Polycystic ovary syndrome

Ricardo Azziz[1,2], Enrico Carmina[3], ZiJiang Chen[4,5], Andrea Dunaif[6], Joop S. E. Laven[7], Richard S. Legro[8], Daria Lizneva[1,9], Barbara Natterson-Horowtiz[10], Helena J. Teede[11] and Bulent O. Yildiz[12]

Abstract | Polycystic ovary syndrome (PCOS) affects 5–20% of women of reproductive age worldwide. The condition is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology (PCOM) — with excessive androgen production by the ovaries being a key feature of PCOS. Metabolic dysfunction characterized by insulin resistance and compensatory hyperinsulinaemia is evident in the vast majority of affected individuals. PCOS increases the risk for type 2 diabetes mellitus, gestational diabetes and other pregnancy-related complications, venous thromboembolism, cerebrovascular and cardiovascular events and endometrial cancer. PCOS is a diagnosis of exclusion, based primarily on the presence of hyperandrogenism, ovulatory dysfunction and PCOM. Treatment should be tailored to the complaints and needs of the patient and involves targeting metabolic abnormalities through lifestyle changes, medication and potentially surgery for the prevention and management of excess weight, androgen suppression and/or blockade, endometrial protection, reproductive therapy and the detection and treatment of psychological features. This Primer summarizes the current state of knowledge regarding the epidemiology, mechanisms and pathophysiology, diagnosis, screening and prevention, management and future investigational directions of the disorder.

Polycystic ovary syndrome (PCOS) is a common disorder in women that is characterized by hyperandrogenism (that is, evidence of excess male hormone or androgen effect; for example, clinically, such as hirsutism, and/or biochemically, such as hyperandrogenaemia or excess levels of androgen), ovulatory dysfunction (including menstrual dysfunction) and polycystic ovarian morphology (PCOM; an excessive number of preantral follicles in the ovaries). The clinical presentation is heterogeneous and can be categorized in several phenotypes, depending on the presence or absence of characteristic features (FIG. 1). Metabolic abnormalities, mainly insulin resistance and compensatory hyperinsulinaemia, are evident in a majority of affected individuals[1], especially among those women who also show hyperandrogenism[2]. Between 1 in 6 and 1 in 20 women of reproductive age (5–20%) are affected by the disorder worldwide. In 2004, the economic impact of PCOS exceeded US$4 billion in the United States alone, even without considering the cost of the increased risk of obstetrical complications, type 2 diabetes mellitus (T2DM) and other disorders[3].

Although signs and symptoms are most evident in women of reproductive age, the disorder also carries risk and symptoms in prepuberty and postmenopause, which are only now beginning to be identified[4]. Children might present with premature pubarche and adolescents with early signs of androgenization (for example, acne and hirsutism) and menstrual irregularity. Postmenopausal women with PCOS carry an increased risk for metabolic and cardiovascular comorbidities, although hyperandrogenic symptoms ameliorate during menopause.

Women with PCOS have an increased risk for metabolic abnormalities and T2DM, infertility, obstetrical complications, endometrial cancer and mood disorders. These women also probably have an increased risk for cardiovascular and cerebrovascular events, venous thromboembolism and ovarian cancer.

Epidemiology

Prevalence

The prevalence of PCOS is remarkably similar worldwide. The prevalence of clinically evident PCOS in women of reproductive age from the United States, Europe, Asia and Australia ranges between 5% and 9%[5] based on the original 1990 US National Institutes of Health (NIH) diagnostic criteria[6] (BOX 1; FIG. 1). Using the broader 2003 Rotterdam criteria[7,8] (FIG. 1), now endorsed by the NIH and accepted internationally, the prevalence of PCOS ranges from 5.5% to 19.9%[5]. The larger variation using the 2003 Rotterdam criteria might be the

Correspondence to R.A. Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, 1120 15th Street, CB-2209, Augusta, Georgia 30912, USA.
RAZZIZ@augusta.edu

Article number: 16057
doi:10.1038/nrdp.2016.57
Published online 11 Aug 2016

Author addresses

[1]Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, 1120 15th Street, CB-2209, Augusta, Georgia 30912, USA.
[2]Department of Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia, USA.
[3]Department of Health Sciences and Mother and Child Care, University of Palermo, Palermo, Italy.
[4]Center for Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China.
[5]Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Shanghai, China.
[6]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.
[7]Division of Reproductive Medicine, Department of OBGYN, Erasmus Medical Centre, Rotterdam, The Netherlands.
[8]Department of Obstetrics and Gynecology, College of Medicine, Pennsylvania State University, Hershey, Pennsylvania, USA.
[9]Department of Reproductive Health Protection, Scientific Center of Family Health and Human Reproduction, Irkutsk, Russian Federation.
[10]Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles, California, USA.
[11]Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University in partnership with Monash Health, Clayton, Victoria, Australia.
[12]Division of Endocrinology and Metabolism, Department of Internal Medicine, Hacettepe University School of Medicine, Hacettepe, Ankara, Turkey.

consequence of variation in the sensitivity of the tests used for detecting the disorder.

The characteristic features of PCOS lead to several different phenotypes (FIG. 1). The phenotypic distribution of PCOS in epidemiological studies in unselected (unbiased) populations is 40–45% for phenotype A and phenotype B combined, ~35% for phenotype C and ~20% for phenotype D[5]. An important point to keep in mind is that only studies in unselected (medically unbiased) populations will enable us to clearly identify the true phenotype of PCOS. Compared with unselected patients, patients with PCOS in the clinical setting are more obese, more hirsute, more hyperandrogenaemic and show a greater proportion of phenotype A and phenotype B[9], reflecting substantial referral bias.

Dermatological abnormalities

Hirsutism, acne and androgenic alopecia are clinical signs and symptoms of hyperandrogenism. In clinical studies, hirsutism affects ~65–75% of black and white patients with PCOS, which is dramatically higher than otherwise expected (0–2%)[10]. Acne affects 15–25% of patients with PCOS and varies with ethnicity; although it is unclear whether the prevalence of acne is significantly increased in these patients over that observed in the general population[10].

Although hirsutism is frequently defined visually by a modified Ferriman–Gallwey (mFG) score of ≥6, which corresponds to the 95th percentile of the population studied, other studies indicate that an mFG score of ≥3 should be considered abnormal in white or black, and probably even in Mongoloid or Asiatic, women[11]. Indeed, in a study of 228 patients with minimal unwanted hair growth (with an mFG score of ≤5), >50% demonstrated an androgen excess disorder[12]. Thus, many women have excessive or unwanted hair growth but may not be afforded appropriate evaluation because they are not deemed to be 'sufficiently' hirsute.

Metabolic dysfunction

Many women with PCOS demonstrate basal and glucose-stimulated hyperinsulinaemia and are insulin resistant, independent of body mass index (BMI). Insulin-mediated glucose disposal, quantitated by euglycaemic clamp, was on average 35–40% lower in patients with PCOS than in matched controls[1,13].

Data indicate that the incidence of metabolic syndrome, gestational diabetes mellitus, impaired glucose tolerance (IGT) and T2DM is increased in premenopausal women with PCOS compared with age-matched and BMI-matched controls[14]. No less than 2% of women with PCOS progress from baseline normoglycaemia to T2DM every year and 16% progress from IGT to T2DM[15,16]. The prevalence of T2DM in PCOS continues to increase during the late reproductive years[17,18]. Data on the prevalence of T2DM in postmenopausal women with PCOS are limited, but the few reports available do not demonstrate a further substantial increase in the incidence of IGT or T2DM in postmenopausal women with PCOS[18,19].

In a systematic review and meta-analysis on metabolic syndrome, the prevalence of IGT (odds ratio (OR): 2.4; 95% CI: 1.4–4.5) and T2DM (OR: 4.43; 95% CI: 4.1–4.8) was far higher in patients with PCOS than in controls and the risk of metabolic disease in those with PCOS was clearly demonstrated[14]. In this systematic review, on subgroup analysis, increased prevalence of IGT and metabolic syndrome was observed when comparing lean women with and without PCOS, although no study actually compared the prevalence of T2DM in these populations.

Obesity

The effect of obesity on PCOS and PCOS on obesity is complex, and strong evidence of an association is currently lacking. Although PCOS occurs in obese and lean women, a recent systematic review and meta-analysis concluded that obesity was more prevalent in women with PCOS than in women without PCOS[20]. However, all but two of the studies reviewed recruited their patients from hospitals or clinics. By contrast, studies in unselected (medically unbiased) populations have suggested that BMI distribution was more similar between patients with PCOS identified in unselected populations and controls and that BMI was higher than in patients with PCOS in referral (clinically biased) settings[9,21]. These data indicate that much of the obesity in women with PCOS may be driven by self-referral, as obesity is one of the primary depressors of quality of life (QOL)[22–24].

In addition, evidence that obesity drives the development or prevalence of PCOS is conflicting. A higher incidence of PCOS was observed among those who were

obese based on studies of women seeking bariatric surgery or dietary interventions[25,26] in a retrospective study of a national birth cohort using self-reported symptoms[27] and in a community-based longitudinal observational study[28]. However, in an unselected population in the United States, no significant difference in PCOS prevalence according to BMI was detected[29], although another similarly designed study in Turkey showed greater rates of PCOS as mean BMI increased[30]. The fact that there is no relationship between PCOS prevalence in different countries, which differ in mean population BMI, further supports that obesity does not drive the development of PCOS[5]. In addition, no association between genetic variants in genes known to be involved in obesity and genes involved in PCOS has been found[31–33].

Subfertility

PCOS is the primary cause of anovulatory subfertility, with major health and economic costs; however, community-based data are limited on prevalence and treatment trends in infertility in PCOS. Most infertility and PCOS data are based on selected populations managed in hospital or in fertility clinics, and national funding policies on assisted reproduction vary substantially, making comparisons difficult. In a community-based study, the self-reported prevalence of PCOS was 5.8%. Infertility was noted by 72% of women reporting PCOS compared with 16% of those not reporting PCOS ($P < 0.001$); infertility was 15-fold higher in women reporting PCOS, independent of BMI[34]. One retrospective study followed a cohort of 786 women with PCOS who were diagnosed >30 years ago from hospital records[35]. In this selected population, 66% of women reported infertility. Overall, PCOS seems to be the most common cause of anovulatory infertility and further studies are needed on the natural history of this feature in community-based samples.

Psychological manifestations

Depression and anxiety are more common and more severe in women with PCOS than in women without the disorder[36–38], regardless of the phenotype of PCOS or the presence of obesity[37,39]. Interestingly, depression scores seem to be significantly correlated with the degree of insulin resistance[40]. A meta-analysis of 28 studies including 2,384 patients with PCOS and 2,705 controls found that more-severe emotional distress was present in women with PCOS than in controls[38]. However, even though the hirsutism, obesity and infertility associated with the syndrome were shown to be in some way linked to severe emotional distress in women with PCOS, these factors alone did not fully or consistently account for the high prevalence of anxiety and depression[38].

Long-term morbidity

In addition to the complications of subfertility, metabolic dysfunction and dysglycaemia, and psychological dysfunction, patients with PCOS are at long-term risks for additional disorders.

Obstetrical complications. Patients with PCOS are at risk of experiencing complications during pregnancy. A population-based study of singleton births among 3,787 women with PCOS and >1 million without PCOS registered in the Swedish medical birth registry between 1995 and 2007 indicated that pregnancies in women with PCOS had significantly higher rates of pre-eclampsia, very preterm birth (defined as <32 weeks of gestation in the study) and gestational diabetes mellitus[41]. Infants born to women with PCOS had a higher risk of being large for gestational age, having meconium aspiration syndrome (in which the stool of the infant defecated into the amniotic fluid, generally under stress, is inhaled) and having a low (<7) Apgar score (which assesses the condition of the newborn by valuing breathing effort, heart rate, muscle tone, reflexes and skin colour) at 5 minutes. The increased risk of adverse pregnancy and birth outcomes could not be fully explained by the use of assisted reproductive technologies, which are used more frequently by women with PCOS[41]. Other studies have confirmed these findings[42–44], regardless of the criteria used to define PCOS. Metformin treatment in pregnant women with PCOS does not seem to reduce pregnancy complications in the disorder[45].

