens, whereas the estrogen component of the OCPs raises SHBG, thus lowering free testosterone levels. This has a positive effect on menstrual regularity, acne clearance, and hair reduction, especially in the case of female-pattern baldness, and it also helps the endometrium stay healthy. A trial with 242 women (121 in the OCP and 121 in the non-OCP group) has shown that women who used OCPs had a shorter stimulation period, required fewer gonadotropin doses, and had lower LH/FSH ratios at the beginning of treatment. Although the number of oocytes retrieved in the OCP group was lower, fertilisation and embryo development outcomes were, however, non-OCP users significantly better.

2. Metformin: Metformin is mainly used in PCOS patients with insulin resistance or metabolic problems. It improves insulin sensitivity, reduces blood glucose levels, and indirectly lowers ovarian androgen secretion. Addressing insulin resistance helps restore more regular menstrual cycles, improves metabolic health, and can even trigger spontaneous ovulation in some women. Metformin is often combined with clomiphene in resistant cases to improve ovulation and pregnancy rates.

3. Clomiphene: Clomiphene is the go-to medication for ovulation induction in women seeking to get pregnant. Its mechanism of action consists of blocking estrogen receptors in the hypothalamus, leading to a GnRH release increase and thereby promoting FSH and LH secretion which causes the growth of follicles and eventually ovulation. Besides, it is used together with oral contraceptives or GnRH antagonists to prevent the occurrence of LH surges and thus improve the success rates of assisted reproductive techniques. Table 5.1

3.3 Limitations

Compared to East Asian or Caucasian women, women of Middle Eastern, Mediterranean, Indian, and South Asian descent have greater frequencies and/or more severe cases of hirsutism in PCOS. East Asian women had less severe hirsutism, which is probably due to their low 5-α reductase activity. When it comes to blood pressure, cholesterol, and glucose levels, Hispanic and white women are similar [14]. At diagnosis, Hispanic teenagers with PCOS had greater levels of alanine aminotransferase (ALT) and HbA1c than those with just one elevated marker. Our knowledge of PCOS will surely grow as a result of additional clarification of the complex regulatory networks involving mRNAs, which could also result in the creation of innovative diagnostic and treatment approaches.

Table 5.1: Comparative overview of conventional versus nanomedicine approaches in diagnosis, treatment, and monitoring of PCOS.

Aspect	Conventional Approach	Nanomedicine Approach
Diagnosis	Ultrasound imaging, hormonal assays (LH/FSH ratio, AMH, insulin resistance tests)	Nano-biosensors for rapid hormone detection, lab-on-chip diagnostics, nano-enabled molecular imaging tools
Drug Delivery	Oral tablets (metformin, clomiphene, oral contraceptives), injectable hormones	Targeted nanoparticles (liposomes, polymeric NPs, dendrimers) ensuring site-specific drug delivery
Therapeutic Efficacy	Highly variable, depends on individual patient response; lacks personalization	Personalized, biomarker-driven therapy with enhanced bioavailability and precision
Side Effects	Gastrointestinal disturbances (metformin), hormonal imbalance (OCPs), systemic toxicity	Reduced systemic exposure, controlled and sustained drug release, and lower adverse events
Monitoring	Periodic laboratory testing and ultrasound follow-up	Real-time monitoring via nanosensors, theranostic nanosystems enabling simultaneous diagnosis and therapy
Patient Compliance	Low, due to pill burden, side effects, and long treatment duration	Improved compliance through minimally invasive nanosystems, transdermal patches, or implantable devices
Fertility Management	Conventional ovulation induction (clomiphene citrate, gonadotropins), assisted reproductive technologies	Nano-formulated fertility drugs with enhanced ovarian targeting, potential nanocarriers for oocyte protection
Metabolic Management	Lifestyle changes, metformin for insulin resistance, statins for dyslipidemia	Nano-formulated anti-diabetic and lipid-lowering agents with improved efficacy and reduced systemic toxicity
Oxidative Stress	Antioxidant supplements (vitamin E, C, CoQ10)	Nano-antioxidants (nano-curcumin, nano-resveratrol, cerium oxide NPs) with enhanced ROS scavenging
Hormone Regulation	Hormonal replacement therapy, oral contraceptives	Nano-encapsulated hormone modulators allowing controlled release and targeted ovarian delivery
Future Potential	Symptomatic management, not curative	Theranostic nanomedicine offering simultaneous diagnosis, therapy, and monitoring towards personalized care

