Natural History of Polycystic Ovary Syndrome and New Advances in the Epidemiology

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women, affecting up to 15% of the female population. The natural history of the syndrome is complex, including both androgen exposure in early life and adiposity-driven dysfunction in the hypothalamus–ovarian crosstalk. The manifestations can arise as early as childhood or puberty onward, suggesting that genetic susceptibility is an important etiological factor. Epidemiological studies on large datasets offer an excellent opportunity to evaluate health effects and costs related to the syndrome. In adulthood, women with PCOS present with reproductive, metabolic, and psychological health issues at a population-based level. Hospital or insurance-based datasets are also available; however, the results are not representative of the female population in the community. More longitudinal studies spanning from early childhood to late adulthood are needed to assess the long-term health impact and early manifestations of PCOS. Moreover, the identification of women with PCOS from large datasets can be expensive. Self-reported symptoms or PCOS diagnosis may offer a feasible approach.

Keywords
► PCOS
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► epidemiology

Natural History of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) represents the most common endocrinopathy in women, with a prevalence of 5 to 15%, depending on the diagnostic criteria used and the study population.[1] PCOS is a highly heritable syndrome, with the daughters of women with PCOS carrying a fivefold greater risk of developing PCOS compared with daughters of controls.[2] The diagnosis is based on three criteria: (1) oligo-anovulation, (2) hyperandrogenism (clinical or biochemical hyperandrogenism), and (3) polycystic ovary morphology (PCOM). Two out of three criteria are sufficient to establish a diagnosis, and four different phenotypes may be derived from the criteria (A–D) (►**Table 1**). Genome-wide association studies (GWAS) have tried to identify candidate genes that may explain heritability. The results of these studies indicate roles for gonadotrophins, steroid hormone regulation, anti-müllerian hormone (AMH) signaling, metabolism, cellular proliferation/differentiation, transcription regulation, chromatin structure/DNA repair, and ovarian aging in PCOS pathogenesis.[3–8] Even though twin studies indicate that the variance in the pathogenesis of PCOS is 72% due to genetic influences, the genetic variants identified to date account only for less than 10% of the heritability.[9,10] It seems plausible that rare variants with big effect sizes occurring in genes that regulate relevant disease pathways are responsible for the heritability. For this reason, larger cohorts are needed to identify the candidate genes.

Q4 **Table 1** Q4

Criteria	Phenotypes			
	A	B	C	D
Hyperandrogenism	√	√	√	
Oligo-anovulation	√	√		√
Polycystic ovarian morphology	√		√	√
Rotterdam 2003	√	√	√	√
NIH 1990	√	√		
AE-PCOS 2006	√	√	√	

Interestingly, the GWAS also indicate that despite the diagnostic criteria used for PCOS, whether from Rotterdam, the National Institute of Health, or even self-reported, women share similar genetic architecture.[11] However, when women are classified into reproductive and metabolic subtypes, based on luteinizing hormone (LH), follicle-stimulating hormone, sex-hormone-binding globulin, fasting insulin and fasting glucose levels, as well as body mass index (BMI), genetic differences can be observed between these subtypes, confirming the heterogeneity in PCOS and, possibly, different origins. The different phenotypes seem to be conserved within families.[3] To date, no data are available on whether the heritability of PCOS is different between phenotypes or subtypes.

Studies also support the causative role of prenatal androgen exposure in PCOS.[12–14] In animals, androgen exposure during pregnancy predisposes the offspring to a PCOS-like phenotype, which seems to carry over several generations.[2] Instead of direct exposure to androgens, high AMH levels during pregnancy also result in PCOS-like phenotypes in mouse offspring, inducing both hyperandrogenism and morphological changes in the brain, leading to hyperactivation of GnRH neurons, increased LH pulsatility, and anovulation.[15] Based on animal studies, genetic and epigenetic modifications in the germline induced by prenatal androgen exposure appear to be the mechanism of transgenerational transmission.[2] Changes in the expression of genes involved in DNA repair, germ cell and reproductive processes, glucose homeostasis, and steroid hormone signaling pathways were detected in the oocytes, closely resembling the functions of genes identified in GWAS, even though the genes do not include the exact loci identified in GWAS.[2,16] Some hypotheses suggest that development of PCOS requires not only genetic susceptibility but also a trigger during adolescence. Obesity and insulin resistance are strong candidates for such triggering events during puberty.[17–19] Stress, mood problems, and eating disorders during adolescence may also disturb neuroendocrine signaling.[20] Given that the natural history of PCOS suggests early onset, follow-up studies and large datasets may reveal both patterns that are important in the understanding of the onset of the syndrome and also longitudinal health risks. The following sections describe the epidemiological advances and challenges in the field of PCOS.