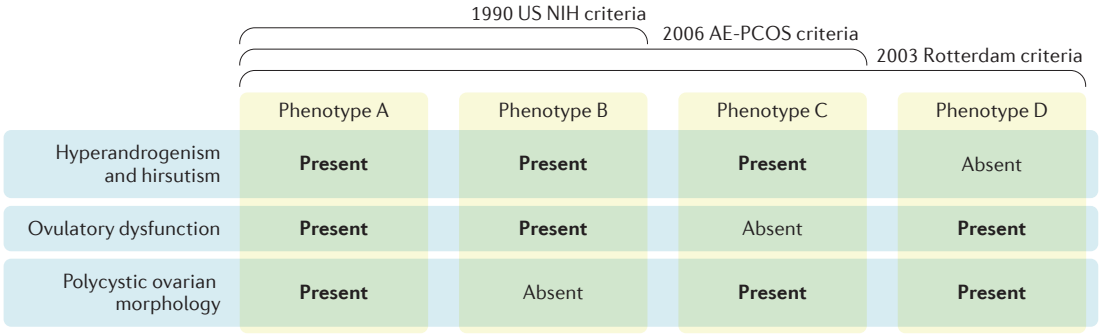

Figure 1 | **Diagnostic criteria and phenotypes of PCOS.** Polycystic ovary syndrome (PCOS) is classified into four separate phenotypes (A–D), according to the presence or absence of three characteristics: hyperandrogenism (either biochemical or clinical), ovulatory dysfunction and polycystic ovarian morphology. Only phenotype A requires all three features of PCOS to be present. The various diagnostic criteria currently available for PCOS include a greater or fewer number of PCOS phenotypes. AE-PCOS, Androgen Excess-PCOS Society; NIH, National Institutes of Health.

Cardiovascular and cerebrovascular complications. Cardiovascular disease (CVD) markers (for example, vascular calcification and the thickness of the vascular wall) point to a higher risk of CVD in women with PCOS than in controls, although an increased number of actual cardiovascular events has been difficult to demonstrate[46]. Compared with healthy controls, significant coronary calcification is more prevalent in women with PCOS[47,48]; the thickness of the intimal layer of the carotid wall has been reported to be greater in women with PCOS[49,50]; the incidence of aortic calcification was reported to be higher in one study[48], and the Dallas heart study showed that arterial stenosis was more prevalent in women with PCOS based on coronary angiography[51]. Questions have been raised as to whether these findings indicate a true increase in actual cardiovascular mortality.

Data on cardiovascular events (for example, myocardial infarctions) in PCOS are conflicting. The incidence of CVD strongly increases after 50 years of age in the general population, and a similar increase is expected to be present after menopause in women with PCOS[52]. The few follow-up studies available do not demonstrate a greater number of cardiovascular events in women with PCOS who are of late reproductive age than in age-matched controls[53–55], although the number of patients followed is too few to be able to detect small changes in incidence. Hospitalization data in PCOS have indicated that the number of cardiovascular events might be increased during late reproductive years, although these studies have many biases[56]. Two small studies[52,57] and one 20-year retrospective cohort study[58] reported increased risk of myocardial infarction in patients with PCOS as compared with controls.

In addition, in women with the more-severe phenotype of PCOS (that is, phenotype A and phenotype B), the relative risk for CVD was reported to be 1.3 (REF. 59). However, negative studies have also been reported; Wild *et al.*[60] did not find any difference in cardiovascular mortality in women with PCOS versus controls when controlling for BMI. The Mayo Clinic cohort did not reveal any increase in cardiovascular morbidity, including myocardial infarction[61]. A 21-year longitudinal study in Sweden demonstrated that the incidence of cardiovascular events was comparable between women with PCOS and controls[19]. To date, studies investigating the risk of cardiovascular events in PCOS are derived from clinical cohort studies and are, therefore, subject to referral bias[9]. In addition, substantial variability in ethnicity, PCOS criteria and study design confound the findings.

The incidence of cerebrovascular events was slightly increased in older women with PCOS compared with the general population[62,63]. The risk of venous thromboembolisms is increased (OR: 1.5) compared with BMI-matched controls[64], with the risk of venous thromboembolisms being twofold higher in women with PCOS who take oral contraceptive pills (OCPs) than in the general population[56,65].

Risk of malignancies. Not unexpectedly, considering the concurrence of hyperoestrogenic anovulation and hyperinsulinaemia, women with PCOS have an increased risk for endometrial cancer (OR: 2.7). They may also have an increased risk for ovarian cancer, although the OR for this malignancy is unclear. However, no associated increased risk of breast cancer has been shown[66].

Box 1 | **Diagnostic criteria for PCOS***

1990 US NIH criteria‡

Patients are diagnosed with polycystic ovary syndrome (PCOS) if they have all of the following criteria:

- Oligo-anovulation
- Clinical and/or biochemical signs of androgen excess

2003 Rotterdam criteria§

Patients are diagnosed with PCOS if they have two of the following three criteria:

- Oligo-anovulation
- Clinical and/or biochemical signs of androgen excess
- Polycystic ovarian morphology (PCOM)

2006 Androgen Excess-PCOS Society criteria‖

Patients are diagnosed with PCOS if they have all of the following criteria:

- Clinical and/or biochemical signs of androgen excess
- Ovarian dysfunction, including oligo-anovulation and/or PCOM

*All criteria require the exclusion of similar, mimicking disorders, such as thyroid dysfunction, hyperprolactinaemia, adrenal hyperplasia, androgen-secreting tumours and iatrogenic androgen excess, among others. ‡See REF. 6. §Criteria proposed by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine expert conference held in Rotterdam[7,8]. ‖Criteria proposed by an expert Task Force of the Androgen Excess and PCOS Society[140]. NIH, National Institutes of Health.

Mechanisms/pathophysiology

The pathophysiology and intrinsic mechanisms underlying PCOS are complex because aetiologies vary and the different features are considerably intertwined (FIG. 2). The interplay between these mechanisms results in and perpetuates the clinical features of PCOS, including hyperandrogenism, PCOM and ovulatory dysfunction, in addition to the associated mood disturbances, psychosexual dysfunction and long-term morbidities. In addition, the development of PCOS has a strong genetic component.

Genetic factors

Familial clustering and the results from twin studies strongly support an underlying genetic basis for PCOS. For example, having a mother or sister with PCOS conveys a 30–50% risk of developing PCOS[67–69]. The correlation for PCOS between monozygotic twin sisters was twice as high as the dizygotic twin correlation. Genetic factors were suggested to explain 66% of the variance according to the univariate genetic model[2]. To date, large numbers of genetic studies have identified almost 100 susceptibility genes related to PCOS. Although the candidate gene approach is reasonable to explore the genetic origin of PCOS, it is neither an efficient nor a consistent

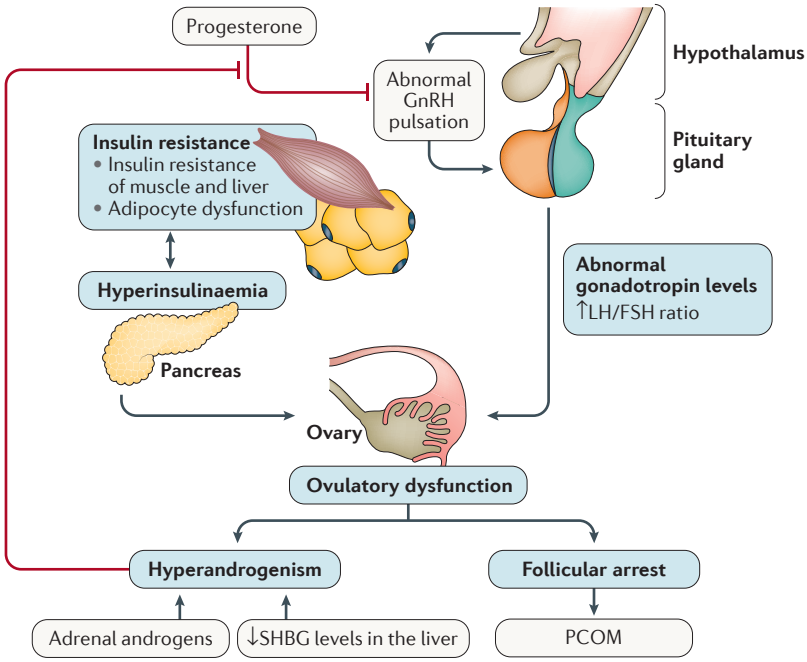

Figure 2 | **The pathophysiology of PCOS.** The pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus is often disturbed in polycystic ovary syndrome (PCOS), leading to luteinizing hormone (LH) hypersecretion by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This perturbed secretion of LH seems to arise early in puberty and is related to disturbed inhibition of GnRH secretion by progesterone. Although serum follicle-stimulating hormone (FSH) levels are generally normal, follicles seem to be more resistant to FSH in women with PCOS than in controls. This effect might be due to increased levels of intra-ovarian anti-Müllerian hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to susceptibly for most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion. PCOM, polycystic ovarian morphology; SHBG, sex hormone-binding globulin.

method for such a complex polygenetic disease[70] (BOX 2). High-throughput genome-wide association studies (GWAS) provide a more comprehensive, unbiased, discovery-driven approach to explore the genetic basis of complex disorders (TABLE 1).

Two GWAS in Han Chinese women with PCOS identified 11 susceptibility loci[71,72]. Some of these genes, such as *INSR*, *FSHR* and *C9orf3*, have been confirmed in subsequent family-based studies[73,74]. A genome-wide association study in a population of white women with European ancestry identified two novel loci in the region of *GATA4–NEIL2* and *FSHB–ARL14EP*[75]. The loci near *C9orf3*, which was also observed in Han Chinese studies, was also confirmed. In a second genome-wide association study including white women of European descent, three novel susceptibility genes — *ERBB4*, *RAD50* and *KRR1* — were observed with genome-wide significance. The Mendelian randomization analyses suggested a causal role of PCOS risk single-nucleotide polymorphisms for higher BMI, insulin resistance and lower levels of sex hormone-binding globulin (SHBG) in PCOS. Other previously reported genes, namely, *YAP1*, *THADA* and *FSHB*, were also replicated[76]. Notably, the loci identified in GWAS so far account for perhaps no more than 10% of the heritability of the disorder[77].

Phenotypes associated with the variants discovered may also provide an insight into the pathophysiology conferred by the susceptibility genes. Genotype–phenotype correlation studies in Han Chinese women with PCOS demonstrated that the *THADA* and *DENND1A* variants were associated with endocrine and metabolic disturbances[78]. In populations of European ancestry, *DENND1A* was observed to be a risk allele for androgen excess and anovulation[79], a variant near *FSHR* was associated with lower levels of follicle-stimulating hormone (FSH)[79] and a variant near *RAB5B* seemed to be associated with glucose metabolism dysfunction[80].

Studies in women with a single PCOS clinical feature identified a specific genetic association for *LHCGR* and *INSR* with anovulation, and *THADA* and *DENND1A* with polycystic ovaries. *C9orf3* and rs4385527 conferred a particular risk for all three of the definitive manifestations of PCOS (that is, hyperandrogenism, ovulatory dysfunction and PCOM), which suggests their fundamental role in the aetiology of the disorder[81]. *In silico* analysis based on data from GWAS is another approach that may assist in deciphering the mechanisms underlying PCOS. According to pathway analysis, *INS*, *GNAQ*, *PLCB3*, *STXBP1*, *SMC3*, *PLCB2* and *PLCZ1* are significantly associated with oocyte meiosis and the regulation of insulin secretion[82].