4. OVERVIEW OF NANOCARRIERS (LIPOSOMES, POLYMERIC, NPS, METALLIC NPS EXOSOMES)

4.1 Liposomes: Liposomes are the small round and self-organizing structures composed of one or more lipid molecules with a thickness of two layers. These non-toxic and biodegradable structures provide an easy and flexible way to deliver a variety of drugs. They can transport very different kinds of materials, such as very small water-soluble and very small water-insoluble molecules, proteins, and nucleic acids. Liposomes do reduce the overall toxicity that goes with the use of a drug, and by doing so they also improve the effectiveness of the drug, and even help the drug get to the right place in the body by stabilizing the chemical and overcoming the absorption barrier of the cells. Resveratrol, a polyphenolic compound with health benefits including fertility enhancement, is limited in its application due to its poor bioavailability. DMU-212, a methoxy analog of resveratrol, has lipophilic properties and thus offers higher bioavailability [15].

4.2 Metallic NPs nanomedicine: To cure PCOS, recent research has turned its attention to novel therapeutic nanoparticles, including silver and selenium. In rats with PCOS, silver nanoparticles show potential in decreasing inflammatory markers and alleviating inflammation. According to research, iron nanoparticles laden with curcumin can successfully prevent ovarian damage cells from dying, which may help treat PCOS. By lowering androgen synthesis and interfering with the excessive androgen cycle through decreased androgen receptor expression, selenium nanoparticles have also demonstrated efficacy in the treatment of PCOS.

4.3 Polymeric Nps: The corpus luteum, follicular cells, granulosa cells, and the cells are among the secretory cells that can be directly activated by NPs, especially polymeric nanoparticles utilised as nano-carriers. This can alter the synthesis and release of hormones. These findings underline the necessity of more research to clarify the mechanisms and long-term effects of NPs on the female reproductive system [16].

4.4 Exosomes: Numerous investigations using human samples and other experimental models have been conducted to determine the function of exosomal RNAs and proteins during the advancement of PCOS. These miRNAs were linked to various amino acid metabolism pathways. Another study showed that the expression of miRNAs was altered in circulating exosomes in PCOS follicular fluid. More significantly, generated exosomes from PCOS patients' serum significantly stimulated the migration and invasion of endometrial cancer cell lines, according to a recent study.

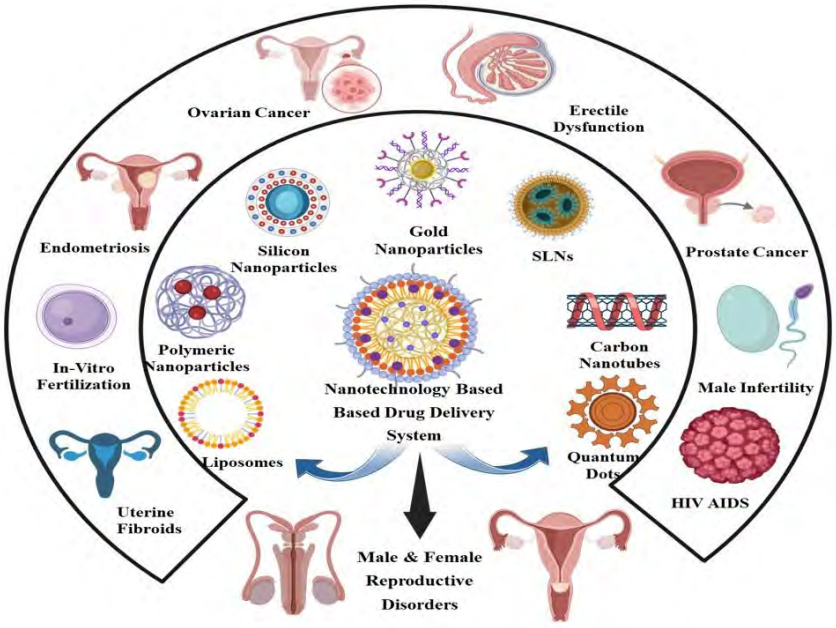

Figure 5.2: Treatment of various male & female reproductive disorders through nanotechnology-based drug delivery systems

4.2 Advantages

Researchers find herbal-based nanoformulations to be an appealing alternative. Among the many significant advantages were:

- Greater local drug concentrations.
- little individual variability.
- Reduced variance in transit time across the gastrointestinal tract.
- Less adverse effects, a low chance of dose dumping, the option to administer drugs by parenteral, oral, or inhalation, and the use of both hydrophilic and hydrophobic drugs.

