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Polycystic Ovary Syndrome (PCOS) - From in Utero to Menopause

Belinda George and M Ganapathi Bantwal*

Department of Endocrinology, St. John's National Academy of Health Sciences, India

Review Article

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***Corresponding author:** Ganapathi Bantwal, Department of Endocrinology, St. John's National Academy of Health Sciences, Bangalore, Karnataka-560034, India, Tel: 09448067318; Email: mallyaganapathi@rediffmail.com

Abstract

Polycystic ovary syndrome (PCOS) usually presents during the reproductive years with hyperandrogenism, oligo-anovulation and/or polycystic ovaries on ultrasonography. The identification of PCOS was largely restricted to these reproductive years earlier. However, with improved understanding of the disease, currently there is data to describe the PCOS phenotype from infancy up to the post menopausal years. The spectrum of presentation of PCOS phenotype changes across the life span of a given individual. Early identification of high risk individuals during childhood and pre-pubertal years will enable the clinician to incorporate therapeutic or lifestyle preventive measures at an earlier age. Intra uterine programming of the foetus exposed to elevated testosterone and gestational hyperglycemia are also being shown to contribute significantly to the phenotypic expression in later years. The data on post menopausal women with PCOS is also increasing. Contrary to what was expected, except for a subgroup of women with persistent hyperandrogenism, available data does not seem to indicate an increase in cardiovascular morbidity or all cause mortality among post menopausal women with previous history suggestive of PCOS.

Introduction

The syndrome of poly cystic ovaries is typically diagnosed during the adolescent period or during the reproductive years when the patients present with menstrual irregularities and evidence of hyperandrogenism [1]. 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. Diagnosis of PCOS is based on presence of hyperandrogenism, oligo-anovulation and polycystic ovaries on ultrasonography (presence of any two features adequate as per Rotterdam criteria) [2]. This Criteria permits four different phenotypes of PCOS: 1) all three criteria present; 2) hyperandrogenism with oligo-anovulation and normal appearance of ovaries on USG; 3) hyperandrogenism with poly cystic ovaries, but no menstrual irregularities; 4) oligo-anovulation and poly cystic ovaries without hyperandrogenism. The NIH Criteria for diagnosis of PCOS require presence of both hyperandrogenism and oligo-anovulation, and hence the last two phenotypes are not considered as PCOS based on this criterion (Table 1). The Endocrine Society guidelines recommend the use of Rotterdam criteria for diagnosis of PCOS [3]. There is significant variability in the phenotypic expression of PCOS. Weight loss, particularly induced by bariatric surgery and treatment with insulin sensitizers can ameliorate the phenotypes 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.

Criteria	Rotterdam (2 out of 3)	NIH	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)
Oligo-anovulation	May be present	Should be present	May be present
Polycystic appearance of ovaries	May be present	May be present	May be present

Table 1: Summary of proposed criteria for PCOS.

Foetal 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 phenotypy 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 pre-pubertal and adolescent period, hyperandrogenism predominates the phenotypy of PCOS; the spectrum expands to include reproductive dysfunction along with hyperandrogenism during later years up to menopause; following menopause, the persistent metabolic derangements appear to be the most pronounced phenotypic expression [4] (Table 2).

	PCOS	Non-PCOS
Predisposing factors	Genetic factors, in utero programming	-
Childhood (pre pubertal years)	Increased AMH levels	-
Puberty	Premature adrenarche	Acne
	Hyperandrogenism	Increased ovarian volume
	Increased GnRH pulse frequency	Irregular menstrual cycles
	Increased AMH levels, ovarian volume	Insulin resistance of puberty
	Hyperinsulinemia	
Reproductive years	Irregular cycles	Decreasing androgen levels with age
	Hyperandrogenism	Decreasing AMH, ovarian reserve and antral follicle count with age
	Subfertility/ infertility	
	Increased AMH, antral follicle count, ovarian volume	
	Glucose intolerance, insulin resistance	
Post menopausal years	Increased prevalence of hypertension	Increased cardio metabolic risk factors with menopause - glucose intolerance, adiposity, hypertension
	Increased triglycerides	

Table 2: Phenotype of PCOS across the life span in comparison with controls.

Genetics of PCOS

The heritable nature of PCOS was identified early on based on twin studies and familial clustering of the disorder. Around 20 to 40% of first degree female relatives are known to be affected by the poly cystic ovary syndrome [5]. The search to identify a genetic cause has mostly used candidate gene association techniques, in which changes in a particular gene of interest are studied and evaluated for correlation with PCOS. However, to date, such studies have not been very successful in identifying convincing genetic associations with PCOS [6]. The syndrome of poly cystic ovaries seems to be a complex genetic disorder like type 2 diabetes mellitus, where in 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 [7]. 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 1member 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 favours the polygenic theory proposed for origin of PCOS with or without accompanying developmental environmental factors [8].

