Lifecycle of Polycystic Ovary Syndrome (PCOS): From In Utero to Menopause

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Context: Polycystic ovary syndrome (PCOS) is diagnosed during the reproductive years when women present with 2 of 3 of the following criteria: 1) irregular menstrual cycles or anovulation, 2) hyperandrogenism, and 3) PCO morphology. However, there is evidence that PCOS can be identified from early infancy to puberty based on predisposing environmental influences. There is also increasing information about the PCOS phenotype after menopause. The goal of this review is to summarize current knowledge about the appearance of PCOS at different life stages and the influence of reproductive maturation and senescence on the PCOS phenotype.

Evidence: PubMed, the bibliography from the Evidence-Based PCOS Workshop, and the reference lists from identified manuscripts were reviewed.

Evidence Synthesis: The current data suggest that daughters of women with PCOS have a greater follicle complement and mild metabolic abnormalities from infancy. PCOS is often diagnosed in puberty with the onset of hyperandrogenism and may be preceded by premature pubarche. During the reproductive years, there is a gradual decrease in the severity of the cardinal features of PCOS. Menopausal data suggest that the majority of women who had PCOS during their reproductive years continue to manifest cardiovascular risk factors. However, the majority do not present an increased risk for cardiovascular morbidity and mortality, perhaps because women with no history of PCOS may catch up after menopause.

Conclusion: The current data provide a comprehensive starting point to understand the phenotype of PCOS across the lifespan. However, limitations such as a bias of ascertainment in childhood, age-based changes during reproductive life, and the small numbers studied during menopause point to the need for additional longitudinal studies to expand the current knowledge.

ISSN Print 0021-972X  ISSN Online 1945-7197
Printed in U.S.A.
Copyright © 2013 by The Endocrine Society
Received May 29, 2013. Accepted September 9, 2013.
First Published Online September 24, 2013

Abbreviations: AMH, anti-Mullerian hormone; BMI, body mass index; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome.

Symptoms of polycystic ovary syndrome (PCOS) present during adolescence with menstrual irregularities and signs of hyperandrogenism, but the appearance of the disorder may be influenced by environmental and genetic factors that operate during earlier periods of life. Animal models suggest that fetal exposure to androgens can precipitate PCOS-like phenotypes and associated metabolic symptoms, such that the predilection to PCOS could begin in utero through environmental or epigenetic mechanisms (1). Low birth weight has also been associated with the eventual development of PCOS (2). In addition, understanding of the genetic predisposition to PCOS is emerging (3, 4). If these early predictors of PCOS are accurate, the phenotype of PCOS could be elucidated from infancy through menopause. However, we are just beginning to understand these predisposing genetic and environmental influences.

This review will outline studies examining PCOS from early life through puberty using proxies for these early predictive factors (Table 1). It will then discuss the stable symptoms that occur after puberty through the mid to late 30s, after which spontaneous changes in ovarian function
and metabolic regulation modify the expression of the disorder. Finally, it will examine the persistent metabolic components of the disorder and the variable ovarian endocrine influences and environmental factors that may play a role in the morbidity of the syndrome in menopause.

Taken together, the expression of PCOS may begin early and the symptoms change across the lifespan. Determining the appearance and expression of the syndrome at each stage of life will be important to expand the diagnosis and treatment of PCOS.

### In Utero and Early Life

It is impossible to diagnose PCOS in infants and children by symptoms, and genetic testing is not yet available to determine which girls might be at risk. However, daughters of women with PCOS have been studied in infancy and childhood as proxies for children with PCOS based on the strong heritability of PCOS in families (5, 6) and the possibility that in utero factors predispose to PCOS risk (1, 2).

In these studies, anti-Mullerian hormone (AMH) levels are used to assess antral follicle count because levels are highly correlated with antral follicle count on ultrasound and reflect the number of small antral follicles in the ovary (7). AMH levels also cluster with hyperandrogenism in principle component analyses of PCOS, suggesting that AMH levels can be used as a surrogate for ovarian hyperandrogenism in women with PCOS (8). When AMH levels were examined in daughters of women with PCOS, they were increased in infancy, early childhood, and prepubertally (9–11). The increased AMH levels were associated with higher leptin levels in cord blood in infants and an increased insulin response to glucose prepubertally compared with controls (11). However, cord blood insulin levels did not differ, and low-density lipoprotein (LDL) and triglyceride levels were lower in these infants of women with PCOS (12). Thus, it appears that girls at risk for PCOS based on heritability have evidence for an increased follicle complement and mild metabolic abnormalities compared with controls.