In addition, functional studies focusing on the loci elucidated by GWAS have been performed. A recent study measured DNA methylation and gene expression of 11 Chinese GWAS risk loci in subcutaneous adipose tissue of patients with PCOS. This study found that the genetic variants in *LHCGR* and *INSR* might have changed the expression level via modification on methylation. Hypomethylation of *LHCGR* was concordant with *LHCGR* overexpression in non-obese patients, but not in the obese ones, whereas hypermethylation of *INSR* was not associated with different gene expression between obese and non-obese women with PCOS. In this study, no significant difference was found in genes of other GWAS loci, after correction for multiple testing[83].

Despite the vast progress in the identification of PCOS loci, the quantitative traits associated with the disorder and the underling mechanisms are still largely unknown. However, the elucidation of genotype–phenotype associations should be the aim in the 'post-GWAS' era.

Gonadotropic derangements

In normal circumstances, immature oocytes mature under the influence of several hormones, most notably FSH, and ovulation as well as final maturation occur upon luteinizing hormone (LH) stimulation. A neuroendocrine abnormality in PCOS may include increased gonadotropin-releasing hormone (GnRH) pulse frequency, which increases the frequency and pulse amplitude of LH over FSH production. This abnormality results in increased circulating LH/FSH ratio and is frequently observed in lean, but not obese, women with PCOS[84,85]. The finding that increased LH pulses and enhanced daytime LH pulse secretion

Box 2 | **Selected genetic variants associated with PCOS**

Candidate gene studies[70] have identified genes involved in:

- Androgen biosynthesis: *CYP1A1*, *CYP11A*, *CYP17A1*, *CYP19* and *HSD17B6*
- Androgen action: *AR*, *SHBG*, *SRD5A1* and *SRD5A2*
- Insulin signalling: *INSR*, *IRS1*, *IRS2*, *PPARG* and *CAPN10*
- Metabolism: *ADIPOQ* and *FTO*
- Folliculogenesis: *FSHR*, *LHCGR* and *AMHR2*
- Inflammation: *IL1A*, *IL1B*, *IL6*, *IL18*, *PAI1*, *FBN3*, *TNF* and *MEP1A*

are already observed early during puberty in girls with hyperandrogenism indicates that abnormalities in the pulsatile release of GnRH might underlie the development of PCOS, at least in some patients[86]. The increased LH/FSH ratio, and the resistance to FSH in the ovaries (see below), further enhances hypersecretion of androgens in theca cells in ovarian follicles, which impairs follicular development[86] and reduces the inhibition of GnRH pulse frequency by progesterone, further promoting the development of the PCOS phenotype[86].

Ovarian follicular arrest

The coordination and interaction of LH, FSH, insulin-like growth factor 1 (IGF1), anti-Müllerian hormone (AMH), enzymes involved in androgen conversion and possibly other factors are disturbed in PCOS — leading to oligo-ovulation (irregular ovulation) or anovulation (the absence of ovulation)[87] (FIG. 3). In PCOS, the selection of a dominant follicle (that is, the follicle that proceeds to ovulation in each cycle) does not occur regularly[88], which is a consequence of insufficient secretion of FSH and local inhibition of FSH action.

Follicular FSH resistance might be caused by other intra-ovarian regulators of FSH action. One such factor is the increased levels of AMH in PCOS, which might reduce the FSH sensitivity of individual ovarian follicles[89] and block the conversion of androgens to oestrogens via the inhibition of aromatase activity, thereby further contributing to hyperandrogenism. Finally, genetic variations from normal in the FSH molecule itself and in its receptor might be partially responsible for some of the differences in FSH sensitivity between patients with PCOS and healthy controls[90].

Increased circulating levels of AMH arise as a consequence of an increased number of small antral (maturing) follicles and increased production of AMH per follicle[91]. Although reduced levels of AMH in small primordial and transitional follicles of women with anovulatory PCOS can initially promote the recruitment of additional growing follicles[92], hypersecretion of AMH in granulosa cells of more-mature small antral follicles could subsequently impair further follicular growth by inhibiting FSH and aromatase action[89,93]. Thus, in patients with anovulatory PCOS, circulating FSH levels, although at low-to-normal concentrations, generally will not be enough to overcome the inhibition of aromatase activity by AMH in the antral follicle[94].

LH hypersecretion is also detrimental to normal follicular growth and might cause premature luteinization of granulosa cells (leading to hypertrophy, lipid accumulation and other changes in the follicle that normally occur after ovulation)[87]. Follicular growth often resumes following the replacement of oestradiol and progesterone during the luteal phase of the menstrual cycle in women with PCOS characterized by anovulation, which might be related to the reduction in the LH/FSH ratio and ovarian FSH resistance[95].

Similarly, reduction in negative-feedback mechanisms at the level of the pituitary gland by administrating anti-oestrogens or by reducing the conversion of androgens to oestrogens through the administration of aromatase inhibitors will lead to increased release of FSH and subsequent resumption of follicular growth in anovulatory PCOS[87]. Overstimulation of LH induces hypersecretion of theca cell-derived androgens, which further impairs follicular maturation by promoting the initiation of primordial follicle growth and increasing the number of growing small antral follicles[96]. Overstimulation of theca cells by LH is further exacerbated by the gonadotropic action of insulin on theca cells, acting either directly through the insulin receptor or indirectly through the IGF1 receptor[97].

Intra-ovarian factors that modulate follicular recruitment and growth, including members of the transforming growth factor-β family (for example, AMH, inhibins, activins, bone morphogenetic proteins and growth differentiation factors (GDFs)), other growth factors and cytokines might also contribute to the abnormal follicle development and function seen in PCOS[87]. The oocyte and its surrounding granulosa cells produce many of these factors[98]. For example, oocyte-derived GDF9 is crucial for normal folliculogenesis and is dysregulated in women with PCOS[99]. Although inhibins, activins, follistatin and IGF1 all have a crucial role in folliculogenesis, their possible permissive role in the pathophysiology of ovarian dysfunction in women with PCOS remains to be demonstrated[87].

Insulin resistance and hyperinsulinaemia

Under normal circumstances, as insulin sensitivity decreases, insulin secretion increases to maintain a constant hyperbolic relationship, a relationship that is expressed by the Disposition Index[100]. In women with PCOS, basal insulin secretion rates are increased[101], although insulin secretory responses to a glucose load are generally inadequate, resulting in a lower Disposition Index than age-matched and BMI-matched control women[101–103]. Thus, despite the presence of hyperinsulinaemia, women with PCOS have relative pancreatic β-cell dysfunction[104]. Women with PCOS also demonstrate decreased hepatic extraction of insulin[105,106], which contributes to their hyperinsulinaemia.

The molecular mechanisms that drive insulin resistance in PCOS differ from those in other common insulin-resistant states, such as obesity and T2DM. In muscle, serine phosphorylation of the insulin receptor and of insulin receptor substrate 1 (IRS1) is increased[107], resulting in impaired insulin signalling[108,109]

and in constitutive activation of MEK1 and MEK2 (MEK1/2) in PCOS[110,111] (FIG. 4). The PCOS-associated insulin resistance is selective, affecting metabolic, but not mitogenic, signalling pathways[110,112], which might explain the paradox of the persistent reproductive actions of insulin in the face of systemic insulin resistance. Defects in insulin signalling persist in cultured cells[107,113]. Two studies have suggested that skeletal muscle is no longer insulin resistant in long-term culture[113,114], whereas one study found persistent defects in insulin responsiveness in cultured PCOS myotubes[115]. The reasons for these discrepant findings are unclear, although these observations suggest that both intrinsic abnormalities and extrinsic factors in the *in vivo* environment account for insulin resistance in skeletal muscle of women with PCOS[113,114]. Abnormalities in insulin action are also observed in adipose tissue and adipocytes in women with PCOS, although the nature of the defects differs[113,115].

Adipose tissue dysfunction

Although women with PCOS can show little difference in fat distribution and possibly in overall BMI, strong evidence supports that adipocytes and adipocyte function are aberrant in PCOS, favouring insulin resistance and subclinical inflammation. The peripheral insulin resistance observed in PCOS might be the result, at least in part, of adipocyte dysfunction (FIG. 5). For example, inflammatory cytokines (such as tumour necrosis factor and IL-6) suppress insulin-mediated glucose transport more in adipocytes derived from patients with PCOS than in adipocytes derived from matched controls[116]. Women with PCOS seem to have larger adipocytes[117], lower lipoprotein lipase activity[117] and impaired catecholamine-induced lipolysis[118] compared with matched controls.

Inflammatory cytokines also suppress adiponectin secretion to a greater degree in adipocytes derived from patients with PCOS than in matched controls, favouring the development of a more pro-inflammatory, insulin-resistant environment[116]. Glucose transporter 4 (GLUT4; also known as SLC2A4) protein expression is decreased in adipocytes in PCOS[119], similar to levels observed in adipocytes derived from patients with T2DM[120–122]. Overall, adipocyte functioning, including the stimulation of glucose transport[109], GLUT4 production[119,123],

Table 1 | **Current genome-wide association studies in PCOS**

Number (cases; controls)	Susceptibility loci	Mapped genes	SNPs	Refs
Han Chinese ethnicity				
Discovery set: 744; 895	2p16.3	*LHCGR*	rs13405728	72
First replication set: 2,840; 5,012	2p21	*THADA*	rs12478601 and rs13429458	
Second replication set: 498; 780	9q33.3	*DENND1A*	rs2479106 and rs10818854	
Discovery set: 2,254; 3,001	2p16.3	*FSHR*	rs2268361 and rs2349415	71
Replication set: 8,226; 7,578	9q22.32	*C9orf3*	rs3802457 and rs4385527	
	11q22.1	*YAP1*	rs1894116	
	12q13.2	*RAB5B* and *SUOX*	rs705702	
	12q14.3	*HMGA2*	rs2272046	
	16q12.1	*TOX3*	rs4784165	
	19p13.2	*INSR*	rs2059807	
	20q13.2	*SUMO1P1*	rs6022786	
European ancestry				
Discovery set: 984; 2,964	8p32.1	*GATA4–NEIL2*	rs804279	75
Replication set: 1,799; 1,231	11p14.1	*KCNA4–FSHB*	rs11031006	
	9q22.32	*C9orf3*	rs10993397	
Discovery set: 5,184; 82,759	2q34	*ERBB4*	rs1351592	76
Replication set: 7,229*; 181,645	11q22.1	*YAP1*	rs11225154	
	2p21	*THADA*	rs9563201	
	11p14.1	*FSHB*	rs11031006	
	5q31.1	*RAD50*	rs13164856	
	12q21.2	*KRR1*	rs1275468	
	12q13.2	*ERBB3*	rs7312770	
	17q12	*ERBB2*	rs7218361	
	9q33.3	*DENND1A*	rs10760321	

PCOS, polycystic ovary syndrome; SNP, single-nucleotide polymorphism. *Cases were defined by either the 1990 US National Institutes of Health (NIH) criteria or the 2003 Rotterdam criteria.