In Utero Foetal Programming

Animal studies in rodents, sheep and monkey have repeatedly shown that in utero exposure to increased foetal testosterone along with hyperglycemia and hyperinsulinemia determines PCOS phenotype in adulthood [9]. 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 foetuses. However, it is difficult to prove this theory in humans because of the technical difficulties which prevents safe estimation of human foetal testosterone levels in the early and mid gestation periods [10]. Moreover, theoretically, the activity of placental aromatase enzyme should preclude foetal exposure from increased maternal androgens. Subtle reductions in activity of aromatase and 3 beta hydroxyl steroid dehydrogenase enzymes have been demonstrated in placentas of women with PCOS [11]. Most of the studies done in humans have relied on indirect evidence of foetal hyperandrogenism or on umbilical cord testosterone levels at birth [12]. Increased mid gestational maternal testosterone levels have found to predict high anti Mullerian hormone (AMH) in adolescents born to PCOS mothers [13]. AMH is known to be characteristically elevated in women and adolescents with PCOS and also in newborn daughters of women with PCOS [14,15]. Hence, this provides an indirect evidence of in utero foetal programming caused by maternal hyperandrogenism. Elevated mid gestational amniotic fluid testosterone levels suggest a foetal source of androgens, and is predictive of increased PCOS risk in later life [16]. Onset of labour 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 with some showing positive, negative or no correlation.

The foetal origin of adult diseases (FOAD) proposed initially by Barker suggests that in utero factors which lead to permanent changes in organ functions as a result of intra uterine foetal growth restriction is a strong predictive factor for the development of various metabolic diseases later in life [17]. This intra uterine programming effect has been linked to cardio metabolic diseases like type 2 diabetes mellitus, insulin resistance and cardiovascular diseases in low birth weight infants [18-20]. The population at maximum risk are the small for gestational age (SGA) babies with catch up growth who have higher BMI and fat mass during childhood [21,22]. In addition to the association between foetal under nutrition and insulin resistance, this intra uterine programming can also affect functions of other organs like 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 [23,24].

The initial study to report this association was from Spain; however, other studies have not been able to consistently replicate this data [25,26]. 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 pre-pubertal children, the associations 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 pre-pubertal girls between 3 to 10 years were similar to appropriate for gestational age (AGA) children [27,28]. Hence, it is unclear from these studies whether there is a change in follicular function or reserve among SGA children.

Contrary to the conflicting data among girls with restricted intra uterine nutrition, over nutrition in utero has been clearly linked to increased risk of developing PCOS. Higher birth weight infants born to overweight mothers and increased birth weight are both independent risk factors for developing PCOS later in life [29]. 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 [30]. This may be due to altered intra uterine programming secondary to foetal exposure to adverse environment as proposed by Barker's hypothesis. Overall, these studies suggest that at least some components of PCOS are affected by intra uterine programming, particularly the metabolic features like obesity, visceral fat mass and insulin resistance [31].

Early Life and Childhood

Currently, it is not possible to diagnose PCOS in infants and children using symptomatology 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 [14,15]. AMH levels reflect the number of antral follicles because they have been shown to correlate very well with antral follicle count obtained by ultrasonography. As patients with PCOS have been shown to have elevated AMH levels, particularly in those with hyperandrogenism, they are used as a surrogate marker for ovarian hyperandrogenism in women with PCOS. Based on studies done in pre pubertal girls born to mothers with PCOS, it is now known that AMH levels may be useful even in this population [32].

Childhood obesity is an independent predictor of early adrenarche and development of PCOS subsequently [33]. 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 [34]. Hence, along with intra uterine programming in genetically predisposed individuals, environmental and dietary practices which lead to childhood obesity worsens the risk of insulin resistance, hyperandrogenism and subsequent PCOS.

Puberty and Adolescence

Premature pubarche, defined as onset of pubic and auxiliary hair before the age of 8, has been considered to be a fore runner of PCOS [35]. Premature pubarche is usually seen in adrenal disorders like non classic 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) [36]. 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 [37].

It is difficult to convincingly diagnose PCOS during puberty and adolescence as there is considerable overlap between the clinical features of PCOS and normal pubertal development [38]. Menstrual irregularities are common for the first two years after onset of menarche; hence irregular cycles alone are not indicative of PCOS in the peri-pubertal period. Ovarian volumes also increase over time and reach its maximum by 1 1/2 to 3 1/2 years after onset of menarche. The ovarian size and follicle number shows considerable overlap between adolescents with PCOS and normal controls. Puberty itself may lead to multi cystic appearance of ovaries on ultrasonography. As the ovarian function in adolescent girls is either in immature quiescence or behaves very similar to PCOS, it has been proposed that the diagnosis of PCOS should be delayed for at least two years after menarche and there should be at least two years of intermittent and irregular cycles suggesting persisting oligo-anovulation. 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 [39]. 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 [40].