Based on data from animal models, it has been suggested that an androgenic in utero environment is associated with PCOS-like features in exposed progeny. However, there are no data to support the model in humans. Placental aromatase aromatizes maternal testosterone before fetal exposure, and there should be no androgen elevation in amniotic fluid. Subtle lower 3β-hydroxysteroid dehydrogenase 1 and aromatase activity has been described in the placentas of women with PCOS (13). However, a large prospective study of maternal and umbilical cord testosterone levels found no relationship with the subsequent development of PCOS (14).

Other in utero factors may predispose to the development of PCOS. Intrauterine factors with resulting effect on birth weight and possible changes in the intrauterine environment as a function of birth order are variables that could play a role. Retrospective studies suggest that a subset of girls born small for gestational age will later develop early pubarche, early menarche, and PCOS (2, 15). Using AMH as a proxy for increased follicle number, newborns with low and high birth weights have higher AMH levels than normal birth weight infants when measured at 2 to 3 months of age.

### Table 1. Phenotype of Women with PCOS Across the Lifespan and Similarities in Controls

<table>
<thead>
<tr>
<th>PCOS</th>
<th>Controls: Similarities to PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposing factors</td>
<td>None</td>
</tr>
<tr>
<td>Infancy</td>
<td>None</td>
</tr>
<tr>
<td>Childhood</td>
<td>Acne, irregular menses, and increased ovarian volume</td>
</tr>
<tr>
<td>Puberty</td>
<td>None</td>
</tr>
<tr>
<td>Reproductive years</td>
<td>Decreases in androgen levels, ovarian volume, and follicle number</td>
</tr>
<tr>
<td>Menopause</td>
<td>Weight, waist to hip ratio, systolic blood pressure, prevalence of type 2 diabetes, fasting glucose, insulin, HOMA, LDL, and cardiovascular morbidity and mortality</td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/jcem/article-abstract/98/12/4629/2834024 by guest on 21 April 2019
months of age (16). High birth weight infants have lower adiponectin, suggesting decreased insulin sensitivity. They also demonstrate higher GnRH-stimulated FSH levels, and both low and high birth weight infants had higher stimulated estradiol levels, suggesting an increased follicle complement secreting estradiol either independently or in response to greater FSH stimulation (16). However, studies in large groups of women did not demonstrate an increased prevalence of low or high birth weight in women with PCOS (17, 18), suggesting that it may be an uncommon mechanism. Differences in the intrauterine environment related to birth order, with contributing factors such as higher weight in the mother with increased parity, older maternal age, and placental problems with multiparity, does not account for the familial difference in the development of PCOS among sisters (19). Caveats exist to the data provided by studies evaluating the influence of in utero factors on PCOS. In fact, not all female offspring of women with PCOS will have PCOS. Only 50% of sisters will manifest PCOS. These sisters manifest PCOS through hyperandrogenism with irregular menstrual cycles or hyperandrogenism with regular menstrual cycles (5). Therefore, the data are diluted by girls who will likely never go on to develop PCOS. There is also a high bias of ascertainment when studying only the daughters of women with PCOS as they may be the most highly affected or have a more severe form of the disorder. It is clear that an intrauterine environment that might result in risk for PCOS also produces girls without PCOS based on the family data (5).

Puberty and Adolescence

During puberty and adolescence, the signs and symptoms that characterize PCOS overlap with normal and may require some time to be established to make a definitive diagnosis (20). Menstrual irregularities are typical for at least 2 years after menarche. Irregular menstrual cycles, by themselves, should therefore not be used as a sole criterion for the diagnosis of PCOS. Ovarian volume reaches its maximum at 1.2 to 3.8 years after menarche (21), and follicle number and volume can exhibit great overlap in adolescents with PCOS and controls at this time of life (21). Acne is a common problem in adolescents and is therefore not a symptom that can be used to identify hyperandrogenism. Hirsutism may require several years before adequate expression. Hyperandrogenemia, as documented by an elevated androgen level, is the most persistent and therefore the most useful diagnostic criterion in adolescents (22). Taken together, perhaps the most reliable diagnostic criteria for PCOS in adolescence is the presence of all 3 cardinal symptoms of PCOS: hyperandrogenemia, irregular menses that persists 2 years after menarche, and PCO morphology as suggested by increased ovarian volume. However, a reliable diagnosis can be made using irregular menses in association with hyperandrogenemia if an ultrasound is not available (23).