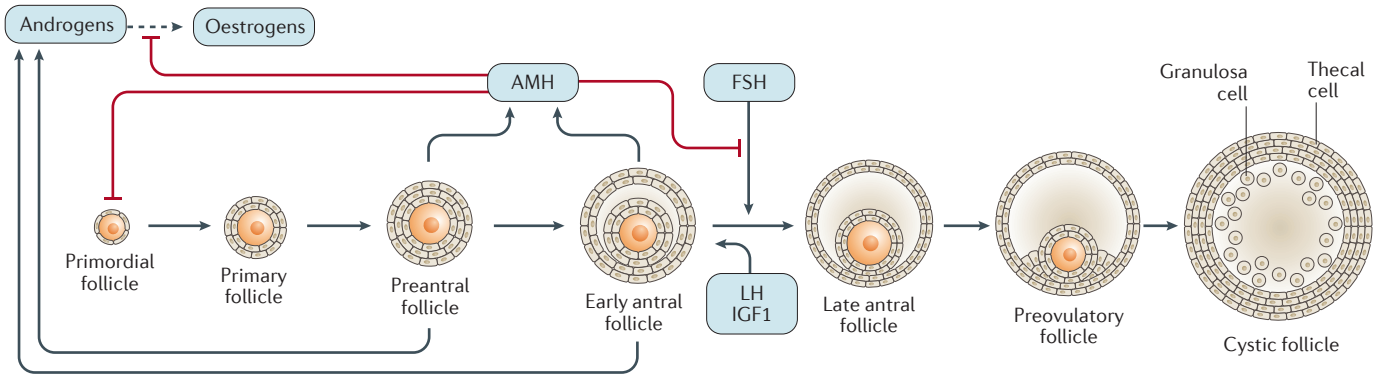

Figure 3 | **Ovarian follicular maturation arrest in PCOS.** Normal ovulation is the result of synchronized signalling between centrally released gonadotropins and factors produced in the developing follicle of the ovary. Anovulation in women with polycystic ovary syndrome (PCOS) is characterized by arrested follicle growth at the early antral stage. Hypersecretion of luteinizing hormone (LH) and insulin-like growth factor 1 (IGF1) leads to hyperandrogenism, which results in follicular maturation arrest[93]. In addition, high levels of anti-Müllerian hormone (AMH) in PCOS block follicle-stimulating hormone (FSH) action, contribute to hyperandrogenism and inhibit the recruitment of further primordial follicles. Dashed line indicates androgen to oestrogen conversion.

and insulin-stimulated inhibition of lipolysis[124,125], are defective in PCOS. Epigenetic dysregulation of adipocyte function has been observed in PCOS, primarily of microRNA-93 (miR-93) and miR-223, which seem to have a role in suppressing GLUT4 content and altering glucose transport[123,126]. In contrast to myocytes, no defects have been found in the classic insulin signalling pathway in adipocytes in PCOS, including in insulin binding and in insulin receptor expression[123].

Hyperandrogenism

The increased ovarian androgen production observed in PCOS is mainly due to enhanced androgen synthesis by follicular theca cells, which show an increased expression of several genes encoding steroidogenic enzymes[127]. A recent study reported that a candidate gene for PCOS, *DENND1A*, was overexpressed in theca cells obtained from patients with PCOS[127], further supporting the notion that, at least in some patients, ovarian androgen excess is a genetically determined feature of PCOS. In addition, the expression of the gene encoding the rate-limiting enzyme in androgen biosynthesis (*CYP17A1*) is increased in theca cells obtained from women with PCOS, which might contribute to a higher conversion of progestogen precursors to androgens[127]. Theca cells isolated from women with PCOS are more responsive in terms of androgen secretion to insulin and LH than theca cells of healthy controls[97]. In addition to directly stimulating ovarian androgen secretion, hyperinsulinaemia contributes to hyperandrogenism in PCOS by reducing hepatic synthesis of SHBG, leading to increased free testosterone fractions[104].

Although the ovaries are the main source of hyperandrogenism in PCOS, between 20% and 30% of patients also show adrenal androgen excess suggesting adrenocortical hyperfunction[128]. Adrenocortical dysfunction in PCOS might be secondary to a generalized exaggeration in the responsivity, but not sensitivity, to adrenocorticotropic hormone, but genetics might have a role.

One of the consequences of hyperandrogenism is hirsutism. Androgens, primarily testosterone and dihydrotestosterone, through their effect on the androgen receptor, stimulate, among other factors, ornithine decarboxylase synthesis in the hair follicle, which in turn stimulates polyamine production. Polyamines are multifunctional cationic amines that are indispensable for cellular proliferation, including hair growth in the hair follicle.

Mood disturbances and psychosexual dysfunction

Causal factors underpinning the mood disturbance in PCOS remain unclear. The complex hormonal milieu might contribute, although the clinical features of PCOS seem to also adversely affect mood[36,129,130]. Further potential contributors might include delayed diagnosis, poor diagnostic experience and the chronic and complex nature of the condition[131,132].

Diagnosis, screening and prevention

Diagnosis

There are currently three main diagnostic criteria for defining PCOS (BOX 1; FIG. 1). The evaluation of PCOS entails determining the presence or absence of: hyperandrogenism, ovulatory dysfunction and PCOM. Hyperandrogenism is clinically determined based on the presence of hirsutism using a visual scoring system, such as the mFG method[11], and biochemically measuring the levels of circulating androgens. The clinical detection of ovulatory dysfunction is generally based on a history of polymenorrhoea or oligo-amenorrhoea, or by assessing ovulatory function using luteal phase progesterone levels in hirsute women who are otherwise eumenorrhoeic. Ovarian ultrasonography (FIG. 6) is used to identify PCOM.

All current criteria also call for the exclusion of related or mimicking disorders. Hyperprolactinaemia and thyroid dysfunction, which can result in ovulatory dysfunction, should be excluded. Non-classic adrenal hyperplasia, androgen-secreting neoplasias, rare

syndromes of insulin resistance, with or without lipodystrophy, and the use of anabolic or androgenic drugs and idiopathic hirsutism, which can also present with signs and symptoms of androgen excess, should also be excluded. Regardless of the criteria used to define PCOS, greater emphasis should be given to defining the actual phenotypes of PCOS (FIG. 1). Different diagnostic criteria take different phenotypes into account. Phenotypes A–C are considered hyperandrogenic, whereas phenotype D is non-hyperandrogenic. In addition, phenotype A and phenotype B and, to a somewhat lesser extent, phenotype C, are associated with a higher risk of concomitant metabolic dysfunction, which is less so for phenotype D[133–136]. Overall, most investigators today use the broader 2003 Rotterdam criteria for PCOS, but stress that the specific phenotypes included must be clearly recognized and documented as they differ substantially.

Screening and prevention of PCOS

As the cause of PCOS is still unclear, and is probably multifactorial, a specific plan for early risk prediction of diagnosis and treatment is not yet possible. However, studies in at-risk paediatric populations, principally first-degree female relatives of women with PCOS, have elucidated various features that will facilitate the clinician to identify those at risk for developing PCOS (BOX 3). Given that longitudinal studies are few and generally short term, the exact extent to which these factors determine the risk of PCOS, particularly in families without other first-degree relatives with PCOS, is not well defined.

To what extent early prediction and treatment of PCOS can ameliorate the disorder is unclear. Early treatment of excess weight gain, hyperandrogenic symptom and menstrual dysfunction will result in clinical improvement, although it is unclear whether this will prevent further progression of the disorder. One study reported on the possibility that early treatment with metformin might reduce progression to PCOS in girls with low birth weight and precocious pubarche[137]. Further studies of early markers of disease and early intervention trials of at-risk children and adolescents are crucially needed.

Screening for associated morbidities

Rigorous international evidence-based guidelines clearly recognize the need to routinely screen for metabolic (glucose tolerance and lipid status) and psychological (anxiety and depression) features associated with PCOS[36,138]. Screening of metabolic abnormalities should not include testing fasting insulin levels in routine practice as available assays lack adequate accuracy and sensitivity[36]. Fasting blood glucose levels alone to detect dysglycaemia is not recommended as they seem to underdiagnose IGT and T2DM in PCOS, in which patients primarily demonstrate skeletal muscle-based and adipocyte tissue-based insulin resistance, rather than hepatic resistance[36,104]. Although visually evident acanthosis nigricans (hypertrophy of the basal layers of the epidermis of the skin, usually in body folds) seems to be a good predictor of insulin resistance and hyperinsulinaemia, well-controlled prospective studies of the predictive value of this dermatological sign are lacking.

Current recommendations are to screen all women with PCOS for glucose intolerance using a 2-hour oral glucose tolerance test. Frequency of testing remains to be determined and ranges from every other year in all patients with PCOS to recurrent testing only in those with additional diabetes risk factors, including obesity[36,138–140].

Assessment of general CVD risk factors, including age, BMI, sleep apnoea, smoking status, family history, lipid and liver enzyme profiles and blood pressure, is recommended at diagnosis. Subsequent assessment should be based on individual overall risk, with the frequency of re-testing still under discussion[36,138,139,141]. For women with a long history of irregular menstrual cycles without endometrial protection, screening for endometrial hyperplasia might also be relevant, given the high risk of endometrial cancer in women with PCOS[56].

Screening for psychological features is important given their high prevalence. Effective, readily available screening questionnaires have been developed to assist screening for mood disorders in PCOS in clinical practice[36]. If depression, anxiety and psychological features are detected, treatment also includes conventional treatment for mood disorders and treatment of factors that could affect QOL, such as hirsutism and excess weight[36].

Management

Therapy of PCOS should be tailored to the individual patient, and is often multifactorial. Lifestyle interventions are first-line treatment for PCOS, and small lifestyle changes can improve metabolic dysfunction, ovulation, fertility and mood[142]. Other management options are aimed at improving metabolic dysfunction, hyperandrogenism, reproductive therapy, and psychological and emotional status.

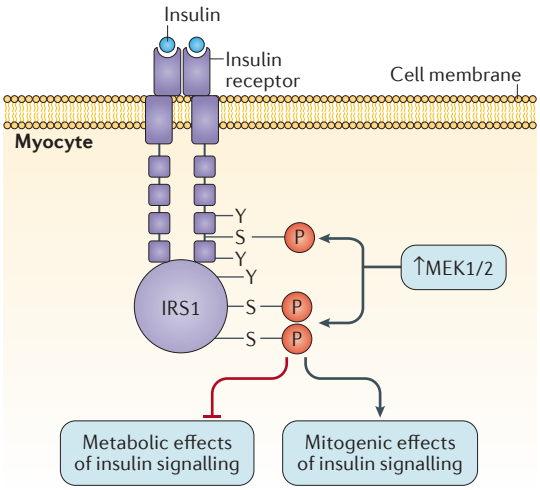

Figure 4 | **Molecular mechanisms of insulin resistance in muscle in PCOS.** In myocytes (and fibroblasts), constitutive activation of MEK1/2 leads to increased phosphorylation (P) of serine (S) residues on the insulin receptor and on insulin receptor substrate 1 (IRS1), which hampers insulin signalling in the metabolic, but not the mitogenic, pathways. PCOS, polycystic ovary syndrome; Y, tyrosine.

Metabolic dysfunction and obesity

Lifestyle modification. Lifestyle intervention is the primary treatment of metabolic dysfunction in PCOS and also improves fertility[143]. Lifestyle intervention programmes improve ovulation in 40–50% of women with PCOS, 30–40% of whom are able to achieve a spontaneous pregnancy[144]. Reduction of body weight in women with PCOS who are overweight or obese improves their metabolic profile and induces ovulatory cycles[145]. A small reduction in body weight (of at least 5%) can improve ovulation, suggesting that the results depend more on energy restriction or changes in fat distribution than on weight loss per se[146].

Different hypocaloric diets with various macronutrient compositions have been used with no significant differences in results[147]. In some patients, high-protein diets might be better tolerated and lead to more satiety[148,149]. However, long-term results of any diet are poor because of early dropout and low long-term compliance.

Physical exercise can also help to reduce body weight[150], but most studies only show modest or no weight loss in women with PCOS, even with intensified exercise programmes[151,152]. However, physical exercise improved insulin resistance, promoted changes in fat distribution and reduced cardiovascular risk in women with PCOS[151], but should be performed at least 30 minutes per day for at least 5 days per week. An effective lifestyle programme should always include psychological support, social support and avoidance of toxic substances (for example, smoking, alcohol and drugs).