4.3 Potential application in PCOS

- **Increased local drug concentration:** Drugs are directly or effectively concentrated in the reproductive tissue of the ovary.
- **There is little individual variability:** My answer is steady and predictable.
- **Less variation in GI transit time:** Oral delivery and absorption are consistent, and the effects of treatment are dependable.
- **Reduced side effects and regulated release:** There is a risk of side effects, dosage dumping, and the possibility of controlled or sustained release.
- **Various modes of administration:** PCOS medications are administered orally, parenterally, or by inhalation [17].

- Hydrophilic and hydrophobic medications are used to treat PCOS. Various kinds, such as hormonal, antihyperglycemic, and herbal extracts, are readily administered.

5. THERANOSTIC APPLICATIONS

Theragnostic is an emerging multidisciplinary field that integrates diagnostics and therapeutics to provide more precise and personalised illness management. This field involves the integration of custom-made treatment options along with advanced diagnostic tools, to which we have added Polycystic Ovary Syndrome (PCOS) to our focus. Also, the role of nanotechnology, which is key in this area, in the development of nanodiagnostics for early hormone detection and ovarian imaging and nanotherapeutics for site-directed drug delivery for site-specific delivery of agents like insulin sensitisers, antioxidants, and anti-androgens. [18-20]. Continuous assessment of hormone levels, illness development, and treatment response is a core component of integrated theragnostic combines diagnostic and therapeutic functions within a single platform. This personalised approach is applied to PCOSS for its metabolic and reproductive issues, which also improves drug efficacy and reduces systemic adverse effects. In that respect, theragnostic applications have great promise for precision medicine, which in turn offers innovative strategies that can transform PCOS patient care and results.

5.1 Nanotherapeutics in PCOS

Nanotechnology is used in nanotherapeutics to introduce drug delivery methods, which in turn improve safety, efficacy, and targeting of treatment in a complex clinical condition. Polycystic Ovary Syndrome is a common yet difficult-to-treat condition that presents issues like poor target specificity, large-scale adverse effects, and poor absorption of drugs from the system. But with nanotherapeutic approaches, that a way to deliver the meds right to the affected areas in the body, like the ovaries, fat tissue, and endocrine structures, which in turn should improve the health results of the patient while at the same time reducing unwanted side effects. [21].

5.1.1 Targeted Delivery of Insulin Sensitizers

PCOS consists of hyperandrogenism, metabolic complications, and insulin resistance. There are insulin-sensitising medications such as metformin and thiazolidinediones that can be used for encapsulation in liposomes, polymeric nanoparticles, liposomal nanoparticles, and solid lipid nanoparticles for insulin resistance targeted delivery. It increases the concentration of the drug in the insulin-resistant liver, adipose, and skeletal muscle, enhances the bioavailability, increases therapeutic efficacy while reducing the detrimental effect on other organ systems, and consequently, alleviates the metabolic, reproductive, and insulin disorders.

5.1.2 Delivery of Antioxidants

Owing to its role in follicular development and oocyte quality, which in turn affects the pathophysiology of PCOS. Some antioxidant-containing nanocarriers are highly

effective in targeting the ovary, for instance, those with vitamin E, quercetin, and resveratrol. And the improvement in ovarian function from these nanocarriers, which also ensures that the classical therapies' performance is enhanced, which in turn indicates sustainability in the improved function of the ovaries. The improved ovarian functions are also a result of classical therapies, which in turn note improvements which also attributed to the nanocarriers' role in reducing the accumulation of reactive oxygen species (ROS) and in the provision of a constant level of antioxidant action. [22].

5.1.3 Anti-Androgen Nanotherapy

Hyperandrogenism is a hallmark feature of PCOS that leads to hirsutism, acne, and alopecia. Nanoparticle delivery of anti-androgen drugs flutamide and spironolactone allows intense local action on the ovary or peripheral tissue. This reduces the negative effects of systemic exposure and efficiently reduces androgens.

5.1.4 Significance of Nanotherapeutics

Nanotechnology in the field of PCOS presents solutions to the complex issues of the disease through targeted, controlled, and extended drug delivery. These tools improve drug performance, which reduces side effects and also supports combined therapy for androgen excess, insulin resistance and oxidative stress [23]. In the case of PCOS treatment with nanotechnology are present, move toward individualised treatment plans which cater to each affected woman's unique metabolic and reproductive issues, thus indicating a major step forward in the fields of personal and precision medicine.

