Editorial 2

Polycystic Ovary Syndrome: From *in utero* to Menopause

INTRODUCTION

The syndrome of polycystic ovaries is typically diagnosed during the adolescent period or during the reproductive years, when the patients present with menstrual irregularities and evidence of hyperandrogenism. However, data from animal models and epidemiological studies indicate that development of this disorder may be influenced by genetic and environmental factors that occur during early life.

There is significant variability in the phenotypic expression of polycystic ovary syndrome (PCOS) (Table 1). Weight loss, particularly induced by bariatric surgery and treatment with insulin sensitizers, can ameliorate the phenotype of PCOS from a severe form expressing all the three criteria included in Rotterdam consensus, to a milder phenotype expressing only one or two of the clinical features. On the contrary, obesity is known to worsen the phenotypic expression of PCOS. Hence, environmental and epigenetic factors may modify and affect the phenotypic presentation of PCOS independent of the underlying genetic predisposition. Fetal exposure to androgens and low-birth weight has been positively associated with development of PCOS in later life. This improved understanding has allowed us to characterize the phenotype of PCOS in these earlier years. The expression of PCOS may begin early and the symptoms and signs of the disease changes across the lifespan of the individual. During the prepubertal and adolescent period, hyperandrogenism predominates the phenotype of PCOS; the spectrum expands to include reproductive dysfunction along with hyperandrogenism during later fears up to menopause; following menopause, the persistent metabolic derangements appear to be the most pronounced phenotypic expression.

Table 1: Summary of proposed criteria for polycystic ovary syndrome

Criteria	*Rotterdam (2 out of 3)*	*National Institute of Health*	*Androgen excess society (AES)*
Hyperandrogenism clinical or biochemical	May be present	Should be present	Should be present (along with 1 of the 2 remaining criteria)
Oligoanovulation	May be present	Should be present	May be present
Polycystic appearance of ovaries	May be present	May be present	May be present

GENETICS OF PCOS

Around 20 to 40% of first degree female relatives are known to be affected by the PCOS.[4] The PCOS seems to be a complex genetic disorder, such as type 2 diabetes mellitus, wherein several genetic variants are present and each contributes to a modest effect along with environmental factors known to affect expression of the disease.

Currently, only a few PCOS susceptibility genes have been identified repeatedly replicating initial associations found in independent cohorts.[5,6] These genes are: fibrillin-3 (FBN3), DENN/MADD domain containing 1A (DENND1A), pro-opiomelanocortin (POMC), and luteinizing hormone receptor (LHR). Genes for which well-conducted replication studies failed to confirm the association found initially are: cytochrome p450 side-chain cleavage enzyme (CYP11A), insulin, and aldo-keto reductase family 1 member c3 (AKR1C3), also known as the 17β-hydroxysteroid dehydrogenase type 5 gene. However, in most of the studies, majority of patients with PCOS were found to be negative for a genetic variant involving the aforementioned genes. This favors the polygenic theory proposed for origin of PCOS with or without accompanying developmental environmental factors.

IN UTERO FETAL PROGRAMMING

Animal studies in rodents, sheep, and monkeys have repeatedly shown that *in utero* exposure to increased fetal testosterone along with hyperglycemia and hyperinsulinemia determines PCOS phenotype in adulthood.[7] Based on these findings, it has been proposed that an androgenic *in utero* environment is associated with PCOS phenotype later in life in exposed female fetuses. However, it is difficult to prove this theory in humans because of the technical difficulties which prevent safe estimation of human fetal testosterone levels in the early and mid-gestation periods.

Anti-Müllerian hormone (AMH) is known to be characteristically elevated in women and adolescents with PCOS and also in newborn daughters of women with PCOS. Hence, this provides an indirect evidence of *in utero*

fetal programming caused by maternal hyperandrogenism. Elevated mid-gestational amniotic fluid testosterone levels suggest a fetal source of androgens, and are predictive of increased PCOS risk in later life. Onset of labor is known to variably reduce testosterone levels; hence, studies looking at umbilical cord testosterone levels and risk of developing PCOS subsequently have yielded conflicting results.