Bariatric surgery. For those women who fail to control their weight on diet alone, bariatric surgery is an important option, but should be reserved for women with PCOS with severe obesity (a BMI of >40) or with moderate obesity (a BMI of >35) who also have additional health issues. A meta-analysis of 13 primary studies has shown that bariatric surgery decreased the incidence of PCOS symptoms from 45.6% to 7.1%, with a mean weight loss of 57.2%[153].

Medical treatment. Several pharmacological interventions can be used when lifestyle modifications fail to manage metabolic dysfunction and dyslipidaemia in women with PCOS. Many of these may also have indirect beneficial effects on the hyperandrogenism and ovulatory dysfunction of the disorder. Metformin, a biguanide approved for the treatment of T2DM that suppresses hepatic gluconeogenesis and improves peripheral insulin sensitivity, can be used for the prevention of T2DM and impaired glucose tolerance when lifestyle modification fails. Metformin improves body composition and insulin levels in women with PCOS who are not obese, but has no significant effect on BMI, fasting glucose or lipid levels[154]. A recent systematic review and meta-analysis suggests that the combination of lifestyle modification with metformin reduced BMI in women with PCOS to a greater degree than lifestyle modification alone[155].

Thiazolidinediones (peroxisome proliferator-activated receptor agonists or activators) are more effective than metformin in lowering fasting insulin and in improving insulin resistance in PCOS[156], yet less effective in reducing BMI and triglyceride levels[157]. Owing to potentially serious adverse effects, thiazolidinediones are not currently recommended for the routine treatment of insulin resistance in PCOS[138,158].

Inositol isomers (secondary messengers involved in several signalling pathways, including the insulin pathway), in particular, combinations of myo-inositol and D-chiro-inositol, have been shown to have insulin-mimetic properties and to lower post-prandial blood glucose. In PCOS, treatment with inositol isomers has been shown to significantly improve the regularity of the menstrual cycle, the endocrine and metabolic parameters and insulin resistance[159]. However, controversy remains regarding the extent of the benefit and the exact dosing of these substances[160].

A meta-analysis evaluating acarbose (an α-glucosidase inhibitor) treatment in PCOS demonstrated significant improvement in lipid profile, but an inconclusive effect on BMI[161].

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which reduce cholesterol synthesis) can be used according to standard indications in PCOS. Statins are more effective than placebo in reducing total cholesterol and triglyceride levels in PCOS[162]. In combination with metformin, they further improve dyslipidaemia and markers of inflammation,

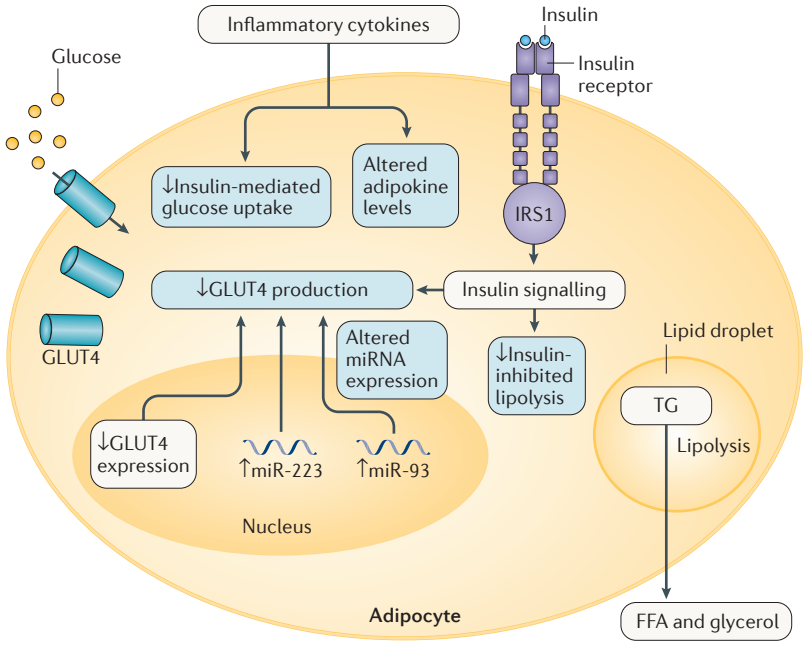

Figure 5 | **Molecular mechanisms of insulin resistance in adipose tissue in PCOS.** Although adipose tissue accounts for only 10% of insulin-stimulated whole-body glucose uptake[232], this tissue is crucial in determining systemic glucose homeostasis. For example, adipose tissue controls plasma free fatty acid (FFA) levels and secretes adipokines, among other substances, that substantially modulate insulin action and control systemic insulin sensitivity, energy balance and metabolic homeostasis. Adipocyte dysfunction in polycystic ovary syndrome (PCOS) results in decreased levels of insulin-stimulated glucose transport, decreased glucose transporter 4 (GLUT4; also known as SLC2A4) production, decreased insulin-stimulated inhibition of lipolysis and altered microRNA (miRNA) expression. IRS1, insulin receptor substrate 1; TG, triglyceride. Image courtesy of Y.-H. Chen, Augusta University, Augusta, Georgia, USA.

but the combination is less effective in improving insulin sensitivity than metformin alone[163]. The risk of statins in human pregnancy remains controversial and current guidelines recommend discontinuing use before conception.

Various pharmacological agents have been approved for use in weight loss[164]. The use of orlistat (a lipase inhibitor that reduces the intestinal absorption of fat) is associated with a reduction in BMI in women with PCOS, but its effect on insulin sensitivity remains controversial[165]. Several studies have been conducted on the use of vitamin D in PCOS, but data from a recent meta-analysis does not support the suggestion that vitamin D supplementation improves insulin sensitivity in the disorder[166].

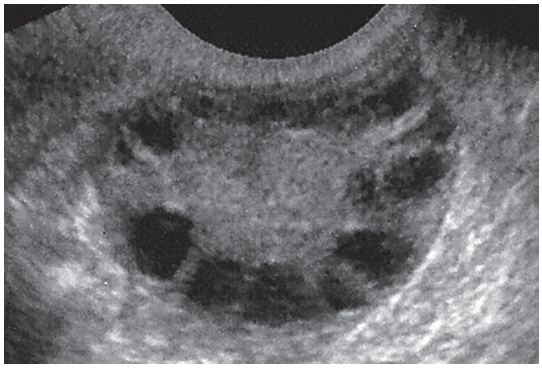

Figure 6 | **Typical polycystic ovarian morphology.** Polycystic ovarian morphology is characterized by enhanced central thecal–stromal volume and increased numbers of preovulatory follicles ringing the ovarian cortex. Image courtesy of J.S.E.L.

Hyperandrogenism

Suppression of ovarian androgen secretion. Combination OCPs and the less commonly used transdermal combination contraceptives effectively suppress ovarian androgen excess and are recommended as first-line management for the treatment of menstrual abnormalities, hirsutism and acne in women with PCOS who are not seeking fertility[138]. OCPs suppress gonadotropin release and consequently inhibit ovarian androgen secretion in women with PCOS. The oestrogen in OCPs also stimulates hepatic production of SHBG, which in turn reduces the free (active) fraction of circulating androgens (and oestrogens) (an effect that is not achieved by transdermal contraceptive preparations). Progestins in OCPs can also directly inhibit androgen biosynthesis and impair androgen receptor binding[167]. In addition, OCP use considerably reduces the risk of endometrial hyperplasia and endometrial cancer[66], while providing effective contraception when anti-androgen therapy is also used.

The most widely prescribed OCPs contain ethinyl estradiol and progestin, although there is no evidence that any one formulation is superior to any other for the treatment of PCOS[138]. Whether increased risk of cardiovascular, venous thromboembolism and metabolic comorbidities associated with OCP use should be considered, especially as women with PCOS are already at increased risk, remains controversial[168,169]. Appropriate contraindications should be elucidated and excluded before starting OCP use[170].

Other medical avenues to suppress ovarian steroidogenesis in patients with PCOS include continuous treatment with progestin[66] or administration of a long-acting GnRH analogue[171], but these are used much less frequently than OCPs. Insulin-sensitizing agents (for example, metformin and thiazolidinediones) also provide modest improvement in hyperandrogenism[172].

In addition to medical therapy, ovarian surgery can reduce ovarian steroidogenesis. For example, ovarian wedge resection (surgical removal of part of an ovary) decreases the number of antral follicles, suppresses the secretion of androgens, improves the endocrine status of other intra-ovarian factors and enables many patients with PCOS to achieve regular ovulatory cycles[173]. More recently, laparoscopic ovarian drilling (LOD; in which 10–15 small holes are burned into the surface of the ovary in patients with PCOS via laparoscopy) has been suggested as an alternative treatment to ovarian wedge resection because of the lower risk of complications, including pelvic adhesions and premature ovarian failure[174]. However, LOD only modestly suppresses androgen production in PCOS[175].

Anti-androgens. Drugs that block the action of androgens are off-label medications used in the management of PCOS[176–182] and availability varies internationally. This group includes androgen receptor blockers (for example, spironolactone, flutamide and cyproterone acetate) and 5α-reductase inhibitors (for example, finasteride)[176,183] (TABLE 2). Anti-androgens need to be prescribed along with secure contraception owing to their teratogenic potential (that is, risk of feminization of a male fetus)[177]. Anti-androgens also have variable adverse effect profiles, which can be considerable in the case of finasteride and flutamide. A combination therapy of anti-androgens with OCPs should be considered after failure to achieve the desired outcome with the OCP alone, or as initial therapy in more-severe cases of hirsutism. Improvement in hirsutism is usually observed after >6 months. Most anti-androgens can be used in adolescents, but the efficacy and safety of spironolactone and finasteride have not been well established in these younger patients. In addition to anti-androgens, a topical solution of eflornithine (also known as α-difluoromethylornithine) hydrochloride — an irreversible inhibitor of follicle ornithine decarboxylase — can be used to treat unwanted facial hair growth[184].

Cosmetic treatments. Hormonal suppression of androgen secretion and peripheral androgen blockade will ameliorate the effects of androgens on hair follicles, minimizing the progression and further development of the dermatological symptoms of the disorder, including hirsutism, acne and androgenic alopecia. However, these therapies will be less effective for the treatment of these features once established. Consequently, hormonal therapy should be combined with counselling regarding the use of cosmetic treatments for hirsutism (for example, shaving, depilation, laser epilation and electrology),

Box 3 | **Risk factors for the development of PCOS**

Family history is the most important risk factor for developing PCOS[67–69]. Other risk factors, depending on age, include:

- Before birth
  - Small for gestational age*
- Childhood and peripuberty
  - Early-onset obesity[219–222]
  - Increased dehydroepiandrosterone sulfate levels during the onset of puberty[219–222]
  - Premature pubarche[223,224]
  - Hyperinsulinaemia[219–222]
- Adolescence[225–228]
  - Obesity, overweightness or rapid weight gain[225–228]
  - Irregular menstrual or oligo-amenorrhoea[225–228]
  - Presence of polycystic ovarian morphology[225–228]
  - High androgen levels[225–228]
  - Development of unwanted terminal hair growth on the face or body[229]

*Although some investigators have suggested that girls born small for their gestational age are at higher risk for insulin resistance and possibly PCOS[230], other studies have indicated that most women with PCOS are actually born of normal or large size for gestational age[27,231].

acne (for example, topical antibacterials, and topical or oral retinoids) and androgenic alopecia (for example, minoxidil and hair transplantation)[185].