Premature pubarche, or the development of pubic hair and axillary hair before age 8 years, may be an early sign of PCOS (24). Although premature pubarche may occur as a result of some adrenal androgen disorders (nonclassic congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing’s syndrome), it can also be due to an idioopathic early activation of adrenal androgen secretion from the zona reticularis with production of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) in the Δ5 steroid pathway. Premature adrenarche is not experienced by all girls with PCOS, suggesting that it may account for one subtype of PCOS (25). On the contrary, premature adrenarche does not result in PCOS in all cases (26). Thus, continued monitoring is suggested for girls given the diagnosis of premature pubarche (26). Persistent hyperandrogenism remains a distinct feature of girls with premature pubarche who go on to develop PCOS, and the hyperandrogenism is exacerbated if a child develops obesity (27).

It is well understood that GnRH pulse frequency is increased in women with PCOS, resulting in high LH levels and an elevated LH to FSH ratio (28). Increased pulse frequency of GnRH and an altered diurnal pulse pattern, occurring even before menarche, is also a prominent feature in adolescents who develop PCOS (29). The increased GnRH pulse frequency in adolescents is resistant to suppression by progesterone (30). The increased GnRH pulse frequency is highly associated with hyperandrogenism and increased ovarian volume (29). Therefore, the entire reproductive axis is activated in adolescents with PCOS.

The increased AMH and glucose-stimulated insulin levels that are seen prepubertally remain elevated throughout all stages of puberty compared with controls, in the absence of differences in body mass index (BMI) (9–11, 31, 32). In an analysis of 135 daughters of women with PCOS and 93 daughters of controls, the daughters of women with PCOS with the highest AMH also had the lowest FSH levels, which were expected because a larger follicle number would be associated with greater secretion of inhibin B and estradiol. Increased glucose-stimulated insulin levels are also a consistent phenotype in the daughters of women with PCOS in mid to late puberty (11, 32). Thus, higher follicle number, as suggested by AMH levels, and metabolic features may be an early sign in girls who may go on to develop PCOS but are not part of the clinical diagnosis in adolescents.
Based on the relationship between obesity and earlier menarche, it might be expected that girls who go on to develop PCOS experience an earlier age at menarche. However, menarche in girls with PCOS can exhibit a much wider age range than in control subjects, ranging from early menarche at or before the age of 9 years to primary amenorrhea, in which menarche has not yet occurred by the age of 16 years or 4 years after the onset of thelarche (33). There is very sparse literature examining the underlying predictors for age at menarche in PCOS (19, 33–36). In a retrospective analysis, women with PCOS were more likely to report early or late menarche compared with their peers (19). There was also a strong inverse relationship between reported age and weight at menarche, suggesting that girls who were overweight had an earlier menarche, whereas those who were thin compared with their peers experienced a later menarche (19). Earlier menarche in girls with PCOS might be expected based on findings that overweight girls experience earlier pubarche, thelarche, and menarche than those with a normal BMI (37, 38). The later age at menarche in girls who report lower weight than their peers during the menarcheal window may be related to lower estradiol production, although estradiol levels have not been examined in this group. In addition, the group with later menarche may have higher androgen levels, as suggested by data from girls with primary amenorrhea (34, 39). Girls with primary amenorrhea had higher androgen levels and were more likely to be overweight (34, 36, 39) or have a family history of overweight (34), which exacerbates hyperandrogenemia. They also had more features of metabolic syndrome than girls who had an earlier menarche (34, 36, 39). Taken together, overweight may play a greater role in those with earlier menarche, whereas those presenting with later menarche may be a mixed group. Lower estradiol and/or higher androgen levels exacerbated by obesity may be distinguishing features in girls with later menarche. More work is needed to dissect this group and their metabolic risk.