5.2 Nanotherapeutics in PCOS

In the area of nanotechnology, the development of drug delivery methods, which in turn improves the accuracy, efficacy, and safety of therapeutic interventions that may be termed nanotherapeutics. For PCOS, which has up till now seen nonspecific tissue targeting, large-scale side effects, and low bioavailability from conventional treatments, the issue of poor results persists. What nanotherapeutic does is allow for site-specific delivery, regulated release, and better absorption of therapeutic agents, which include insulin sensitisers, antioxidants, and anti-androgens, thus in that regard ameliorating the above-mentioned issues.

5.2.1 Targeted Delivery of Insulin Sensitizers

One of the most important pathological characteristics in PCOS is insulin resistance. It creates further complications with metabolic dysregulation, hyperandrogenism, and hyperinsulinemia. Medications that improve insulin sensitivity, such as metformin and thiazolidinediones, have been studied with nanosystems like liposomes, polymeric nanoparticles, and solid lipid nanoparticles. Besides customised distribution aimed at insulin-resistant tissues, these nanosystems improve therapeutic absorption, prolong circulation times, minimise systemic exposure, and reduce hyperandrogenism. Overall,

this approach improves glucocentric control and alleviates the metabolic and reproductive dysfunctions of PCOS [24,25].

5.2.2 Delivery of Antioxidants

Insulin resistance is one of the pathological hallmarks of PCOS. It complicates metabolic dysregulation along with hyperandrogenism and hyperinsulinemia. Insulin-sensitising medications like metformin and thiazolidinediones are used with liposomes, polymeric and solid lipid nanoparticles, and other therapeutic nanosystems. In addition to improved therapeutic absorption, extended circulation, reduced systemic exposure, and decreased hyperandrogenism, tailored distribution towards insulin-resistant tissues is beneficial. This strategy improves glucocentric control and provides relief from the metabolic and reproductive dysfunctions of PCOS.

5.2.3 Anti-Androgen Nanotherapy

Alopecia, acne, and hirsutism are but a few of the clinical signs of PCOS that result from hyperandrogenism. Anti-androgen drugs like flutamide or spironolactone, which via nanocarrier-mediated delivery may be targeted precisely to ovarian or peripheral tissues. This approach reports a decrease in circulating testosterone levels, improves drug efficacy and may also help to reduce adverse effects like hepatotoxicity, which is seen with traditional flutamide therapy [26].

5.3 Integrated Theranostics in PCOS

The treatment of Polycystic Ovary Syndrome (PCOS) is pushed to the next level by integrated theranostics which involves merging the diagnostic and the therapeutic features into one single platform. Unlike traditional methods, which are based on a sequence of diagnosis and then treatment, the integrated systems allow for the simultaneous detection, monitoring, and targeted therapy, which makes the whole process of illness management more precise and personalized. This integration works really well for PCOS because it is a case of intertwined hormonal, metabolic, and ovarian problems that are very complicated[27].

5.3.1 Combined Diagnostic-Therapeutic Platforms

The base of integrated theranostics is nanotechnology, which puts out the production of multipurpose nanoparticles that can do diagnosis and treatment. For example, nanoparticles are designed to release insulin sensitizers or anti-androgen meds at the same time they are detecting high insulin or androgen levels, which have been seen in experimental models and which put us on a path toward real-time clinical application.

5.3.2 Mechanisms and Advantages

At the base of integrated theranostics nanotechnology, which is responsible for the production of multipurpose nanoparticles that perform diagnosis and treatment. That is the design of nanoparticles to release insulin sensitizers or anti-androgen drugs at the

same time they are detecting high insulin or androgen levels, which are reported in experimental models and which put on a path toward real-time clinical application [28].

The advantages include:

- Early detection and continuous monitoring of hormonal and structural abnormalities
- Enhanced drug efficacy through targeted and controlled release
- Reduced systemic toxicity and adverse effects
- Personalized treatment strategies based on real-time physiological data

5.3.3 Clinical Implications

The issue of PCOS' complexity is addressed by a single platform that puts diagnosis and treatment together; this in turn targets metabolic and reproductive breaks at the same time. Puts forth tailored treatments which improve ovarian function, correct hormone imbalances, reduce oxidative stress, and manage insulin resistance, thus are able to practice precision medicine. In terms of transforming PCOS management, are great promise as integrated theranostic research reports with comprehensive patient-specific solutions, which in turn improve therapy results and the long-term picture [29,30].