Endometrial protection

Owing to their hyperinsulinaemic hyperoestrogenic anovulatory state, patients with PCOS are at increased risk for endometrial hyperplasia and/or endometrial carcinoma. They are also at increased risk for unpredictable abnormal uterine bleeding, which, in addition to being disruptive and a nuisance, can result in bouts of severe dysfunctional uterine bleeding and consequent anaemia. As such, protecting the endometrium from excessive uncontrolled oestrogenic proliferation is crucial in patients with PCOS. This can be readily achieved by treating the patients with a progestogenic agent, most often in the form of a combination OCP or a cyclic progestogen (such as oral micronized progesterone and medroxyprogesterone acetate). Although some agents, such as insulin-sensitizing agents, might seem to improve the regularity of vaginal bleeding, this alone is not a guarantee that the bleeding is resulting from regular progesterone-induced withdrawals (for example, ovulation) and that the patient's endometrium is protected.

Reproductive therapy

Women with PCOS should be counselled to seek pregnancy earlier rather than later, unless further data regarding the possibility of a prolonged reproductive window owing to improved ovarian reserve emerge. In either case, timely intervention will allow optimal preconception, amelioration of risk factors for pregnancy complications and adequate time to pursue effective, but relatively safe, and affordable treatment strategies rather than at a later stage.

The goal of fertility treatment in women with PCOS is to restore monofollicular ovulation and achieve singleton pregnancy, given the predisposition of women with PCOS to adverse pregnancy outcomes, including pre-eclampsia, gestational hypertension, gestational diabetes mellitus and preterm labour[186]. Fertility treatment should start with counselling about success rates, discontinuation of harmful habits (especially smoking), screening for medical comorbidities and treating excess weight. Pursuing 'low-tech' therapies, such as lifestyle modification and/or dose escalation of oral medications (for example, clomifene or letrozole; see below) to achieve ovulation, often requires patience of both the clinician and the patient. The chance of conceiving is only 5–10% per ovulatory cycle in women with PCOS (versus 10–15% per cycle in women without PCOS)[187,188].

Medical treatment. First-line treatment for infertility is aimed at restoring ovulation by interfering with inappropriate oestrogen feedback mechanisms (for example, clomifene citrate, a selective oestrogen receptor modulator) or oestrogen production in adipose tissue (for example, letrozole, an aromatase inhibitor). Letrozole is superior to clomifene at achieving a live birth by 40–50%[188], although the benefit might be greater in obese women with PCOS. Multiple pregnancy rates with these medications are in the range of 3–8% (that is, 3–8% of the pregnancies are not singletons).

Metformin is a relatively ineffective infertility agent in PCOS. When used alone, it has the lowest pregnancy rates compared to other oral agents, but also the lowest multiple pregnancy rates[154]. Thus, metformin tends to be used in combination with other medications. For example, the combination of clomifene and metformin may be superior to treatment with clomifene alone[187,189]. The optimal number of ovulatory cycles with oral ovulatory agents without achieving a pregnancy before moving on to other therapies is unknown, but is probably no more than five or six[187,188].

Second-line treatment tends to be gonadotropin therapy (either as a combination of LH and FSH, or FSH only), which is used in a low-dose regimen to minimize the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). The risk of OHSS is increased in PCOS owing to a higher chance of multiple follicular recruitment. Gonadotropin therapy in expert hands with strict cancellation guidelines if evidence of excessive ovarian follicular recruitment is observed can result in low multiple pregnancy rates (<5%)[190,191]. Pregnancy rates with gonadotropins are probably higher than with first-line oral treatment[192], although the greater expense and higher potential risks outweigh their choice as first-line option.

Ovarian surgery. Ovarian surgery can also be used to induce ovulation. Although bilateral ovarian wedge resection is relatively effective at inducing ovulation in patients with PCOS who are resistant to clomifene[173] and can be performed laparoscopically[193], LOD has become the preferred surgical alternative because of the lower risk of complications, particularly postoperative

adhesion formation[174,175]. LOD is generally recommended in patients with increased levels of LH, clomifene citrate resistance, an inability or unwillingness to proceed to gonadotropin ovulation induction and/or needing to undergo laparoscopy for other indications[174,194]. Long-term complications of LOD mainly include adhesion formation and diminished ovarian reserve, especially when a large amount of drilling is performed[195].

In vitro *fertilization.* Third-line therapy for women with PCOS is *in vitro* fertilization (IVF). If IVF is used, women with PCOS have similar or better pregnancy rates than women with other indications, and long-term follow-up studies suggest that, over a lifetime, fecundity of women with PCOS may match population means[196]. In the United States, IVF is associated with multiple pregnancy rates of ~30%. This rate will probably be lower in other countries in which single embryo transfer is recommended, possibly even lower than the multiple pregnancy rates observed using other ovulation induction methods.

Several modifications to IVF have been proposed to prevent multiple births and OHSS in patients with PCOS, including *in vitro* maturation (IVM) of immature oocytes that are retrieved without gonadotropin stimulation[197] and elective cryopreservation of all embryos and transfer in a subsequent frozen embryo transfer cycle after ovarian recovery. Pregnancy rates are lower with IVM than with IVF[198,199], although IVF results might be better overall with elective cryopreservation than with fresh IVF embryo transfer[200]. However, randomized trials in women with PCOS are lacking for both of these IVF modifications. Metformin treatment in patients with PCOS undergoing IVF might also reduce the risk of OHSS[201,202].

Quality of life

Health-related QOL is a multidimensional concept that includes domains related to physical, mental, emotional and social functioning in response to the effects of specific diseases, treatments, and short-term and long-term disabilities from the perspective of the patient[203]. The QOL of patients with PCOS is significantly reduced in all domains (including functional ability, physical aspects, general health perception, vitality, social and emotional aspects and mental health) compared with healthy women[204]. Important negative determinants of the QOL of patients with PCOS include the presence of obesity, hirsutism, androgenic alopecia, acne, menstrual dysfunction and infertility, among others.

The PCOS health-related QOL questionnaire (PCOSQ) developed by Cronin *et al.*[205] is the only validated PCOS-specific tool and includes items in five domains, including body hair, emotions, weight, infertility and menstrual problems[205]. A modified version of the questionnaire, adding four acne-related items, has been proposed[206]. Studies using the PCOSQ or the modified version of this tool consistently report reduced QOL with different contributing factors, including menstrual disturbances, hirsutism, acne, obesity and infertility[38]. Interestingly, although depression scores are significantly correlated with insulin resistance, PCOSQ scores are not[40].

Limited available data indicate that weight loss in overweight or obese women with PCOS achieved by dietary restriction alone or combined with exercise improves both depressive symptoms and PCOS-specific QOL scores, except for the scores in the body hair domain[142]. An observational study of metformin treatment in women with PCOS reported improvements in health-related QOL scores and emotional well-being, and these improvements significantly correlated with body weight reduction and menstrual cycle normalization[207]. However, subsequent randomized controlled trials have not supported this observation, and the addition of metformin to lifestyle modification did not seem to have an effect on QOL[208]. Similarly, a randomized trial assessing lifestyle modification programme combined with OCP use in obese adolescents with PCOS showed an improvement in PCOSQ scores, whereas the addition of metformin

Table 2 | **Anti-androgens available for use in PCOS**

Agent	Mechanism of action	US FDA-approved indication	Adverse effects	Refs
Spironolactone	Competitive inhibitor of AR binding, antimineralocorticoid, limits suppression of 5α-reductase activity and suppresses LH	Treatment of low renin hypertension, hypokalaemia and Conn syndrome	Dyspepsia; dry skin; decreased libido; hypotension; polyuria; menstrual irregularity and polymenorrhoea when not administered with an OCP; teratogenic in early pregnancy, principally on male fetuses; rare skin sensitivity to sunlight; and rare hypokalaemia	178, 179
Cyproterone acetate	Competitive inhibitor of AR binding, limits suppression of 5α-reductase activity and decreases LH-dependent androgen secretion	Palliative treatment of patients with advanced prostatic carcinoma	Breast swelling; amenorrhoea; decreased libido; teratogenic in early pregnancy, principally on male fetuses; rare liver toxicity; rare reduced adrenal response to ACTH stimulation; and rare oestrogen-related osteoporosis	180
Flutamide	Competitive antagonist of AR and reduces synthesis of DHT	Management of locally confined stage B2–stage C and stage D2 metastatic carcinoma of the prostate	Dry skin; discoloured (green) urine; decreased libido; teratogenic in early pregnancy, principally on male fetuses; and rare liver toxicity (occasionally fulminant)	176, 181
Finasteride	Competitively binds to and inhibits steroid type II 5α-reductase	Treatment of benign prostatic hyperplasia	Dry skin; headache; decreased libido; and teratogenic in early pregnancy, principally on male fetuses	182

ACTH, adrenocorticotropic hormone; AR, androgen receptor; DHT, dihydrotestosterone; LH, luteinizing hormone; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome.

to the lifestyle modification programme combined with OCPs did not influence PCOSQ scores further[209]. Finally, OCP use improves hirsutism and menstrual disturbances along with PCOSQ scores, but without any significant change in depression or anxiety symptoms[210].

Women with PCOS also have a more negative body image than women without PCOS, worsened by the presence of hirsutism and weight gain[130], which is associated with greater depression and anxiety[211] and a lower QOL. Likewise, the prevalence of eating disorders, which are in turn also significantly associated with depression and anxiety, is increased in PCOS[36]. Women with PCOS also suffer from greater psychosexual dysfunction, which correlates with poor QOL, sexual dissatisfaction and reduced feminine identity[207,212]. Overall, mood disorders seem to be more common and more severe in women with PCOS, and clinician awareness and corresponding screening are important.

Outlook

Although important advances have been made in our understanding of PCOS in the past two decades, much remains to be elucidated. We highlight some, although certainly not all, areas in which research is needed.

Metabolic dysfunction

Currently, limited data are available on the tissue-specific aetiologies of the metabolic dysfunction underlying PCOS, and further studies are needed to better understand the molecular and genetic aetiologies of these pathologies in muscle, fat and other tissues. Furthermore, we need improved understanding of how metabolic dysfunction relates, in a temporal manner, to the development of the other clinical features of the disorder (for example, ovarian dysfunction), perhaps through prospective studies of at-risk children.

Future studies should also focus on the development of preventive therapies to minimize the development of obesity in peripubertal and adolescent girls. In addition, greater clarity is needed regarding the effect of metabolic dysfunction on the cardiovascular and cerebrovascular complications associated with PCOS, and whether managing metabolic complications might reduce the risk of these complications. In addition, well-controlled prospective studies concerning the predictive value of acanthosis nigricans as a predictor of insulin resistance and hyperinsulinaemia in PCOS are needed.

Finally, as it is clear that insulin resistance alone is not sufficient to induce the full metabolic dysfunction of PCOS, better understanding of what other aetiological factors are necessary or permissive is also needed. Furthermore, a male phenotype of PCOS, most notably around defects of metabolic action, is likely to exist, based on the absence of sex linkage[213–216]; however, this potential syndrome remains to be demonstrated, better characterized and its risks defined.

Reproductive dysfunction

A better understanding of the dose–response relationships between the amount of weight loss and improvements in ovulation is needed. Establishing low-cost ovulation induction therapies, with a low risk of adverse events including multiple pregnancies, is also desirable. These therapies might involve repurposing other drugs (such as those developed for T2DM, breast cancer or psychiatric indications) or developing new drugs specifically for PCOS. For example, a neurokinin receptor antagonist has been shown to suppress sex steroid levels through alteration in gonadotropin modulation[217]. Further candidate genes identified by GWAS in women with PCOS offer supposition about potential pathways, including through phosphoinositide 3-kinase and mitogen-activated protein kinase, among other pathways[127]. Such strategies could also potentially be used for other reproductive disorders

Hyperandrogenism

Although the skin complications are often viewed as purely cosmetic aspects of the disorder, these features are among the most injurious of the traits of PCOS, substantially affecting self-esteem, psychosocial adaption and QOL. Future studies must focus on better understanding of the physiology and mechanism underlying hair follicle cycling and hair growth, and the impact of androgens, other steroid hormones, skin environment, as well as identifying how this process can be targeted, including defining the period and mechanisms by which this process becomes irreversible. These studies will permit the elucidation of novel approaches to the inhibition and treatment of unwanted excess hair terminalization (hirsutism) or miniaturization (androgenic alopecia).