The fetal origin of adult diseases (FOADs) proposed initially by Barker suggests that *in utero* factors that lead to permanent changes in organ functions as a result of intrauterine fetal growth restriction is a strong predictive factor for the development of various metabolic diseases later in life. This intrauterine programming effect has been linked to cardiometabolic diseases, such as type 2 diabetes mellitus, insulin resistance, and cardiovascular diseases in low-birth weight infants. The population at maximum risk are the small for gestational age (SGA) babies with catch up growth who have higher body mass index (BMI) and fat mass during childhood. In addition, to the association between fetal undernutrition and insulin resistance, this intrauterine programming can also affect functions of other organs, such as the ovary and the adrenals. Young adults with history of low-birth weight, catch up growth, and hyperinsulinemia were found to have precocious pubarche and an increased prevalence of PCOS manifested as oligomenorrhea and hyperandrogenism.[9] The initial study to report this association was from Spain; however, other studies have not been able to consistently replicate this data. We need more longitudinal data to assess the association between SGA with premature adrenarche and PCOS. As AMH levels are found to positively correlate with PCOS phenotype even among prepubertal children, the association of SGA and AMH levels have been looked into. Higher AMH levels have been shown in SGA infants with catch up growth by 2 to 3 months of age, but AMH levels among prepubertal girls between 3 and 10 years were similar to appropriate for gestational age (AGA) children. Hence, it is unclear from these studies whether there is a change in follicular function or serve among SGA children.

Contrary to the conflicting data among girls with restricted intrauterine nutrition and overnutrition *in utero* has been clearly linked to increased risk of developing PCOS.[10] Higher birth weight infants born to overweight mothers and increased birth weight are both independent risk factors for developing PCOS later in life. However, babies with low ponderal index (low weight for length), who are thin at birth, have also been found to be at a higher risk for developing PCOS features in adulthood. This may be due to altered intrauterine programming secondary to fetal exposure to adverse environment as proposed by Barker's hypothesis. Overall, these studies suggest that at least some components of PCOS are affected by intrauterine programming, particularly the metabolic features, such as obesity, visceral fat mass, and insulin resistance.

EARLY LIFE AND CHILDHOOD

Currently, it is not possible to diagnose PCOS in infants and children using symptomatology, V and genetic tests are not yet available for identifying high-risk population. Most studies have taken daughters of women with PCOS as proxies for children with PCOS while trying to elucidate the clinical and biochemical characteristics of PCOS in infancy and childhood. In these studies, AMH levels were found to be increased in daughters of women with PCOS during infancy, childhood, and adolescence.[11] Anti-Müllerian harmone levels reflect the number of antral follicle.

PUBERTY AND ADOLESCENCE

Premature pubarche, defined as onset of pubic and axillary hair before the age of eight, has been considered to be a forerunner of PCOS. Premature pubarche is usually seen in adrenal disorders, such as nonclassic congenital adrenal hyperplasia and Cushing's syndrome. It may also be seen due to idiopathic early activation of adrenal androgen secretion leading to elevated levels of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). However, premature pubarche is not seen in all girls with PCOS; and all children with premature adrenarche will not develop PCOS subsequently. However, persistent hyperandrogenism is a characteristic feature of PCOS, and girls with persistent hyperandrogenism and premature adrenarche are more likely to progress to PCOS.

Menstrual irregularities are common for the first 2 years after onset menarche; hence, T-irregular cycles alone are not indicative of PCOS in the peripubertar period. Ovarian volumes also increase over time and reach the maximum by 11/2 to 31/2 years after onset of menarche. The ovarian size and follicle number shows considerable overlap between adolescents with PCOS and normal controls.

It has been proposed that the diagnosis of PCOS should be delayed for at least 2 years after menarche; and there should be at least 2 years of intermittent and irregular cycles suggesting persisting oligoanovulation.