6. PERSONALIZED NANOMEDICINE FOR PCOS

One of the greatest varieties of what women's health issues present, Polycystic Ovarian Syndrome (PCOS) does so in a wide array of reproductive, metabolic, and psychosocial ways. It is because of this large spectrum of symptoms that the "one size fits all" approach to treatment does not do the best job and, in some cases, causes serious side effects. To that end, which is on the pursuit of creating treatment plans that are based on each person's unique genetic and clinical make-up that are Personalised Nanomedicine steps in as a game changer. In this section, look at how nanotechnology, biomarker identification, AI, and multi-omics are coming together to bring in a new age of very precise PCOS treatments [31].

6.1 The Concept of Individualized Therapy in PCOS

Individualised therapies are put in place to address the root causes, which are unique to each patient, and go beyond just symptom control. For instance that in severe insulin resistance, which is the main issue in one case of PCOS, in another, the hyperandrogenism may be due to the adrenal glands and in a third, it is chronic inflammation. This is made possible by nanomedicine, which in turn enables us to develop very specific drug delivery systems, which in turn may be liposomes, polymeric nanoparticles, and dendrimers [32]. To provide targeted and customized

therapy, one can attach a drug (e.g., a small interfering RNA directed against one of the key steroidogenic enzymes) at the site of the pathology to limit the systemic side effects. Systemic side effects can be further reduced if the drug, loaded in a nanoparticle, is modified with a ligand that binds to receptors overexpressed in the ovarian theca cells of a hyperandrogenic patient.

6.2 Biomarker-Driven Selection of Treatment.

The remarkable finding of biomarkers that divide patients into distinct endotypes is a precondition for an effective personalized nanomedicine. These biomarkers can be genetic (for example, genetic variants associated with steroidogenesis or insulin signalling), metabolic (for instance, adipokine profiles, particular miRNA signatures in blood circulation), or hormonal (for example, certain androgen ratios, AMH). To illustrate, an anti-inflammatory nanoparticle (like the one containing curcumin or metformin) targeted for accumulation in the visceral fat area can be recommended to a patient with a notably high level of an inflammatory biomarker, for example, IL-6 or TNF-α. Another patient with a particular miRNA signature indicating severe metabolic failure may receive a different treatment with nano-based insulin sensitizers. This strategy not only ensures the right drug goes to the right patient but also greatly amplifies the success rate of the treatment [33].

6.3 AI/Machine Learning in Personalizing Nanomedicine.

Advanced computational tools are required because of the complexity of PCOS and the large patient datasets (clinical, biomarker, and omics). Machine learning (ML) and artificial intelligence (AI) are essential for:

- **Patient stratification:** By analysing multi-omics data, unsupervised machine learning techniques (such as clustering) can discover new PCOS subtypes that go beyond the existing Rotterdam criteria, resulting in data-driven endotypes.
- **Predictive Modelling:** By using a person's biomarker profile to forecast how they will react to a particular nanotherapy, supervised machine learning algorithms can optimise treatment selection before administration.
- **Nanoparticle creation:** By forecasting the ideal size, surface charge, and material composition for targeting a particular cell type (granulosa vs. theca cells, for example) or for overcoming biological obstacles, artificial intelligence (AI) might speed up the creation of nanoparticles, therefore personalizing the "vehicle" itself [34].

6.4 Multi-Omics Approaches for Target Discovery.

A comprehensive understanding of the molecular abnormalities in PCOS is offered by multi-omics, which is the integrative study of genetics, transcriptomics, proteomics, and metabolomics. This catalyzes the discovery of new nanomedicine targets and biomarkers. For example:

- **Genomics/Transcriptomics:** In ovarian tissues from particular PCOS subtypes, elevated genes or pathways can be found using genomics and transcriptomics.

- **Proteomics/Metabolomics:** In serum or follicular fluid, proteomics/metabolomics can identify correspondingly changed proteins and metabolites. The design of nanomedicine can be directly influenced by these findings. The target of ligand-decorated nanoparticles is an overexpressed protein on the surface of a target cell. An inhibitor encapsulated in nanoparticles targets an intracellular enzyme that is dysregulated. The roadmap for creating the customized treatment is provided by multi-omics [35,36].