The development of novel and improved peripheral androgen receptor blockers, particularly those that do not have systemic effects, is necessary. Anti-androgens are needed that can be administrated, even topically, without the need for concomitant OCPs or other forms of contraception. In addition, approval of the use of current and novel anti-androgens from the appropriate government agencies is urgently needed, as the lack of such approvals has a negative impact on their use in many parts of the world.

Evolutionary aspects of PCOS

Every aspect of human health and disease has emerged through evolutionary processes, including natural selection, and many of the current ailments affecting our society stem directly from evolutionary maladaptation. PCOS seems to be an evolutionary-conserved disorder: PCOS is a relatively common disorder with a uniform prevalence worldwide, is heritable with similar genetic variants across ethnicities and was described in the medical literature as early as 1,000 years ago[218]. An evolutionary biology approach to studying PCOS that focuses on factors leading to its development and persistence might help to elucidate its fundamental pathophysiology.

When considering the evolutionary aspects of PCOS, it is peculiar that the condition has persisted given its effect on reproduction. This paradoxical feature might be explained by a vulnerability to PCOS, which refers to the inherent potential for pathology to be embedded within biological characteristics associated with

normal physiological development and function. For example, a vulnerability to PCOS, although detrimental to the fertility of affected individuals, could be associated with improved fertility or fetal outcomes, or other fitness-enhancing physiological phenomenon, in most of the other related women within a population. Ultimately, novel insights into the evolutionary origins of PCOS will emerge through a broad consideration of the potential adaptive and beneficial aspects of vulnerability to the disorder. For example, the study of isolated populations of people who have uncontrolled fertility, high levels of exposure to natural pathogens and low consumption of processed carbohydrates might be instrumental.

Epidemiology of PCOS

More precise population studies of the epidemiology, phenotype and genetics of PCOS worldwide are crucially needed, and will also help to elucidate the evolutionary path of PCOS as humanity marched across the continents. These studies should be carried out in various racial and ethnic groups in different parts of the world and in similar or related racial and ethnic groups who have lived for some time in different geographical regions or environs (for example, West Africans compared with African-Americans). These investigations will also assist in understanding the role of environmental factors on the epidemiology, phenotype and possibly genetics and epigenetics of PCOS.

1. Stepto, N. K. *et al.* Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. *Hum. Reprod.* **28**, 777–784 (2013).
2. Vink, J. M., Sadrzadeh, S., Lambalk, C. B. & Boomsma, D. I. Heritability of polycystic ovary syndrome in a Dutch twin-family study. *J. Clin. Endocrinol. Metab.* **91**, 2100–2104 (2006).
This study clearly demonstrates the very high heritability of PCOS through twin studies.
3. Azziz, R., Marin, C., Hoq, L., Badamgarav, E. & Song, P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. *J. Clin. Endocrinol. Metab.* **90**, 4650–4658 (2005).
4. Diamanti-Kandarakis, E., Spritzer, P. M., Sir-Petermann, T. & Motta, A. B. Insulin resistance and polycystic ovary syndrome through life. *Curr. Pharm. Des.* **18**, 5569–5576 (2012).
5. Lizneva, D. *et al.* The criteria, prevalence and phenotypes of PCOS. *Fertil. Steril.* **106**, 6–15 (2016).
6. Zawadzki, J. & Duniaf, A. in *Polycystic Ovary Syndrome* (eds Dunaif, A., Givens, J. R., Haseltine, F. P. & Merriam, G. R.) 377–384 (Blackwell Scientific Publications,1992).
7. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum. Reprod.* **19**, 41–47 (2004).
8. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil. Steril.* **81**, 19–25 (2004).
9. Ezeh, U., Yildiz, B. O. & Azziz, R. Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **98**, E1088–E1096 (2013).
This is the first study to clearly demonstrate that the phenotype of PCOS observed in clinical studies may be very different from that observed in medically unbiased populations, indicating the need to better understand the true phenotype of PCOS.
10. Azziz, R. *et al.* The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil. Steril.* **91**, 456–488 (2009).
11. DeUgarte, C. M., Woods, K. S., Bartolucci, A. A. & Azziz, R. Degree of facial and body terminal hair growth in unselected black and white women: toward a populational definition of hirsutism. *J. Clin. Endocrinol. Metab.* **91**, 1345–1350 (2006).
12. Souter, I., Sanchez, L. A., Perez, M., Bartolucci, A. A. & Azziz, R. The prevalence of androgen excess among patients with minimal unwanted hair growth. *Am. J. Obstet. Gynecol.* **191**, 1914–1920 (2004).
13. Dunaif, A., Segal, K. R., Futterweit, W. & Dobrjansky, A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* **38**, 1165–1174 (1989).
This is one of the first studies to conclusively demonstrate that women with PCOS have significant insulin resistance that is independent of obesity, changes in body composition and impairment of glucose tolerance, and that hyperinsulinaemia in PCOS is not the result of decreased insulin clearance.
14. Moran, L. J., Misso, M. L., Wild, R. A. & Norman, R. J. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum. Reprod. Update* **16**, 347–363 (2010).
15. Legro, R. S., Gnatuk, C. L., Kunselman, A. R. & Dunaif, A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J. Clin. Endocrinol. Metab.* **90**, 3236–3242 (2005).
16. Norman, R. J., Masters, L., Milner, C. R., Wang, J. X. & Davies, M. J. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum. Reprod.* **16**, 1995–1998 (2001).
17. Hudecova, M. *et al.* Diabetes and impaired glucose tolerance in patients with polycystic ovary syndrome — a long term follow-up. *Hum. Reprod.* **26**, 1462–1468 (2011).
18. Gambineri, A. *et al.* Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. *Diabetes* **61**, 2369–2374 (2012).
19. 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.* **96**, 3794–3803 (2011).
20. Lim, S. S., Davies, M. J., Norman, R. J. & Moran, L. J. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum. Reprod. Update* **18**, 618–637 (2012).
21. Luque-Ramirez, M. *et al.* Referral bias in female functional hyperandrogenism and polycystic ovary syndrome. *Eur. J. Endocrinol.* **173**, 603–610 (2015).
22. Guyatt, G., Weaver, B., Cronin, L., Dooley, J. A. & Azziz, R. Health-related quality of life in women with polycystic ovary syndrome, a self-administered questionnaire, was validated. *J. Clin. Epidemiol.* **57**, 1279–1287 (2004).
23. Khomami, M. B., Tehrani, F. R., Hashemi, S., Farahmand, M. & Azizi, F. Of PCOS symptoms, hirsutism has the most significant impact on the quality of life of Iranian women. *PLoS ONE* **10**, e0123608 (2015).
24. Dilbaz, B., Cinar, M., Ozkaya, E., Tonyali, N. V. & Dilbaz, S. Health related quality of life among different PCOS phenotypes of infertile women. *J. Turk. Ger. Gynecol. Assoc.* **13**, 247–252 (2012).
25. Gosman, G. G. *et al.* Reproductive health of women electing bariatric surgery. *Fertil. Steril.* **94**, 1426–1431 (2010).
26. Alvarez-Blasco, F., Botella-Carretero, J. I., San Millan, J. L. & Escobar-Morreale, H. F. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Arch. Intern. Med.* **166**, 2081–2086 (2006).
27. Laitinen, J. *et al.* Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. *Int. J. Obes. Relat. Metab. Disord.* **27**, 710–715 (2003).
28. Teede, H. J. *et al.* Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring)* **21**, 1526–1532 (2013).
29. Yildiz, B. O., Knochenhauer, E. S. & Azziz, R. Impact of obesity on the risk for polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **93**, 162–168 (2008).
30. Yildiz, B. O., Bozdag, G., Yapici, Z., Esinler, I. & Yarali, H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Hum. Reprod.* **27**, 3067–3073 (2012).
31. Ewens, K. G. *et al. FTO* and *MC4R* gene variants are associated with obesity in polycystic ovary syndrome. *PLoS ONE* **6**, e16390 (2011).
32. Cai, X., Liu, C. & Mou, S. Association between fat mass- and obesity-associated (*FTO*) gene polymorphism and polycystic ovary syndrome: a meta-analysis. *PLoS ONE* **9**, e86972 (2014).
33. Louwers, Y. V. *et al.* BMI-associated alleles do not constitute risk alleles for polycystic ovary syndrome independently of BMI: a case–control study. *PLoS ONE* **9**, e87335 (2014).
34. Joham, A. E., Teede, H. J., Ranasinha, S., Zoungas, S. & Boyle, J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. *J. Womens Health (Larchmt)* **24**, 299–307 (2015).
35. Wild, S., Pierpoint, T., Jacobs, H. & McKeigue, P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum. Fertil. (Camb.)* **3**, 101–105 (2000).
36. Teede, H. J. *et al.* Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med. J. Aust.* **195**, S65–112 (2011).
37. Dokras, A., Clifton, S., Futterweit, W. & Wild, R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Obstetr. Gynecol.* **117**, 145–152 (2011). 38.
Veltman-Verhulst, S. M., Boivin, J., Eijkemans, M. J. & Fauser, B. J. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. *Hum. Reprod. Update* **18**, 638–651 (2012).
39. Moran, L. J., Deeks, A. A., Gibson-Helm, M. E. & Teede, H. J. Psychological parameters in the reproductive phenotypes of polycystic ovary syndrome. *Hum. Reprod.* **27**, 2082–2088 (2012).
40. Cinar, N. *et al.* Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome. *Hum. Reprod.* **26**, 3339–3345 (2011).
41. Roos, N. *et al.* Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. *BMJ* **343**, d6309 (2011).
42. Sterling, L. *et al.* Pregnancy outcomes in women with polycystic ovary syndrome undergoing *in vitro* fertilization. *Fertil. Steril.* **105**, 791–797.e2 (2016).
43. Pan, M. L., Chen, L. R., Tsao, H. M. & Chen, K. H. Relationship between polycystic ovarian syndrome and subsequent gestational diabetes mellitus: a nationwide population-based study. *PLoS ONE* **10**, e0140544 (2015).
44. Palomba, S. *et al.* Pregnancy complications in women with polycystic ovary syndrome. *Hum. Reprod. Update* **21**, 575–592 (2015).