Epidemiological Advances

The international PCOS guideline, published in 2018, summarizes the recent evidence-based data on the management of the syndrome, also identifying research gaps and the need for additional studies in these areas.[1] Although randomized controlled trials are the gold standard to assess the efficacy of specific interventions, other approaches are also needed.

Since 2000, the number of epidemiological studies on PCOS have been emerging at an increasing rate, with around 150 publications listed yearly in PubMed. These studies have answered questions on different health risks and cost associations related to PCOS and are thus central in guideline and management development. Moreover, epidemiological studies are also necessary for the evaluation of prevention strategies. To follow up the lifelong health consequences of PCOS and gather populations large enough for analyses with sufficient power, large population-based studies with information on PCOS status are needed. Even though population-based studies, especially those with a longitudinal approach, are time-consuming, tedious, and expensive, they are an invaluable source of information for researchers.

Moreover, register-based studies can also provide a valuable data source. The challenges, however, remain in the identification of the cases, data interpretation (usually associations rather than causations), and in utilizing and combining the already existing datasets. Moreover, usually due to a lack of data and the limited possibility of separating the study population into subgroups, some residual confounders always remain. However, given that epidemiological studies can add substantially to new knowledge in the natural history of PCOS and support other data approaches, more resources are needed to conduct well-constructed longitudinal studies. In addition, strategies and techniques to facilitate modern data capture and usage are likely to be very beneficial.

Identification of Women with PCOS and Different Epidemiological Datasets

Due to limited available resources, it is not always feasible to screen for PCOS by means of physical or laboratory assessments in large populations. An alternative approach is often required in these instances, and self-reported PCOS status or symptoms consistent with PCOS provide a suitable alternative. For example, a symptom-based PCOS diagnosis has been utilized in the Northern Finland Birth Cohort 1966 studies since 1997. In this cohort, women aged 31 years were asked two questions: "*Is your menstrual cycle >35 days more than twice a year?*" (oligomenorrhea, OA) and "*Do you have bothersome hair growth?*" (hirsutism, H). Women who answered "yes" to both were considered to be women with PCOS. These two questions capture a subpopulation of women who have significantly higher androgen levels and impaired glucose metabolism than those not reporting OA and H.[21] The women have also been shown to present with a higher rate of mental distress, as supported by several other studies assessing women with clinically established

diagnoses.[22] When a subgroup of women in this study reporting both symptoms was examined by ultrasound, 70.4% of them also had PCOM, compared with 18.2% among women reporting neither symptom.[23] The validity of this symptom-based approach has also been confirmed by a recent study. It showed that 82.5% of women who reported excessive hair growth (according to the question: "*Do you have male-like hair growth on your upper lip, chin, chest, abdomen, buttocks, or back?*") and irregular menses (according to the question: "*Do you have infrequent or irregular cycles—either more than every 35 days between the beginning of one period and the next or 8 or less cycles per year?*") fulfilled the Rotterdam diagnostic criteria for PCOS when examined by a doctor, compared with 14.4% in women reporting neither.[24] Interestingly, out of the 82.5%, 74.3% also had PCOM. The sensitivity of self-report in predicting PCOS according to Rotterdam criteria was 89%, and the specificity was 78%, offering a good, financially sustainable approach to identifying women with PCOS for larger studies.[24]

On the other hand, questions capturing a PCOS diagnosis previously set by a physician (self-reported PCOS) have been used by some cohort studies, and they identify a female population with typical hormonal, metabolic, and psychological profiles comparable to studies assessing women with clinically determined PCOS cases.[25–30] The validity of self-reporting PCOS is also supported by GWAS findings, which showed no differences in genetic architecture among women diagnosed by National Institute of Health criteria, Rotterdam criteria, or self-report.[11] Some large cohorts have been able to establish PCOS diagnoses based on clinical assessments; however, this diagnostic approach requires greater resources.[26,31–33] The benefit of such studies is that these datasets can also distinguish different PCOS phenotypes (A–D) and thus contribute more widely to the pathogenesis and clinical questions related to the syndrome.