7. EXPERIMENTAL MODELS FOR PCOS: *IN-VITRO*, *IN-VIVO*, *EX-VIVO*.

The development of successful PCOS treatments, which also include the very forefront of research like nanomedicine, depends on our disposal in terms of research models. Do not have a single model which can do justice to the complexity of the human syndrome. To clarify pathogenic mechanisms, to screen therapeutic options, and to determine the safety and efficacy of novel nano formulations before them are used in clinical use require a multi-pronged approach that uses *in vitro*, in vivo, and *Ex vivo* systems..

7.1 *In-vitro* Models: Granulosa/Theca Cell Models, Organoids, Lab-on-Chip.

- **Primary Cell Cultures:** The investigation of cell-type-specific responses requires isolated human or rodent granulosa and theca cells. They are employed to study insulin signalling, steroidogenesis, and the direct impacts of nanotherapeutics on cell division and hormone synthesis. They do not, however, have the follicle's intercellular communication or architectural framework [37].

- **Organoids:** A revolutionary model is 3D ovarian follicle organoids made from primary tissue or stem cells. They can be used to examine paracrine signalling between granulosa, theca, and oocytes because they self-organise to replicate the follicular milieu. They are perfect for investigating the penetration and targeted delivery of nanoparticles inside intricate three-dimensional structures.

- **Lab-on-Chip (Microfluidics):** These gadgets precisely control fluid flow, hormone gradients, and mechanical stimuli by micro-engineering the ovarian environment. To investigate the systemic features of the disease and the kinetics of nanoparticle transport, a "PCOS-on-a-chip" model that combines ovarian cells with endothelial cells under hyperinsulinemic and hyperandrogenic circumstances could be used [38].

7.2 *In-vivo* Models: Rodent PCOS Models and Nanomedicine Testing.

For the study of systemic medication effects and integrated physiology, rodent models are essential.

- **Common Induction Techniques:** Prepubescent rats or mice are utilized to create the most popular models by:
    - Androgen Exposure: Giving dihydrotestosterone (DHT) or dehydroepiandrosterone (DHEA) during pregnancy or after delivery to cause hyperandrogenism and anovulation.
    - Aromatase Inhibitor: Administration of letrozole inhibits the synthesis of estrogen, resulting in polycystic ovaries and hyperandrogenism.
    - Combined Models: to simulate the metabolic phenotype, for example, DHT exposure coupled with a high-fat diet.
- **Testing Nanomedicine:** The effectiveness of nano-formulations in vivo is assessed using these models. Restoring oestrous cyclicity, lowering blood androgen levels, improving insulin sensitivity (for example, through glucose tolerance testing), and evaluating ovarian morphology are important criteria. Importantly, pharmacokinetic and biodistribution experiments employing fluorescent or radiolabelled nanoparticles can be conducted in *in vivo* animals to verify both off-target accumulation and targeted delivery to the ovary [39].

7.3 *Ex vivo* Models: Ovarian Tissue Culture, Precision-Cut Slices

Ex vivo models serve as a link between *in vivo* complexity and *in vitro* reductionism.

- **Ovarian Tissue Explant Culture:** PCOS-model rodents or fresh ovarian tissue from PCOS patients (such as following wedge resection) can be cultivated for a brief period of time. All cell types and the extracellular matrix are preserved along with the natural tissue architecture. It is an effective platform for high-throughput drug testing that enables direct evaluation of the effects of a nano-formulation on gene expression and hormone secretion in a setting analogous to humans [40].
- **Precision-Cut Ovarian Slices (PCOLS):** This technique ensures excellent nutrition and oxygen diffusion for extended culture viability by preparing homogeneous, thin slices of ovarian tissue using a vibratome. The effectiveness and penetration of a nano-formulation in intact tissue from a specific PCOS model can be directly compared to that of its traditional free-drug equivalent using PCOLS, a superior *ex vivo* platform [41,42].

Table 5.2: Comparative overview of *in vitro*, *in vivo*, and *ex vivo* models employed in PCOS nanomedicine research. The table highlights representative examples of each model type, their core applications in theranostic evaluation, and their role in bridging experimental findings to personalized medicine approaches.