45. Vanky, E. *et al.* Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J. Clin. Endocrinol. Metab.* **95**, E448–E455 (2010).
This is the first study to clearly demonstrate that metformin treatment from the first trimester to delivery did not reduce pregnancy complications in women with PCOS.
46. Carmina, E. Polycystic ovary syndrome: metabolic consequences and long-term management. *Scand. J. Clin. Lab. Invest. Suppl.* **244**, 23–26; discussion 26 (2014).
47. Christian, R. C. *et al.* Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **88**, 2562–2568 (2003).
48. Talbott, E. O. *et al.* Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **89**, 5454–5461 (2004).
49. Luque-Ramirez, M., Mendieta-Azcona, C., Alvarez-Blasco, F. & Escobar-Morreale, H. F. Androgen excess is associated with the increased carotid intima–media thickness observed in young women with polycystic ovary syndrome. *Hum. Reprod.* **22**, 3197–3203 (2007).
50. Lass, N., Kleber, M., Winkel, K., Wunsch, R. & Reinehr, T. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima–media thickness in obese adolescent girls. *J. Clin. Endocrinol. Metab.* **96**, 3533–3540 (2011).
51. Chang, A. Y. *et al.* Polycystic ovarian syndrome and subclinical atherosclerosis among women of reproductive age in the Dallas heart study. *Clin. Endocrinol. (Oxf.)* **74**, 89–96 (2011).
52. Dahlgren, E., Janson, P. O., Johansson, S., Lapidus, L. & Oden, A. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet. Gynecol. Scand.* **71**, 599–604 (1992).
53. Carmina, E., Campagna, A. M. & Lobo, R. A. Emergence of ovulatory cycles with aging in women with polycystic ovary syndrome (PCOS) alters the trajectory of cardiovascular and metabolic risk factors. *Hum. Reprod.* **28**, 2245–2252 (2013).
54. Ramezani Tehrani, F. *et al.* Trend of cardio-metabolic risk factors in polycystic ovary syndrome: a population-based prospective cohort study. *PLoS ONE* **10**, e0137609 (2015).
55. Bairey Merz, C. N. *et al.* Cardiovascular disease and 10-year mortality in postmenopausal women with clinical features of PCOS. *J. Womens Health (Larchmt)* 6 June 2016 [epub ahead of print].
56. Hart, R. & Doherty, D. A. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. *J. Clin. Endocrinol. Metab.* **100**, 911–919 (2015).
57. Cibula, D. *et al.* Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum. Reprod.* **15**, 785–789 (2000).
58. Mani, H. *et al.* Diabetes and cardiovascular events in women with polycystic ovary syndrome: a 20-year retrospective cohort study. *Clin. Endocrinol. (Oxf.)* **78**, 926–934 (2013).
59. Krentz, A. J., von Muhlen, D. & Barrett-Connor, E. Searching for polycystic ovary syndrome in postmenopausal women: evidence of a dose–effect association with prevalent cardiovascular disease. *Menopause* **14**, 284–292 (2007).
60. Wild, S., Pierpoint, T., McKeigue, P. & Jacobs, H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin. Endocrinol. (Oxf.)* **52**, 595–600 (2000).
61. Iftikhar, S. *et al.* Risk of cardiovascular events in patients with polycystic ovary syndrome. *Neth. J. Med.* **70**, 74–80 (2012).
62. Carmina, E. Oral contraceptives and cardiovascular risk in women with polycystic ovary syndrome. *J. Endocrinol. Invest.* **36**, 358–363 (2013).
63. Bird, S. T., Hartzema, A. G., Brophy, J. M., Etminan, M. & Delaney, J. A. Risk of venous thromboembolism in women with polycystic ovary syndrome: a population-based matched cohort analysis. *CMAJ* **185**, E115–E120 (2013).
64. Anderson, S. A., Barry, J. A. & Hardiman, P. J. Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Int. J. Cardiol.* **176**, 486–487 (2014).
65. Carmina, E., Campagna, A. M. & Lobo, R. A. A 20-year follow-up of young women with polycystic ovary syndrome. *Obstet. Gynecol.* **119**, 263–269 (2012).
66. Dumesic, D. A. & Lobo, R. A. Cancer risk and PCOS. *Steroids* **78**, 782–785 (2013).
67. Kahsar-Miller, M. & Azziz, R. The development of the polycystic ovary syndrome: family history as a risk factor. *Trends Endocrinol. Metab.* **9**, 55–58 (1998).
68. Legro, R. S., Driscoll, D., Strauss, J. F. 3rd, Fox, J. & Dunaif, A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. *Proc. Natl Acad. Sci. USA* **95**, 14956–14960 (1998).
69. Lerchbaum, E., Schwetz, V., Giuliani, A. & Obermayer-Pietsch, B. Influence of a positive family history of both type 2 diabetes and PCOS on metabolic and endocrine parameters in a large cohort of PCOS women. *Eur. J. Endocrinol.* **170**, 727–739 (2014).
70. Kosova, G. & Urbanek, M. Genetics of the polycystic ovary syndrome. *Mol. Cell. Endocrinol.* **373**, 29–38 (2013).
71. Shi, Y. *et al.* Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. *Nat. Genet.* **44**, 1020–1025 (2012).
72. Chen, Z. J. *et al.* Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. *Nat. Genet.* **43**, 55–59 (2011).
This is the first genome-wide association study of PCOS.
73. Du, J. *et al.* Family-based analysis of *INSR* polymorphisms in Chinese PCOS. *Reprod. Biomed. Online* **29**, 239–244 (2014).
74. Zhao, S. *et al.* Family-based analysis of eight susceptibility loci in polycystic ovary syndrome. *Sci. Rep.* **5**, 12619 (2015).
75. Hayes, M. G. *et al.* Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. *Nat. Commun.* **6**, 7502 (2015).
76. Day, F. R. *et al.* Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome. *Nat. Commun.* **6**, 8464 (2015).
77. Azziz, R. PCOS in 2015: new insights into the genetics of polycystic ovary syndrome. *Nat. Rev. Endocrinol.* **12**, 74–75 (2016).
78. Cui, L. *et al.* Genotype–phenotype correlations of PCOS susceptibility SNPs identified by GWAS in a large cohort of Han Chinese women. *Hum. Reprod.* **28**, 538–544 (2013).
79. Welt, C. K. *et al.* Variants in *DENND1A* are associated with polycystic ovary syndrome in women of European ancestry. *J. Clin. Endocrinol. Metab.* **97**, E1342–E1347 (2012).
80. Saxena, R. *et al.* Han Chinese polycystic ovary syndrome risk variants in women of European ancestry: relationship to FSH levels and glucose tolerance. *Hum. Reprod.* **30**, 1454–1459 (2015).
81. Cui, L. *et al.* Polycystic ovary syndrome susceptibility single nucleotide polymorphisms in women with a single PCOS clinical feature. *Hum. Reprod.* **30**, 732–736 (2015).
82. Shim, U. *et al.* Pathway analysis based on a genome-wide association study of polycystic ovary syndrome. *PLoS ONE* **10**, e0136609 (2015).
83. Jones, M. R. *et al.* Systems genetics reveals the functional context of PCOS loci and identifies genetic and molecular mechanisms of disease heterogeneity. *PLoS Genet.* **11**, e1005455 (2015).
84. Banaszewska, B., Spaczynski, R. Z., Pelesz, M. & Pawelczyk, L. Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia. *Rocz. Akad. Med. Bialymst.* **48**, 131–134 (2003).
85. Dale, P. O., Tanbo, T., Vaaler, S. & Abyholm, T. Body weight, hyperinsulinemia, and gonadotropin levels in the polycystic ovarian syndrome: evidence of two distinct populations. *Fertil. Steril.* **58**, 487–491 (1992).
86. Burt Solorzano, C. M., McCartney, C. R., Blank, S. K., Knudsen, K. L. & Marshall, J. C. Hyperandrogenaemia in adolescent girls: origins of abnormal gonadotropin-releasing hormone secretion. *BJOG* **117**, 143–149 (2010).
87. Dumesic, D. A. *et al.* Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. *Endocr. Rev.* **36**, 487–525 (2015).
This paper provides a comprehensive overview of the complexity of PCOS and also provides some useful practical guidelines on how to take care of these patients in daily practice.
88. Fauser, B. C. & Van Heusden, A. M. Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocr. Rev.* **18**, 71–106 (1997).
89. Broekmans, F. J. *et al.* Anti-Müllerian hormone and ovarian dysfunction. *Trends Endocrinol. Metab.* **19**, 340–347 (2008).
90. Valkenburg, O. *et al.* Genetic polymorphisms of GnRH and gonadotrophic hormone receptors affect the phenotype of polycystic ovary syndrome. *Hum. Reprod.* **24**, 2014–2022 (2009).
91. Laven, J. S. *et al.* Anti-Müllerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. *J. Clin. Endocrinol. Metab.* **89**, 318–323 (2004).
92. Stubbs, S. A. *et al.* Anti-Müllerian hormone protein expression is reduced during the initial stages of follicle development in human polycystic ovaries. *J. Clin. Endocrinol. Metab.* **90**, 5536–5543 (2005).
93. Visser, J. A. *et al.* Increased oocyte degeneration and follicular atresia during the estrous cycle in anti-Müllerian hormone null mice. *Endocrinology* **148**, 2301–2308 (2007).
94. Catteau-Jonard, S. & Dewailly, D. Pathophysiology of polycystic ovary syndrome: the role of hyperandrogenism. *Front. Horm. Res.* **40**, 22–27 (2013).
95. Padmanabhan, V. *et al.* Dynamics of bioactive follicle-stimulating hormone secretion in women with polycystic ovary syndrome: effects of estradiol and progesterone. *Fertil. Steril.* **75**, 881–888 (2001).
96. Webber, L. J. *et al.* Formation and early development of follicles in the polycystic ovary. *Lancet* **362**, 1017–1021 (2003).
97. Nestler, J. E. *et al.* Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J. Clin. Endocrinol. Metab.* **83**, 2001–2005 (1998).
98. Visser, J. A., Schipper, I., Laven, J. S. & Themmen, A. P. Anti-Müllerian hormone: an ovarian reserve marker in primary ovarian insufficiency. *Nat. Rev. Endocrinol.* **8**, 331–341 (2012).
99. Teixeira Filho, F. L. *et al.* Aberrant expression of growth differentiation factor-9 in oocytes of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **87**, 1337–1344 (2002).
100. Bergman, R. N., Ider, Y. Z., Bowden, C. R. & Cobelli, C. Quantitative estimation of insulin sensitivity. *Am. J. Physiol.* **236**, E667–E677 (1979).
101. O'Meara, N. M. *et al.* Defects in beta-cell function in functional ovarian hyperandrogenism. *J. Clin. Endocrinol. Metab.* **76**, 1241–1247 (1993).
102. Ehrmann, D. A. *et al.* Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* **96**, 520–527 (1995).
103. Dunaif, A. & Finegood, D. T. Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **81**, 942–947 (1996).
104. Diamanti-Kandarakis, E. & Dunaif, A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr. Rev.* **33**, 981–1030 (2012).
105. Pasquali, R. *et al.* Insulin and C-peptide levels in obese patients with polycystic ovaries. *Horm. Metab. Res.* **14**, 284–287 (1982).
106. Mahabeer, S. *et al.* Insulin and C-peptide secretion in non-obese patients with polycystic ovarian disease. *Horm. Metab. Res.* **21**, 502–506 (1989).
107. Dunaif, A., Xia, J., Book, C. B., Schenker, E. & Tang, Z. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. *J. Clin. Invest.* **96**, 801–810 (1995).
108. Dunaif, A. *et al.* Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. *Diabetes* **41**, 1257–1266 (1992).
109. Ciaraldi, T. P. *et al.* Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. *J. Clin. Endocrinol. Metab.* **75**, 577–583 (1992).
110. Corbould, A., Zhao, H., Mirzoeva, S., Aird, F. & Dunaif, A. Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome. *Diabetes* **55**, 751–759 (2006).

111. Rajkhowa, M. *et al.* Insulin resistance in polycystic ovary syndrome is associated with defective regulation of ERK1/2 by insulin in skeletal muscle *in vivo*. *Biochem. J.* **418**, 665–671 (2009).
112. Book, C. B. & Dunaif, A. Selective insulin resistance in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **84**, 3110–3116 (1999).
113. Corbould, A. *et al.* Insulin resistance in the skeletal muscle of women with PCOS involves intrinsic and acquired defects in insulin signaling. *Am. J. Physiol. Endocrinol. Metab.* **288**, E1047–E1054 (2005).
114. Eriksen, M. *et al.* Insulin resistance is not conserved in myotubes established from women with PCOS. *PLoS ONE* **5**, e14469 (2010).
115. Ciaraldi, T. P., Aroda, V., Mudaliar, S., Chang, R. J. & Henry, R. R. Polycystic ovary syndrome is associated with tissue-specific differences in insulin resistance. *J. