

## Polycystic Ovary Syndrome: A Multifaceted Enigma

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**Abbreviations**

PCOS : Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is the most common form of ovulatory dysfunction, affecting up to 8% of the population worldwide, or over 100 million women [1-3]. While subject to some controversy, it is diagnosed most frequently by the Rotterdam criteria, which includes irregular menses, laboratory or clinical evidence of hyperandrogenemia, and polycystic ovarian morphology. The diagnosis may be made if a patient has at least two of these criteria, and other possible etiologies are excluded, such as prolactin or thyroid disorders [3]. One needs only to consider the history of the diagnosis of PCOS for a glimpse of the complex nature of this disease. Up to present day, medical professionals and organizations have engaged in contentious debate as to the best way to characterize and define this heterogeneous cohort of patients [4,5]. As an example, the finding of polycystic ovarian morphology on ultrasound exists in a large proportion of women without PCOS, and may in these scenarios be normal [6,7]. Thus, some have argued for more weight placed on the criteria of menstrual regularity or hyperandrogenemia [1].

Hyperandrogenemia may be the most essential component of the Rotterdam criteria; not only due to the poor sensitivity and specificity of polycystic ovarian morphology and broad differential diagnosis of oligo-ovulation, but also due to the inherent pathology due to increased androgen production in an affected female. Hyperandrogenemia from PCOS stems from increased ovarian and adrenal androgen synthesis as well as decreased production of sex hormone binding globulin, resulting in a surplus bioavailability [8]. Downstream effects include alterations in enzymes in the steroid pathway [9-12], and the hypothalamic-pituitary axis [13-15], just to name a few. Further, clinical manifestations of hyperandrogenemia include hirsutism and virilization which cause significant morbidity for patients and can prove to be quite difficult to treat [16].

Despite any controversy in the diagnosis, it remains an important disease to recognize as it carries with it an array of associated risks and comorbidities [17]. PCOS patients have increased risk of chronic metabolic derangements such as hypertension, hyperlipidemia, obesity, and diabetes mellitus which ultimately lead to long term complications such as cardiovascular and renal disease. Patients also have increased risk of depression and anxiety, further affecting their quality of life [18]. Additionally, there is an increased risk of certain cancers, such as endometrial cancer, likely due to anovulation and unopposed estrogen effects. Reproductive physiology is affected as well, with research showing increased incidence of infertility, higher rates of miscarriage [19,20], and significant obstetric risks including preeclampsia, gestational diabetes, preterm delivery, higher neonatal intensive care unit admission, and overall infant mortality [17].

From a research standpoint, PCOS is a fascinating subject, though fraught with difficulty, as it represents a wide array of endocrinopathy leading to its phenotype. PCOS may be described as the common endpoint of several metabolic disturbances, including but not limited to aberrant hypothalamic-pituitary-ovarian signaling, insulin resistance and glucose intolerance, obesity and the metabolic syndrome, hyperandrogenism, environmental and genetic factors, among several others [1,21,22]. This diverse array of pathology provides a helpful illustration of the difficulty inherent in looking at this population.

While this makes PCOS a topic of great interest, it also requires a high level of scrutiny and scientific rigor. There are many contradictory and conflicting studies in the field of PCOS, and this may be in large part due to its heterogeneity. When diagnostic criteria are debated, and patients do not share all the same baseline pathology, confounders are inherently introduced that will skew any results [23]. The quintessential example in the case of PCOS is obesity [24]. Approximately 60-80% of PCOS patients are obese, and obesity has well documented adverse outcomes independent of PCOS, though similar to those listed

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above [24-26]. If obesity is not well controlled for in any PCOS study, there is an obvious potential for inappropriate conclusions. Other confounders exist of course, and will vary depending on the PCOS population being studied, the control population gathered, and the outcomes that are being investigated.

One avenue of study that has been gaining traction recently involves the mitochondria. Recent studies have suggested that PCOS may have an adverse effect on mitochondrial physiology in these patients, which could in part explain some of the phenotype [9,27-31]. This exciting field of research has several implications. First, it may in part explain the adverse fertility and obstetric outcomes seen in these patients. The oocyte is the largest cell in the body, and the mitochondria is the most abundant organelle in that cell. During folliculogenesis, the mitochondria replicated to up to 100,000 or more in number, but from ovulation through fertilization and to implantation, remain quiescent [32-34]. This means that the ovarian environment during the development of an oocyte is critical for the development of competent mitochondria to supply a newly formed preimplantation embryo with enough energy substrate to survive, divide, and grow for days. If there is any compromise to this delicate process, it must only end in cell death and termination of any potential pregnancy.

Further, the method of transmission of mitochondria provides a unique explanation for the inheritance pattern of PCOS. To date, it is well known that PCOS displays some inheritance, thought genetic and epigenetic studies have not been able to uncover any significant candidate genes to explain this, other than a rare few in small cohorts [35-37]. However, recent studies have shown that abnormal mitochondria in the oocytes of mothers may be passed on to offspring with similar phenotypes displayed in the affected progeny, even with no further interventions. These alterations may exist even into the F3 and F4 generations [38]. This example of developmental programming stresses the importance of addressing good health in these patients prior to conception.

In summary, PCOS is a common disease that affects millions of women worldwide and is associated with many comorbidities throughout a patient's life. Despite numerous studies on the disease, many questions remain unanswered and this is in part due to the complex nature of the disease. Future studies focused on strict definitions of PCOS, with rigorous control of potential confounders, asking solid foundational questions to the mechanisms of pathology in place will be instrumental in cracking the code of this multi-faceted pathology. Finding out who these patients are, and how they are different from the general population, and each other, is key in finally understanding what the field of medicine can do to mitigate the risks present in PCOS. Finally, the burgeoning field of mitochondrial biology in PCOS has shown promise in answering some important foundational questions regarding the pathophysiology and has potentially opened a door to explaining the inheritance pattern.

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