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 [41]. 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 [42]. According to the National Health and Nutrition Examination Survey (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 [43].

The gonadotropin releasing hormone (GnRH) pulse frequency is classically increased in PCOS leading to increased luteinizing hormone (LH) levels and a high LH/FSH ratio. 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 [44, 45]. Studies on daughters of women with PCOS during the later stages of puberty (Tanner stage IV & 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[46]. 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 pre-pubertal children, the AMH levels were also found to be elevated in daughters of women with PCOS at all Tanner stages of puberty [14,15]. AMH 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 exhibit 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) [47]. 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 [48]. 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 [49]. The proposed theories are that 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 poly cystic morphology on ultrasonography. The diagnosis of PCO can be made reliably in the presence of the first two criteria if ultrasonography is not available. Other features like a higher follicle number, elevated AMH 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

As mentioned earlier, based on the Rotterdam criteria, there are four possible subtypes of PCOS:

1) Hyperandrogenism, oligo-anovulation and polycystic appearance of ovaries;
2) Hyperandrogenism with oligo-anovulation and normal appearance of ovaries on USG;
3) Hyperandrogenism with poly cystic ovaries, but no menstrual irregularities;
4) Oligo-anovulation and poly cystic ovaries without hyperandrogenism.

The risk for developing metabolic and cardiovascular diseases may be different for each of these subtypes. The first two subtypes which also reflect a more severe phenotype have been shown in several studies to be at the highest risk of developing cardio metabolic disorders [50-52]. Whether the third and fourth subtype characterised by hyperandrogenism with polycystic ovaries and oligo-anovulation with polycystic ovaries have the same future risk for developing cardio metabolic diseases needs to be studied. The least risk for metabolic alterations is seen in the fourth subtype who has oligo-anovulation with polycystic ovaries, but lack hyperandrogenism.

During the reproductive years, one of the major concerns affecting patients with PCOS is sub-fertility/infertility. Infertility was one of the original symptoms of PCOS documented by Stein and Leventhal in the first description of PCOS. The reported incidence of primary infertility is close to 50% and that of secondary infertility is around 25%. 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 [53,54]. 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 sub-fertility rather than infertility [55]. In the subgroup of women with hyperandrogenism and polycystic ovaries without oligo-anovulation, risk of infertility is uncertain. Some women with PCOS and regular menstrual cycles may still experience an ovulation, hence a mid luteal progesterone level may be helpful in identifying this subset of patients. The proposed mechanisms for infertility in PCOS include oligo and/or an ovulation, diminished oocytes competence and endometrial changes discouraging implantation.

The morphology and spectrum of PCOS change over time as the patient ages; features of PCOS remain stable only during early adult age (18–30 years). Normally, in women, there is a mild decrease in both ovarian (between 18 to 35 years) and adrenal (between 40 to 45 years) androgen secretion over time [56]. 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 dehydroepiand rostenedione 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 [47]. 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 [57]. Lower AMH levels (< 4ng/ml), lesser antral follicle count and smaller ovarian volume may be used as predictors to suggest possibility of return of normal ovulatory function [58]. 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 [59]. A lesser decline in ovarian volume despite a similar reduction in antral follicle count suggests that it is probably a prominent ovarian stromal component which accounts for this difference.

Post-Menopausal Years

The diagnosis of PCOS cannot be made in a post menopausal woman 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 post menopausal women without history of PCOS. As a part of the normal ageing 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 woman 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 [60]. Indeed, the two groups (post menopausal women with past history of PCOS and post menopausal women without history of PCOS) did not differ in the prevalence of type 2 diabetes mellitus, fasting insulin and glucose levels, HOMA index even though all these metabolic parameters were significantly higher among the PCOS group initially.

However, women with history of PCOS were found to persistent hypertension and higher triglyceride levels when compared to the control group [61]. This suggests that the normal loss of protective effect in controls led to the equalisation of adverse metabolic conditions seen in the post menopausal status, however, as women with PCOS has had these risk factors from an earlier age; they are exposed to adverse cardiovascular profile for a longer duration. Whether this translates to increased cardiovascular morbidity and mortality in these women is not known. The limited data available does not seem to confer an increased rate of cardiovascular morbidity or all cause mortality in women with previous PCOS. Hence, in all probability, the cardiovascular risk among women with PCOS normalises with age, except in a subgroup of women with persistent hyperandrogenism after menopause. More longitudinal studies involving larger numbers following up post menopausal women are needed to provide an accurate answer to this issue.

Conclusion

Although PCOS classically presents during the reproductive years with menstrual irregularities, hyperandrogenism and metabolic complications, we now understand that the origin of the disorder probably occurs very early starting from foetal 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 post menopausal years is also necessary to clearly define their cardiovascular morbidity and mortality.

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