Acne is also a common symptom seen in normal adolescents and cannot be used with discriminatory value to identify hyperandrogenism among pubertal girls with PCOS. Hirsutism may not be fully expressed at that age and may take several years for manifestation, hence, an elevated androgen level is the most persistent and useful criteria for identifying PCOS in this age group.

All women with PCOS, both lean and obese, are known to have insulin resistance and hyperinsulinemia, which is a significant component of PCOS. When compared to obese non-PCOS girls of same age, BMI and abdominal obesity, adolescent girls with PCOS were found to have 50% lower insulin sensitivity.[14] These adolescents also have a high prevalence of glucose intolerance with 30% being diagnosed with impaired glucose tolerance and 4% with frank type 2 diabetes mellitus. According to the National Health and Nutrition Examination Survey III (NHANES III) data, young women with PCOS were 4.5 times more likely to meet the criteria for metabolic syndrome, when compared to age and BMI-matched controls.

The gonadotropin-releasing hormone (GnRH) pulse frequency is classically increased in PCOS leading to increased luteinizing hormone (LH) levels and a high LH/follicle-stimulating hormone (FSH) ratio.[15] This increase in GnRH pulse frequency and an altered diurnal rhythm is seen early in adolescents in the pubertal period before the onset of menarche. The increase in GnRH pulse frequency has been shown to be positively associated with hyperandrogenism and increased ovarian volume in these adolescents. Studies on daughters of women with PCOS during the later stages of puberty (Tanner stage IV and V), have consistently shown higher basal and leuprolide stimulated LH, higher 17-hydroxy progesterone levels, lower sex hormone-binding globulin (SHBG), and elevated free androgen index. The testosterone levels in these subjects were shown to be positively correlated with 2-hour insulin levels suggesting early onset of metabolic derangements accompanying the hyperandrogenism. Similar to prepubertal children, the AMH levels were also found to be elevated in daughters of women with PCOS at all Tanner stages of puberty.[16] Anti-Müllerian hormone levels showed negative correlation with FSH levels (more number of follicles—more estradiol and inhibin B-lower FSH) and positive correlation with glucose-stimulated insulin levels. It has been suggested that girls with higher AMH levels may reflect an increased risk of developing metabolic dysfunction in adulthood.

Age of menarche is expected to be earlier in girls with PCOS, because of the established relationship between obesity and early menarche. However, in reality, the age of menarche in children with PCOS exhibits a wide range compared to healthy controls, ranging from less than 9 years to primary amenorrhea (defined as absence of menses after 16 years of age or 4 years after onset of thelarche).[17] There are no well-defined predictors for age of menarche in PCOS, but the age of menarche shows a strong inverse relationship with body weight. Hence, girls who are overweight are more likely to have an earlier menarche, while those who were lean compared to peers were likely to have a later menarche. Earlier, age of menarche is explicable in these overweight children as they have premature pubarche, premature thelarche, and earlier menarche when compared to age-matched controls. However, the later onset of menarche is not so clearly understood. The proposed theories are low levels of estradiol (particularly in the lean children), and elevated levels of androgen. Hyperandrogenemia may be exacerbated by being overweight and due to the underlying genetic predisposition to PCOS.

In summary, the most reliable diagnostic tool for PCOS in adolescence is the presence of all the three cardinal symptoms of PCOS: hyperandrogenemia, irregular menstrual cycles persisting beyond 2 years after menarche, and polycystic morphology on ultrasonography. The diagnosis of PCOS can be made reliable in the presence of the first two criteria, if ultrasonography is not available. Other features, such as a higher follicle number, elevated. Anti-Müllerian hormone levels, and metabolic features accompanying insulin resistance, may be an early sign in adolescent girls who develop PCOS later in adulthood, but are not part of the diagnostic evaluation currently.

REPRODUCTIVE YEARS

Population-based studies on infertility have shown that around 25 to 40% of all cases of infertility may be due to ovulatory dysfunction, for which PCOS is the leading cause, contributing to 70 to 90% of all ovulatory disorders. However, lifetime fecundity of women with PCOS was similar to controls in a Swedish cohort, and almost 75% of women with PCOS conceived spontaneously, making PCOS a cause for subfertility rather than infertility.[19] In the subgroup of women with hyperandrogenism and polycystic ovaries without oligoanovulation, risk of infertility is uncertain. Some women with PCOS and regular menstrual cycles may still experience anovulation, hence, a mid-luteal progesterone level may be helpful in identifying this subset of patients.