Studies utilizing hospital-based registers, national registers linking hospital-based diagnosis, and health insurance datasets are also increasingly being utilized.[34–36] Even though these datasets usually offer the largest target populations, it is essential to remember that hospital-based datasets represent populations needing hospital contact, and thus the derived data must be interpreted in this context and often cannot be generalized to the general PCOS population. Moreover, in these study settings, the diagnoses of PCOS or PCOS symptoms are often identified with the World Health Organization International Classification of Diseases codes. In many cases, only the PCOS or anovulatory infertility codes are captured, without the possibility of phenotype assessment, limiting the interpretation of the data. Moreover, the prevalence of PCOS is commonly very low in these datasets, suggesting poor awareness and underdiagnosis of the syndrome, thereby identifying the need to weight the data or use imputation methods.[37–40] All in all, reliable tools to identify women with PCOS from datasets do exist; however, PCOS underdiagnosis and identification of PCOS phenotypes provide challenges for these approaches.

Diagnosis in Adolescents

While the Rotterdam criteria are currently the most widely used diagnostic criteria for PCOS, their use for adolescents may lead to overdiagnosis of PCOS, due to the greater prevalence of PCOM in this age group. Nor is it uncommon for menstrual cycles to be irregular for the first few years following menarche. The Raine study, a community-based prospective cohort from Western Australia, enrolled and followed up 2,900 pregnant women and their subsequent live births starting in 1989. A substudy of the Raine study examined a cohort of 227 adolescent females who undertook comprehensive PCOS assessment. Use of the original Rotterdam criteria produced a diagnosis of PCOS in 29.1% of adolescents in this study[41] and identified females with similar long-term weight gain compared with females without PCOS.[42] However, when PCOS diagnosis was based on both OA and hyperandrogenism, PCOS was identified in 16.3% of the adolescents,[41] which was consistent with the reported adult prevalence of PCOS.[43,44] These updated diagnostic criteria for adolescents identified females at risk of increased long-term weight gain, demonstrating higher BMI trajectories than those without PCOS, starting from the prepubertal years,[42] a finding also supported by other datasets.[17]

These results validate the 2018 international PCOS guideline, which recommends omitting PCOM as part of PCOS diagnosis in adolescents,[41] as the adult diagnostic criteria are likely to overdiagnose PCOS in adolescents. Instead, the updated diagnostic criteria are more likely to identify adolescents with PCOS at risk of a higher BMI trajectory and more rapid weight gain. Given that weight gain and excess weight contribute significantly to long-term PCOS sequelae,[45] the updated adolescent diagnostic criteria identifies the highest risk group that would benefit from early lifestyle intervention to prevent complications.

Polycystic Ovary Syndrome in the Context of Epidemiological Studies

Obesity

Rates of obesity are rising at alarming levels globally. Excess weight, present in up to 70% of women with PCOS in many countries worldwide, exacerbates the prevalence, incidence, and severity of PCOS,[46–49] particularly the clinical expression of metabolic and reproductive features.[50] A large Australian cohort study reported weight, BMI, PCOS prevalence, and weight gain over time in women with PCOS. PCOS status was based on self-report of physician diagnosis. The study included a large unselected community-based study of primarily Caucasian women.[51] Bodyweight, BMI, and weight gain over 10 years were higher in women reporting PCOS than in women not reporting PCOS. In addition, mean BMI was the strongest correlate of PCOS status on multivariable regression analysis, with the risk of reporting PCOS increasing by 9.2% for each unit of BMI (kg/m^2).[51] A similar result was also reported in population-based data from Finland, revealing a 5% increased risk for PCOS for each BMI unit.[27]