### Reproductive Years

A recent evidence-based methodology workshop recommended maintaining the broad, inclusionary diagnostic criteria of Rotterdam for PCOS (40, 41). Using the Rotterdam criteria, PCOS can be defined when, in the absence of another disorder that can cause the same symptoms, 2 of 3 of the following symptoms or signs are present: 1) irregular menses; 2) hyperandrogenism, either clinical or biochemical; and/or 3) PCO morphology on pelvic ultrasound. Using the Rotterdam criteria, there are 4 possible diagnostic subcategories of PCOS: 1) irregular menses/hyperandrogenism/PCO morphology, 2) irregular menses/hyperandrogenism, 3) hyperandrogenism/PCO morphology, and 4) irregular menses/PCO morphology (Table 2). It is not clear whether all of these PCOS subsets predispose women to the same risks for type 2 diabetes and cardiovascular risk factors. Several studies have demonstrated that women with irregular menses/hyperandrogenism/PCO morphology and irregular menses/hyperandrogenism have the most severe phenotype and greatest number of metabolic risk factors. Whether women with hyperandrogenism/PCO morphology and irregular menses/PCO morphology have the same future cardiovascular risk has to be determined. Women with irregular menses/PCO morphology may have the fewest metabolic risk fac-

### Table 2. Criteria Used to Define Polycystic Ovary Syndrome in Adult Women in Cited Studies

<table>
<thead>
<tr>
<th>Refs.</th>
<th>Defining Criteria</th>
<th>NIH Criteria (84)</th>
<th>Rotterdam Criteria (41)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>33, 52, 76</td>
<td>Ovarian wedge resection</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>71, 46</td>
<td></td>
<td></td>
<td></td>
<td>Oligomenorrhea and normal FSH</td>
</tr>
<tr>
<td>47, 66</td>
<td></td>
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</tr>
<tr>
<td>48</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>49</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>X</td>
<td></td>
<td>Irregular menses and elevated LH/normal FSH</td>
</tr>
<tr>
<td>51, 55</td>
<td></td>
<td></td>
<td></td>
<td>PCO morphology by ultrasound</td>
</tr>
<tr>
<td>53, 54</td>
<td></td>
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<tr>
<td>56</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>70, 73</td>
<td></td>
<td>X</td>
<td></td>
<td>Ovarian dysfunction</td>
</tr>
<tr>
<td>72, 77</td>
<td>Ovarian wedge resection</td>
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<td>82</td>
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<td>X</td>
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<tr>
<td>83</td>
<td>PCO morphology on ultrasound</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviation: NIH, National Institutes of Health.

*a Defining criteria were considered the specific feature used to search for PCOS subjects after which other criteria were also required before a subject was accepted into the study.*
tors but do have elevated LH levels (42–44). Whether all of the PCOS subtypes with amenorrhea have similar infertility risk remains to be determined.

The panel also recognized that the incorporated criteria have limitations, including the fact that the diagnostic features of PCOS may change with age (40). The change in androgens, ovulatory function, and ovarian morphology with age can complicate the diagnosis of PCOS in adolescents and in older reproductive-age women. PCOS remains stable only during early adult age (18–30 years), but after that time, changes in ovarian and adrenal function and in metabolic regulation modify the presentation of the syndrome.

In all women, there is a mild decrease in ovarian androgen secretion of testosterone, particularly in the early reproductive years between ages 18 and 35 (45). There is a more marked decrease in adrenal androgen secretion, including androstenedione and DHEAS, between the ages of 20 to 25 years and 40 to 45 years (45). Androgen levels also decline 20% to 30% in women with PCOS. Older women with PCOS have a lower Ferriman-Gallwey score and testosterone, androstenedione, and DHEAS levels compared with younger women, but all values remain higher than in older control women with the exception of DHEAS (33, 46–51). Testosterone levels also decrease when assessed longitudinally and with a more marked decrease than that in controls, supporting these cross-sectional studies (50, 52).

Ovulatory function also appears to improve with age in women with PCOS. Menstrual frequency increases (50, 53, 54), with approximately 30% of older women developing normal ovulatory function (51, 54–56). It has been suggested that the FSH increase during reproductive aging may drive follicle development in PCOS (50). Consistent with this hypothesis, women with PCOS who gain regular menstrual cyclicity have fewer follicles (53, 54), which would be expected to result in an increased FSH level. The return of ovulatory function may also be predicted by a smaller ovarian volume and lower AMH level, a proxy for follicle number (55). In one study, all subjects aged 35 to 39 years with AMH levels ≤ 4 ng/mL at baseline and 60% of those with AMH levels of ≤ 5 ng/mL at baseline had ovulatory function after 5 years (55). When using these criteria, one must remember that specific AMH levels may vary with the assay used. Of note, there does not appear to be a relationship between weight and cycle regularity in aging (50, 53, 55).

PCO morphology also changes with age (Figure 1). Data were adapted from a previous study with additional subjects recruited using the same criteria in the interim and with identical results (50). Follicle counts in both women with PCOS and controls decrease with age in a linear fashion (50, 57–60). Importantly, follicle number declines in a parallel manner with age, although the follicle number is higher at all ages in women with PCOS compared with control women during the reproductive years.

Ovarian volume exhibits a log linear decline in women with PCOS and in controls, but women with PCOS have a higher initial volume, a lesser slope of decline, and a greater decrement in the volume change from premenopause to postmenopause (50). A correlation between the decrease in follicle number and ovarian volume suggests that the decrease in follicle number may partially explain the decrease in ovarian volume (57, 61–63). However, the volume does not decrease as markedly as follicle number before age 35 years (64), and a lesser decline in the ovarian volume despite a similar decline in follicle number in
women with PCOS compared with controls suggests that a different ovarian compartment, such as the prominent stromal component (65), accounts for the difference in slopes (50). Taken together, the decrease in both ovarian volume and follicle number with age results in loss of PCO morphology with aging when using the current criteria (41).

A model incorporating the ovarian and androgen changes with age has also been developed to predict PCOS at all ages (50). The model includes a combination of age, follicle number, log ovarian volume, and testosterone: log (odds of PCOS) = −10.1302 + 0.0978 × age + 0.2698 × follicle number + 0.6967 × log volume + 0.0632 × testosterone. The model predicted PCOS with a receiver operating characteristic curve area of 0.90. A log (odds of PCOS) score of ≥0.51 results in a specificity of 83% and a sensitivity of 83% for predicting PCOS.

Late Reproductive Age and Menopause

It is not possible to diagnose a woman with PCOS when she has already reached menopause because the cardinal features disappear. Menses cease. Testosterone levels may no longer be higher than in control women, although less conventional measures of androgen excess such as the free androgen index and human chorionic gonadotropin-stimulated androstenedione and 17-hydroxyprogesterone levels remain higher (50, 52, 66). Although it has been suggested that PCO morphology persists into menopause (56), hypoechoic structures on ultrasound in postmenopausal women with PCOS correspond to inclusion cysts and vascular structures rather than follicles, and pathology studies do not demonstrate secondary follicles in postmenopausal ovaries (50, 67).

Thus, one is able to make the diagnosis of PCOS only during the reproductive years.

All women experience increasing insulin resistance and abdominal adiposity along with chronic inflammation and dyslipidemia with age and a specific increase in LDL across the menopausal transition (68, 69). It is therefore possible that the metabolic abnormalities in women with PCOS also worsen with age. Longitudinal studies in women with PCOS suggest that waist circumference, cholesterol, and triglyceride levels increase in women with PCOS as they reach 40 to 50 years (50, 51, 70), whereas BMI increased in some, but not all, studies (50–52). Fasting insulin and the quantitative insulin sensitivity check index, ie, metabolic parameters, and the prevalence of metabolic syndrome did not change over time in women with PCOS (50, 51). In cross-sectional studies, women with PCOS over the age of 35 years have higher BMI, homeostasis model assessment (HOMA), glucose, and triglyceride levels compared with age-matched controls (46, 50, 56, 71, 72). A large longitudinal study of women with PCOS demonstrated a prevalence of type 2 diabetes of 39%, exceeding the prevalence of 5.8% in the general population (73). However, the high prevalence of type 2 diabetes is likely related to the very high BMI in those women (73), because other studies do not demonstrate an increase in diabetes prevalence in this age group (74). Consistently, cross-sectional studies of menopausal women with PCOS compared with menopausal controls demonstrate that only the insulin area under the curve remained significantly higher in women with PCOS when controlled for the higher BMI (66).

There may be a subset of women with PCOS who actually have an improvement in cardiovascular risk with age. In a longitudinal study, the occurrence of ovulatory function with aging in women with PCOS was inversely correlated with changes in LDL-cholesterol. In contrast, women who remained anovulatory had increases in total cholesterol, LDL-cholesterol, and non-high-density lipoprotein-cholesterol levels and cardiovascular risk remained significantly higher than in the general population (51). In contrast, an earlier onset of irregular menses does not appear to be associated with a more severe metabolic phenotype than in women with a later onset of irregular menses (75). The underlying cause of the factor resulting in improvement in ovulatory cycles and cardiovascular risk with age needs to be determined.