The morphology and spectrum of PCOS changes over time as the patient ages; features of PCOS remains stable only during early adult age (18–30 years). Normally, in women, there is a mild decrease in both ovarian (between 18 and 35 years) and adrenal (between 40 and 45 years) androgen secretion over time.[20] In women with PCOS also, the similar reduction in androgen levels with a decline of about 20 to 30% are seen. Older women with PCOS have lower levels of testosterone, androstenedione, and dehydroepiandrostenedione sulfate (DHEAS) along with lower Ferriman-Gallwey score compared to younger women with PCOS, but all values except DHEAS are higher when compared to age-matched controls. The drop in testosterone levels when studied longitudinally were found to be more marked than controls without PCOS. Ovulatory function is also known to improve over time in patients with PCOS, with 30% of women developing normal ovulatory menstrual cycles. Lower AMH levels (<4 μg/ml), lesser antral follicle count, and smaller ovarian volume may be used as predictors to suggest possibility of return of normal ovulatory function.[3] Polycystic morphology of ovaries also changes with time in women with PCOS. This may be contributed to by the reduction in antral follicle count and a lesser reduction in ovarian/volume as well. As in normal women, there is a gradual reduction in follicle number in women with PCOS; however, the change in ovarian volume is not so marked in women with PCOS when compared to controls. A lesser decline in ovarian volume despite a similar education in antral follicle count suggests that it is probably a prominent ovarian stromal component that accounts for this difference.

POSTMENOPAUSAL YEARS

The diagnosis of PCOS cannot be made in a postmenopausal women as the cardinal features of PCOS are no longer manifested. The quiescent ovary is anovulatory with absent Menstrual cycles and the hyperandrogenism declines with testosterone levels being similar to postmenopausal women without history of PCOS. As a part of the normal aging process, all women develop worsening of insulin resistance, abdominal obesity, chronic inflammation, and dyslipidemia during the menopausal transition. Contrary to the expectation that the PCOS women going through menopause may have worsening metabolic parameters, one longitudinal study, which followed-up women with and without PCOS from an early reproductive age into menopause found that the women with PCOS had little or no increase in systolic blood pressure and weight during the menopausal transition. Indeed, the two groups (postmenopausal women with past history of PCOS and postmenopausal women without history of PCOS) did not differ in the prevalence of type 2 diabetes mellitus, fasting insulin and glucose levels, and homeostasis model assessment (HOMA) index, even though all these metabolic parameters were significantly higher among the PCOS group initially. However, women with history of PCOS had persistent hypertension and higher triglyceride levels when compared to the control group. This suggests that the normal loss of protective effect in controls led to the equalization of adverse metabolic conditions seen in the postmenopausal status, however, as women with PCOS have had these risk factors from an earlier age; they are exposed to adverse cardiovascular profile for a longer duration.

Hence, in all probability, the cardiovascular risk among women with PCOS normalizes with age, except in a subgroup of women with persistent hyperandrogenism after menopause. More longitudinal studies involving larger numbers following up postmenopausal women are needed to provide an accurate answer to this issue.

The origin of the disorder probably occurs very early starting from fetal life. *In utero*, exposure to elevated testosterone levels coupled with gestational hyperglycemia may contribute to early differentiation of PCOS or may lead to amplification of the phenotype in genetically predisposed individuals. The spectrum of presentation of PCOS phenotype changes across the life span of a given individual. Improved understanding of the disease spectrum has allowed us to identify endocrine and metabolic changes in the very young subject with high risk of developing PCOS. It is important to establish reliable markers that can be used in childhood to diagnose the subtle metabolic (hyperinsulinemia and adiposity) and endocrine (ovarian and adrenal) derangements that precede onset of PCOS. Identifying, such children will enable the clinician to incorporate therapeutic or lifestyle preventive measures at an earlier age. Following women well into the postmenopausal years is also necessary to clearly define their cardiovascular morbidity and mortality.

Childhood obesity is an independent predictor of early adrenarche and development of PCOS subsequently. Visceral obesity is also a major determinant of insulin resistance in the young. The effect of obesity is compounded by the physiological insulin resistance of puberty. The exaggerated hyperinsulinemia may in turn lead to onset of premature adrenarche and subsequent PCOS in genetically predisposed individuals. Daughters of women with PCOS were also found to have exaggerated adrenarche and early puberty compared to daughters of non-PCOS women.[12]

REFERENCES

1. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;91(3):781-785.
2. Richard Scott Lucidi . 'Polycystic Ovarian Syndrome. Medicine (2011 25 October). Retrieved 19 November 2011.
3. Legro RS, Arslanian SA, Ehrmann DA, et al. Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98(12):4565-4592.
4. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the androgen excess and polycystic ovary syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010;95(5):2038-2049.
5. Urbanek M, Sam S, Legro RS, Dunaif A. Identification of a polycystic ovary syndrome susceptibility variant in fibrillin-3 and association with a metabolic phenotype. J Clin Endocrinol Metab 2007;92(11):4191-4198.
6. Welt CK, Styrkarsdottir U, Ehrmann DA, Thorleifsson G, Arason G, Gudmundsson JA, et al. Variants in DENND1A are associated with polycystic ovary syndrome ii women of European ancestry. J Clin Endocrinol Metab 2012;97(7):E1342-E1347.
7. Padmanabhan V, Veiga-Lopez A. Sheep models of polycystic ovary syndrome phenotype. Mol Cell Endocrinol 2013;373(1):8-20.
8. Keelan JA, Mattes E, Tan H, Dinan A, Newnham JP, Whitehouse AJ, et al. Androgen concentrations in umbilical cord blood and their association with maternal, fetal and obstetric factors. PLoS One 2012;7(8):e42827.
9. Ibanez L, Jimenez R, de Zegher F. Early puberty-menarche after precocious pubarche: relation to prenatal growth. Pediatrics. 2006;117(1):117-121.
10. Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips Dl, Fraser RB. Fetal growth, length of gestation, and polycystic ovaries in adult life. Lancet 1997;350(9085):1131-1135.
11. Sir-Petermann T, Codner E, Maliqueo M, et al. Increased anti-Müllerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91(8):3105-3109.
12. Maliqueo M, Sir-Petermann T, Perez V, Echiburu B, de Guevara AL, Galvez C, et al. Adrenal function during childhood and puberty in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94(9):3282-3288.
13. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol 2010;203(3): 201-205.
14. Apter D, Butzow T, Laughlin GA, Yen SS. Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. J Clin Endocrinol Metab 1995;80(10):2966-2973.
15. Taylor AE, McCourt B, Martin KA, et al. Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. J Clin Endocrinol Metab 1997;82(7):2248-2256.
16. Sir-Petermann T, Ladron de Guevara A, Codner E, et al. Relationship between Anti-Müllerian hormone (AMH) and insulin levels during different tanner stages in daughters of women with polycystic ovary syndrome. Reprod Sci 2012;19(4):383-390.
17. Carroll J, Saxena R, Welt CK. Environmental and genetic factors influence age at menarche in women with polycystic ovary syndrome. J Pediatr Endocrinol Metab 2012;25(5-6):459-466.
18. Bhattacharya S, Porter M, Amalraj E, et al. The epidemiology of infertility in the North East of Scotland. Hum Reprod 2009;24(12): 3096-3107.
19. Hudecova M, Holte J, Olovsson M, Sundstrom Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve. Hum Reprod 2009;24(5):1176-1183.
20. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause and oophorectomy. J Clin Endocrinol Metab 2005;90(7):3847-3853.
21. Schmidt J, Landin-Wilhelmsen K, Brannstrom M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab 2011;96(12):3794-3803.