While many studies have considered BMI a major confounder in the relationship between PCOS and its associated metabolic and reproductive sequelae, longitudinal BMI change is not usually reported. Patterns of BMI change have been noted to be heterogeneous within the general population, with different patterns of BMI change seen among different groups.[51] An Australian study examined changes in weight over 12 years in a community-based sample of women and found three distinct BMI trajectories emerging among women with PCOS.[52] These trajectories are as follows: low stable (63.8%), defined as an average trajectory remaining at approximately 25 kg/m;[2] moderately rising (28.8%), a curvilinear trajectory commencing in a healthy BMI range and terminating in the overweight range; and high rising (7.4%), a curvilinear trajectory commencing and terminating in the obese range.[52] The study also reported that obesity in early reproductive life predicted membership in the higher trajectories.[52] As for early adiposity and weight analysis in PCOS, a longitudinal Finnish birth cohort study following women from birth to age 46 reported BMI patterns of women with PCOS already starting to differentiate from those of women without PCOS before the age of 5, and remaining higher until the age of 46 years.[17] Every 1-year shift in age at adiposity rebound toward earlier onset (normally occurring around the age of 5 years) resulted in a 48% increase in PCOS risk in adulthood, suggesting early BMI deviation is a risk factor for PCOS later in life. The same dataset also showed a 5-kg higher weight gain from age 14 to 31 in women with PCOS than in women without PCOS, highlighting the strong link between PCOS and weight gain.[27]

However, not all studies support higher weight gain in PCOS. A 6-year prospective study in Denmark among women aged 29 to 30 reported a significant increase in mean BMI for both PCOS and non-PCOS groups.[53] Moreover, nonsignificant differences in BMI from baseline were reported in several other studies.[43–45,54] A prospective American study reported no significant rate of BMI change between women with PCOS and controls, although they did report a significant increase in BMI over time in both groups.[55] Nevertheless, high BMI remains one of the main features of PCOS, but evidence for the direction of causality is still lacking, that is, whether PCOS predisposes to high BMI or high BMI to PCOS.

Metabolic Characteristics

A cross-sectional Australian community-based study in women aged between 28 and 33 showed that the prevalence of type 2 diabetes mellitus (T2DM) was 5.1% in women with PCOS and 0.3% in women without PCOS. After adjusting for confounding factors, including BMI, the odds of T2DM were 8.8 times higher in women reporting PCOS.[56] A longitudinal analysis of this study examining the incidence of T2DM over a follow-up of 15 years and 1,919 person-years (PY) found that the incidence rate of T2DM was 4.19 per 1,000 in women with PCOS and 1.02 per 1,000 PY in women without PCOS. On subgroup analyses across healthy weight, overweight, and obese categories of women, the incidence rates for T2DM were 3.21, 4.67, and 8.80 per 1,000 PY, respectively, in women with PCOS.[29] The risk for metabolic alterations

also depends on the population and age of the women assessed. In a Finnish cross-sectional cohort study, there was no difference in T2DM risk in normal-weight 46-year-old women with PCOS; however, a 2.5-fold T2DM risk was observed for overweight/obese women with PCOS when compared with controls in the same weight group.[28] The women who developed T2DM presented with the highest weight gain between ages 14 and 46. A similar result was also reported by an 8-year prospective study among Caucasian women aged 38 to 40 years, which reported a similar incidence rate of T2DM in women with PCOS and controls. However, obese women with PCOS had a fivefold risk of developing T2DM compared with obese controls, whereas there was no significant difference in nonobese women.[57] A 12-year prospective Iranian study revealed a five times higher T2DM risk in women with PCOS than in controls below 40 years of age.[58] The incidence rate of T2DM was significantly higher in women with PCOS (13 per 1,000 PY) than in the control women (4 per 1,000 PY) over a 9-year follow-up period in a prospective Iranian study conducted in women aged 29 years.[59] An 18-year retrospective American study of women aged 29 revealed a 2.6 times higher risk of incident diabetes in women with PCOS compared with women without PCOS.[60]

While PCOS is known to be associated with metabolic complications such as dysglycemia, the association between PCOS and hypertension has remained unclear, with inconsistent results in studies examining hypertension in women with PCOS.[61] An 18-year American retrospective study in women aged 29 reported a similar risk of incident hypertension between PCOS and non-PCOS women.[60] A large prospective Iranian study among women aged between 26 and 29 reported a significantly higher risk of hypertension in women with PCOS than in controls over a 12-year follow-up period; however, this was observed only in the subgroup of younger than 40 years.[62] A cross-sectional community study reported that while hypertension increased in women reporting PCOS, there was only a trend toward significance for PCOS association with hypertension once adjusted for other relevant factors.[63] BMI was increased in PCOS and was associated with hypertension, yet hypertension was associated only with BMI in women not reporting PCOS.[63] The data are consistent with other data suggesting lean women with PCOS are at high metabolic risk independent of BMI. A population-based Finnish cohort study reported that already at 31 years of age, women with self-reported PCOS have significantly higher systolic and diastolic blood pressures, both in normal-weight and overweight/obese groups. At the age of 46 years, women with PCOS have a 1.5-fold risk for hypertension independent of BMI.[64] In a recent longitudinal study, 9,508 women from the general population were followed up for 145,159 person-years. This study reported that the incidence of hypertension was higher in women with PCOS and found that PCOS was independently associated with a 37% greater risk of hypertension, adjusting for BMI and other confounding factors.[65]

A Finnish population-based cohort study reported dyslipidemia associated with PCOS at the age of 31 years.[27] In line

with this, an 18-year retrospective study on 29-year-old women indicated a twofold risk of incident dyslipidemia compared with women without PCOS.[60] However, not all studies agree. No difference in the risk of dyslipidemia between women with PCOS and controls was shown for over 12 years of follow-up among Iranian women.[62]

PCOS is associated with metabolic dysfunction, with a higher risk of T2DM, hypertension, and dyslipidemia, but appears in part related to BMI. However, the development of these metabolic sequelae may be mediated by BMI and maintenance of healthy body weight may help minimize the risk of developing metabolic dysfunction.

Reproductive Function

Testosterone levels decrease in all women over time, initially with a mild decrease in ovarian androgen secretion capacity in early reproductive years and a more marked decrease in later reproductive years.[66,67] Studies consistently show that testosterone levels also decrease longitudinally, but to a greater degree in women with PCOS than in controls.[45,54,68,69] A 6-year prospective Danish study specified that total testosterone levels decreased significantly in both women with PCOS and controls; however, only free testosterone decreased significantly in the PCOS group.[53] An Italian study of women aged 30 reported a more rapid decrease in total testosterone through 10 years of follow-up in women with PCOS.[54] The decline most likely mirrors the decrease in the follicle pool, resulting in decreased AMH levels and thus decreased hypothalamic–pituitary–ovarian (HPO) axis stimulation in PCOS, ultimately manifesting as reduced thecal androgen production. Thus, as women with PCOS age, their HPO axis function seems to normalize.

As for menstrual patterns, a study from the Netherlands showed that women with PCOS had significantly fewer menstrual cycles per year than controls.[69] While OA is a cardinal feature of PCOS, the ovulatory function appears to improve over time in most women with PCOS.[70] Menstrual irregularity, also, often improves over time,[68,71] and it is estimated that 30% of older women with PCOS acquire normal ovulatory function.[71,72]

An Australian cross-sectional community-based study in women aged 28 to 33 years showed that women with PCOS were less likely to be using contraception (61 vs. 79%) and were more likely to be trying to conceive (56 vs. 45%), compared with women not reporting PCOS.[73] Overall, the study reported no significant difference in the number of children between women with and without PCOS. This is also supported by Finnish birth cohort data.[74] Interestingly, a Finnish register study indicates even higher parity among women with PCOS than non-PCOS controls,[40] which may be because PCOS is often diagnosed at fertility clinics, and the diagnosed PCOS population may be overrepresented by women who wish to conceive. Even though women with PCOS reported greater pregnancy loss (20 vs. 15%), PCOS was not independently associated with pregnancy loss, while BMI was independently associated with pregnancy loss in the overweight and obese groups.[73] Fertility treatment use was also independently associated with pregnancy loss. This is consistent with the study by Palomba et al, which reported that women with PCOS had a significantly higher cumulative rate of miscarriage (16 vs. 5.3%) than women without PCOS[75]; however, other studies have reported no significant difference in pregnancy loss in women with PCOS compared with women without PCOS.[76] Women with PCOS may have increased pregnancy loss, but this may be associated with related factors such as BMI and fertility treatment, as opposed to PCOS status per se.