Nano-platform / Payload	Particle Size (approx.)	Model (*In-vitro* / *In-vivo* / *Ex-vivo*)	Dose/Regimen	Key Readouts	Main Outcomes
Curcumin SNEDDS (self-anoemulsifying)	n/r (SNEDDS typically <200 nm)	*In-vivo*: Letrozole + high-fructose rat PCOS	25–100 mg/kg (vs metformin 20 mg/kg)	Estrous cycle, ovarian histology, metabolic indices	Improved ovarian morphology & metabolic profile; superior/competitive to metformin arm
Curcumin self-assembled NPs (Arg-CS-NAcHis/Cur)	~150–250 nm (typical for chitosan NPs; study reports nano-range)	*In-vitro* GCs → *In-vivo* rat PCOS	Study-specific (therapeutic dosing post-characterisation)	Cell uptake, cytokines/ROS; ovarian histology in animals	Reversed multiple PCOS-like symptoms; favourable cytocompatibility
Quercetin (nano/solution forms across studies)	n/r	*In-vivo*: DHEA-induced rat PCOS	100 mg/kg daily gavage	Serum T, E2, LH/FSH, FSH; follicular counts	↓Testosterone & LH/FSH; ↑FSH; restoration of follicles & estrous rhythm
Exosome-based therapy (MSC-EVs)	30–150 nm	*Ex-vivo* / *In-vitro*: human/animal GCs; *In-vivo* in some models	Model-dependent; typically µg EV protein	TNF-α, IFN-γ, IL-10; GC survival/phenotype	Rescued pro-inflammatory state; shifted cytokines to an anti-inflammatory profile
Nanobiosensors (SPRi gold chip for FSH)	n/a (sensor uses nanogold surface)	*Ex-vivo*/*In-vitro* diagnostics	Analytical assay	LOD/LOQ; FSH dynamic range	Sensitive FSH detection in plasma-building block for PCOS panels
Metformin nano-delivery (chitosan-	~100–300 nm (typica	Preclinical (various)	Formulation-specific	PK/half-life; bioavailability; glycemic control	Encapsulation prolongs half-life & improves bioavailability,

based; concept & prototypes)	l; varies)				potentially lowering dose/side-effects
Curcumin-loaded iron NPs	n/r	Preclinical (cell/animal ovarian injury models)	Formulation-specific	Apoptosis markers; ovarian cell injury	Curcumin-iron NPs inhibit apoptosis; potential relevance to PCOS ovarian injury
Selenium NPs (Se-NPs)	50–200 nm (typical)	*In-vivo* rodent PCOS	Study-specific	Lipids; testosterone; oxidative stress	↓Cholesterol & testosterone vs metformin in some reports; antioxidant benefits
Electrochemical nano-biosensors for PCOS hormones (AuNPs, graphene, etc.)	n/a	Point-of-care diagnostics (bench prototypes)	Assay-specific	LH/FSH/AMH sensitivity; turnaround time	Progress toward low-cost POC panels; potential for wearables integration
PCOS-exosome miRNA signatures (e.g., ↓miR-128-3p)	EV 30–150 nm	*In-vivo*/*In-vitro*: mouse/human samples	Observational/functional	Ferroptosis markers; GC health	PCOS EXOs can induce GC ferroptosis; biomarker & therapeutic target space
Microbiome/ BEV-linked nano-approaches (review)	n/a	Cross-cutting	n/a	Systems-level biomarkers	BEVs + AI for phenotyping/personalization in PCOS

8. CLINICAL TRANSLATIONS AND CHALLENGES

Nanomedicine in reproductive health faces clinical translation issues due to still-existing gaps between preclinical discoveries and practical applications. Among the difficulties are the variability in biological responses, the absence of standardised protocols, and the problem of getting lab results applied in clinics. These hurdles must be cleared for patient results to be safe, efficient and reproducible.

8.1 Current status of nanomedicine in reproductive health

With its highly targeted diagnostic and treatment tools for diseases like infertility, polycystic ovarian syndrome (PCOS), endometriosis, uterine fibroids, and reproductive malignancies, nanomedicine has become a game-changer in the field of reproductive health. In the field of growth of imaging tools that do better at what nanoparticles do, they improve the sensitivity and resolution of MRIs and ultrasounds, and also identify at an early stage. Also in the area of targeted drug delivery, nanoparticles act as a

platform that increases the accuracy of the therapy and, at the same time, decreases the system-wide adverse effects. Also, in gene therapy and RNA interference (RNAi) that nanotech is a great tool that allows for more personalised treatments that go after the genetic causes of reproductive issues. While at this stage they are in the early stages and require more validation, what and also seen is that the clinical studies for nano-based diagnostics and treatments in reproductive health are on the rise [43].