There are few studies in which both women with PCOS and controls are followed longitudinally from early reproductive age into menopause. In the available studies, it is interesting to note that weight and systolic blood pressure increase with increasing age in controls, whereas women with PCOS had little to no increase so that there was no difference in these parameters in women with PCOS and controls at the older age (50, 52, 76) (Table 1). Similarly, the waist to hip ratio in the control group matched that of the PCOS group at the older age because of the weight gain in the control group (50, 52, 76). Although there was an increased prevalence of type 2 diabetes in women with PCOS compared with controls at a younger age, the prevalence of type 2 diabetes increased with age in controls, and there was no difference in the prevalence of diabetes 20 years later when women with PCOS had reached menopause (52, 76). There was also no difference in fasting insulin levels, HOMA of insulin resistance, and glucose levels in the two groups at an older age (52). However, the prevalence of hypertension was higher in postmenopausal
women with PCOS compared with controls studied longitudinally, and triglyceride levels increased in both groups but remained higher in the women with PCOS (52, 76, 77). Thus, longitudinal data provide evidence that control women tend to have worsening of some of their metabolic parameters to a range seen in the PCOS subjects over time, whereas women with PCOS have more components of the metabolic syndrome starting at an early age and therefore have a longer exposure to these adverse cardiovascular risk factors.

Despite the longer exposure to these cardiovascular risk factors, it is difficult to demonstrate an increased risk of morbidity and mortality in women with PCOS. There has been only one small longitudinal study and one retrospective cohort study in women diagnosed with PCOS in their reproductive years and controls to assess risk of mortality and cardiovascular morbidity into menopause, up to age 70 years (76, 77). These studies have not demonstrated an increased risk of myocardial infarction or death from cardiovascular disease or increased total mortality from any cause in women with PCOS (76). Only the retrospective cohort study demonstrated an increased risk of stroke (77), but the group also had a higher BMI, more diabetes, and more cardiovascular risk factors overall. Taken together, additional studies are needed to determine whether the increased cardiovascular risk in reproductive life translates into an increased cardiovascular morbidity and mortality in later life for women with PCOS. However, it is possible that in most women with PCOS the cardiovascular risk normalizes with age, whereas in a subgroup, perhaps in the patients maintaining high androgen levels also after menopause, the cardiovascular risk remains increased and affects the morbidity. Only longitudinal studies in large populations of women with PCOS will answer this question.

When diseases are common, it is possible that some aspect of what is now disease gave humans a selective advantage in a different environment. For example, the thrifty gene hypothesis proposes that positive selection of metabolic traits that were advantageous in times of starvation, allowing efficient use of fuels and prevention of weight loss, are disadvantageous in the modern world where food is plentiful (78). These genetic changes may now result in an increased risk of type 2 diabetes (78). Similarly, women with PCOS may have a selective advantage in the population based on a longer reproductive lifespan, but menstrual cycles may become irregular with the weight gain that is common in modern society. The longer reproductive lifespan in women with PCOS is suggested by the greater number of follicles and the attenuated fall in ovarian volume across reproductive aging in both cross-sectional and longitudinal studies (50). Similarly, AMH levels, a marker of antral follicle number (79, 80), exhibit a less pronounced longitudinal decrease across aging in women with PCOS (81), resulting in an estimated menopausal age 2 years later than in controls (82). Although the irregular menstrual cyclicity in women with PCOS might be expected to decrease fertility, one longitudinal study suggested that there was no difference in pregnancy rates for the first child and that a majority of women with PCOS had achieved a spontaneous pregnancy (83). Despite the promising signs of a longer reproductive lifespan, longitudinal and retrospective studies have yet to document a later age at menopause (52, 77). Taken together, the data suggest that ovarian aging in women with PCOS is delayed compared with that in control women, but further longitudinal evidence is also needed.

**Summary**

It is clear that the phenotype in women with PCOS changes across the lifespan. It will be straightforward to create age-based criteria to diagnose PCOS during the reproductive years given the wealth of data. Following women with PCOS into menopause will help define the true cardiovascular morbidity and mortality. Finally, with our increasing understanding of the environmental factors and genes that predispose to PCOS, we may soon be able to fully elucidate the phenotype in prepubertal girls in an unbiased fashion. These ongoing studies will provide a thorough understanding of the PCOS lifecycle, to help with diagnosis and treatment that is no longer limited to the reproductive-age patient.

**Acknowledgments**

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This work was supported by the National Institutes of Health 1R01HD065029 (to C.K.W.), ADA 1-10-CT-57 (to C.K.W.), and 1 UL1 RR025758 to Harvard Clinical and Translational Science Center.

Disclosure Summary: The authors have nothing to disclose.

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