Polycystic Ovary Syndrome: A Multifaceted Enigma

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 heterogenous 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].

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.

Keywords
Polycystic Ovary Syndrome; PCOS; Hyperandrogenism

Abbreviations
PCOS: Polycystic Ovary Syndrome

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*Corresponding author:
Blesson CS
Baylor College of Medicine
Reproductive Endocrinology and Infertility Division
Department of Obstetrics and Gynecology
6651 Main Street, Suite 1050
Houston, Texas 77030
Tel: 832-826-7462
Fax: 832-825-7910
E-mail: selvanes@bcm.edu

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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 mechanism 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 even persist 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 asking solid foundational questions regarding the pathophysiology and has potentially opened a door to explaining the inheritance pattern.

References
1. Azziz R. Introduction: Determinants of polycystic ovary syndrome. Fertil Steril. 2016 Jul;106(1):4-5.
2. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007 Aug;370(9588):685-697.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004 Jan;81(1):19-25.
4. Goodman NF, Cobin RH, Futterweit W, Glaeser JS, Legro RS, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome—Part 1. Endocr Pract. 2015 Nov;21(11):1291-1300.
5. Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, et al. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. Fertil Steril 2017 Jun;107(6):1380-1386.
6. Johnstone EB, Rosen MP, Neril R, Trevithick D, Sternfeld B, et al. The polycystic ovary post-rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. J Clin Endocrinol Metab. 2010 Nov;95(11):4965-4972.
7. Sigala J, Sifer C, Dewailly D, Robin G, Bruyneel A, et al. Is polycystic ovarian morphology related to a poor oocyte quality after controlled ovarian hyperstimulation for intracytoplasmic sperm injection? Results from a prospective, comparative study. Fertil Steril. 2015 Jan;103(1):112-118.
8. Fritz MA, L Speroff. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. 2011 May;1439p.
9. Hickey TE, Marrocco DL, Amato F, Ritter LJ, Norman RJ, et al. Androgens augment the mitogenic effects of oocyte-secreted factors and growth differentiation factor 9 on porcine granulosa cells. Biol Reprod. 2005 Oct;73(4):825-832.
10. Hillier SG, van den Boogaard AM, Reichert LE Jr, van Hall EV. Intraovarian sex steroid hormone interactions and the regulation of follicular maturation: aromatization of androgens by human granulosa cells in vitro. J Clin Endocrinol Metab. 1980 Apr;50(4):640-647.
11. Ma Y, Andrisse S, Chen Y, Childress S, Xue P, et al. Androgen Receptor in the Ovary Theca Cells Plays a Critical Role in Androgen-Induced Reproductive Dysfunction. Endocrinology. 2017 Jan;158(1):98-108.
12. Yang F, Ruan YC, Yang YJ, Wang K, Liang SS, et al. Follicular hyperandrogenism downregulates aromatase in luteinized granulosa cells in polycystic ovary syndrome women. Reproduction. 2015 Oct;150(4):289-296.
13. Morciano A, Romani F, Sagnella F, Scarcini E, Palla C, et al. Assessment of insulin resistance in lean women with polycystic ovary syndrome. Fertil Steril. 2014 Jul;102(1):250-256.
14. Xita N, Tsatsoulis A. Review: fetal programming of polycystic ovary syndrome by androgen excess: evidence from experimental, clinical, and genetic association studies. J Clin Endocrinol Metab. 2006 May;91(5):1660-1666.
15. Yildizhan B, Anik Ihan G, Pekin T. The impact of insulin resistance on clinical, hormonal and metabolic parameters in lean women with polycystic ovary syndrome. J Obstet Gynaecol. 2016 Oct;36(7):1-4.
16. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, et al. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab. 2004 Feb;89(2):453-462.
17. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health. 2015 July;7:745-763.
18. Cooney LG, Dokras A. Depression and Anxiety in Polycystic Ovary Syndrome: Etiology and Treatment. Curr Psychiatry Rep. 2017 Sep;19(11):83.
19. Liu L, Tong X, Jiang L, Li TC, Zhou F, et al. A comparison of the miscarriage rate between women with and without polycystic ovarian syndrome undergoing IVF treatment. Eur J Obstet Gynecol Reprod Biol. 2014 May;176:178-182.
20. Luo L, Gu F, Jie H, Ding C, Zhao Q, et al. Early miscarriage rate in lean polycystic ovarian syndrome women after euploid embryo transfer - a matched-pair study. Reprod Biomed Online. 2017 Nov;35(5):576-582.
21. Baskind NE, Balen AH. Hypothalamic-pituitary, ovarian and adrenal contributions to polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2016 Nov;37:80-97.
22. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011 Apr;7(4):219-231.
23. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2016 Dec;31(12):2841-2855.

24. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity’s impact. Fertil Steril. 2017 Apr;107(4):840-847.

25. Bailey AP, Hawkins LK, Missmer SA, Correia KE, Yanushpolsky EH. Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome. Am J Obstet Gynecol. 2014 Aug;211(2):163.

26. Cardozo E, Pavone ME, Hirshfeld-Cytron JE. Metabolic syndrome and oocyte quality. Trends Endocrinol Metab. 2011 Mar;22(3):103-109.

27. Huang Y, Yu Y, Gao J, Li R, Zhang C, et al. Impaired oocyte quality induced by dehydroepiandrosterone is partially rescued by metformin treatment. PLoS One. 2015 Mar;10(3).

28. Wataru Tarumi, Masanori T, Itoh, Nao Suzuki. Effects of 5alpha-dihydrotestosterone and 17beta-estradiol on the mouse ovarian follicle development and oocyte maturation. PLoS One. 2014 Jun;9(6).

29. Tarumi W, Tsukamoto S, Okutsu Y, Takahashi N, Horiuchi T, et al. Androstenedione induces abnormalities in morphology and function of developing oocytes, which impairs oocyte meiotic competence. Fertil Steril. 2012 Feb;97(2):469-476.

30. Walters KA. Role of androgens in normal and pathological ovarian function. Reproduction. 2015 Apr;149(4):193-218.

31. Walters KA, Allan CM, Handelsman DJ. Androgen actions and the ovary. Biol Reprod. 2008 Mar;78(3):380-409.

32. Babayev E, Seli E. Oocyte mitochondrial function and reproduction. Curr Opin Obstet Gynecol. 2015 Jun;27(3):175-181.

33. St John JC, Fauchoto-Oliveira J, Jiang Y, Kelly R, Salah R. Mitochondrial DNA transmission, replication and inheritance: a journey from the gamete through the embryo and into offspring and embryonic stem cells. Hum Reprod Update. 2010 Sep;16(5):488-509.

34. Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion. 2011 Jan;11(5):797-813.

35. Hayes MG, Urbanek M, Ehrmann DA, Armstrong LL, Lee JY, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun. 2015 Aug;6:7502.

36. Liu H, Zhao H, Chen ZJ. Genome-Wide Association Studies for Polycystic Ovary Syndrome. Semin Reprod Med. 2016 Jul;34(4):224-229.

37. Zhao H, Lv Y, Li L, Chen ZJ. Genetic Studies on Polycystic Ovary Syndrome. Best Pract Res Clin Obstet Gynaecol. 2016 Nov;37:56-65.

38. Saben JL, Boudoures AL, Aghbar Z, Thompson A, Drury A, et al. Maternal Metabolic Syndrome Programs Mitochondrial Dysfunction via Germline Changes across Three Generations. Cell Rep. 2016 Jun;16(1):1-8.