8.2 Safety, toxicity and regulatory issues

Clinical adoption is delayed by serious safety and toxicity issues, which in turn do not do justice to the product's great promise. Some nanomaterials are producers of oxidative stress and free radicals, which in turn cause damage to ovarian cells, disrupt oocyte development, and play a role in fertility issues. Also brought up are issues of fetal safety and the attribute known yet of nanomaterials' translocation across the placenta, which in turn calls for in-depth toxicology research. Because nanomedicines present with different physical and chemical features, which also play into very complex production processes, which in turn cause a lot of bio-interaction, regulatory bodies have a tough time in standardizing evaluation methods [44]. These issues play a role in what makes for a difficult approval process, which in turn requires in-depth safety research, repeatability, and strong quality control before these products are used in the clinical setting.

8.3 Ethical considerations in women's health

Strict ethical oversight is needed when it comes to the use of nanomedicine in women's reproductive health. It that informed consent is obtained and that reduce the risk to pregnant women and fetus which given the very sensitive nature of reproductive tissue and the fact that interventions may have transgenerational results are also to pay great attention to. In the case of health equity issues that play out along lines of socioeconomic status or geography, the ethical frameworks put into play must address fair access to modern nanotech-based drugs. Also, for the issue of trust, have open and free communication of pros, cons and uncertainties. To protect which are the vulnerable groups that require post-market surveillance and large-scale follow-up research in turn will be determined the results will also which will bring to light any unexpected negative results. [45]. To do the best by and do the least harm, that have ethics at the fore of the development and clinical use.

9. FUTURE PERSPECTIVES

Advanced gene editing technologies like CRISPR, wearable device integration, and AI-driven multi-omics platforms are all combining to shape the future of reproductive nanomedicine by providing new levels of accuracy and customisation in reproductive health care.

9.1 Integration with Wearable Devices & Digital Health

Real-time tracking of reproductive health biomarkers is a feature of wearable and digital health technologies which in turn use nanosensors and nanomaterials. In this also a very early and accurate diagnosis of infertility, PCOS, endometriosis, and reproductive cancer is made possible by the very sensitive and specific results that nanosensors report. Also, these wearables supply continuous, personal health data, which in turn greatly improve patient results by way of dynamic therapy modification and early disease relapse diagnosis [46].

9.2 CRISPR/Nanoparticle-Based Gene Editing

CRISPR is reshaping gene editing and enables targeted changes to heal inherited reproductive challenges and boost assisted reproduction, thus greatly improving reproductive care. Delivery of CRISPR tools via nanoparticles has improved the specificity and efficacy of these tools, which in turn reduces off-target effects in reproductive tissues. As CRISPR's therapy use, which includes repair of germline mutations and improvement of embryo editing, is still in development, at the same time, issues of safety, delivery and ethical regulation come up, which in particular play out in gene therapy that goes into clinical trial [47, 48].

9.3 Multi-Omics & AI-Driven Precision Nanomedicine

Artificial intelligence (AI) plays a significant role in the integration and interpretation of various layers of omics data, including genomics, transcriptomics, proteomics, and metabolomics, which can characterize the reproductive problems and promote the innovations in reproductive research and clinical treatment of diseases. By a combination of different data sources, AI can also detect disease biomarkers, foresee the effects of medications and make treatment more tailored. These combinations of technologies have brought diagnosis closer and given a boost to personalized medicine but have also raised significant issues concerning privacy, ethics, and data standardization. Apart from the necessity to research and deploy security measures, the ethical use of these advancements will demand the study of new regulatory frameworks. Innovations that encompass all the above-mentioned, can be a great leap in the area of reproductive nanomedicine that would result in dynamic disease management, complete personalization of care, and a rise in the therapeutic options available [49-52].

CONCLUSION

PCOS, which also includes the term polycystic ovary syndrome, is a very in-depth health issue that requires out-of-the-box solutions beyond what has been done thus far. With their ability to put forward safe, personalized and targeted interventions which integrate diagnosis with treatment into the same platform, nanomedicine and theranostic approaches are a great step forward. We can do away with the one-size-fits-all approaches by means of the use of tailored nanotherapeutics, which in turn use biomarkers, AI, and multi-omics to address each patient's unique pathophysiology. This is a simplified version for clarity and conciseness, and should fit your request. It is also available for adjustment if you have other instructions. If there is more than one request, more than one response is provided.

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