The Australian study found that women with PCOS reported higher infertility rates and that PCOS was associated with a 15-fold increased risk of infertility, independent of BMI. This suggests that PCOS had a strong independent association with infertility that overwhelmed any impact of BMI. This is not consistent with the current understanding that higher BMI per se is a key cause of infertility,[77–79] and it may suggest unnecessary worry over PCOS-related infertility among affected women. Of those who were infertile, more women with PCOS sought help or treatment for infertility.[80] Furthermore, women with PCOS were more likely to undergo fertility hormone treatment, but not in vitro fertilization.

The PCOS research field has for years concentrated mainly on infertility. However, considering the recent studies, even though women with PCOS are subfertile and may require fertility treatment, they do reassuringly have a similar family size compared with women without PCOS.

Psychological Aspects

An Australian study examined the relationship of PCOS with eating disorders, self-esteem, and psychological distress in a community-based sample of women aged between 22 and 27 years.[81] The study showed that PCOS was not associated with anorexic nervosa or bulimia nervosa; however, a multivariable analysis showed that women with PCOS had a twofold increased risk for developing other eating disorders. The ALSWH survey did not specify what was categorized in "other eating disorders," but based on previous literature, this group likely represents binge-eating disorders.[82–84] While low self-esteem and psychological distress were more commonly reported by women with PCOS, the association was negative in the multivariable analysis. This was also supported by a previous Finnish population-based study revealing a 30% increased risk for anxiety and depression symptoms at ages 31 and 46 in women with PCOS even after adjusting for BMI, hyperandrogenism, and socioeconomic status.[22]

A study examining the relationship of PCOS with common perinatal mental disorders found that the prevalence of antenatal depression, postnatal depression, antenatal anxiety, and postnatal anxiety was significantly higher in women with PCOS than in those without PCOS. After controlling for relevant factors such as sociodemographic factors, reproductive history, obstetric complications, and preexisting mood disorders, the findings further illustrated that antenatal but not postnatal depression and/or anxiety was increased by up to twofold in women with PCOS.[30] This study also looked at the association between PCOS and other psychiatric comorbidities in the cohort of women born between 1989 and 1995

in the ALSWH, taking into account the women's sociodemographic factors, BMI, adverse childhood experiences, social support, and perceived stress. In addition to anxiety and depression, this study found that PCOS was also significantly associated with posttraumatic stress disorder and obsessive–compulsive disorder. The study also reported a novel finding of a high prevalence of adverse childhood experiences in women with PCOS. The prevalence of four or more adverse childhood experiences in women with PCOS is twice the prevalence for those without PCOS, and this was associated with a threefold increased risk for psychiatric disorders.[85]

Psychological distress is very common in women with PCOS. Whether this is induced by programming of the central nervous system due to prenatal androgen exposure or whether PCOS features, such as hirsutism, acne, and increased weight, contribute to this distress remains debatable.

Conclusions

The latest studies on animals and humans indicate PCOS as a syndrome with early origins and strong transgenerational transmission. However, many questions remain unanswered. To study different aspects of PCOS in humans, longitudinal datasets with follow-up from childhood to adulthood and possibilities for generational data linkage are warranted. The biggest challenge is identifying women with PCOS from already existing datasets, which would enable the maximal utilization of resources and reduce the need for new expensive studies. In future, self-reported questionnaire data combined with biological markers and possibly genetic approaches may offer applicable tools in detecting women with PCOS in large datasets. Ethnic diversity should also be considered and open data sharing between cohorts encouraged.

The studies conducted so far are often limited regarding participant numbers, PCOS phenotype data, may include self-reported PCOS status or may include PCOS study populations recruited from fertility clinics. Additionally, health professionals often demonstrate suboptimal awareness of PCOS symptoms and morbidities related to it, which results in underdiagnosis of the syndrome and underrepresentation of PCOS in register datasets. Furthermore, the diagnosis is rarely made outside fertility clinics. It is of utmost importance that PCOS awareness is also raised among both general practitioners and specialists in various fields of medicine (e.g., internal medicine, gynecology, psychiatry, and dermatology).

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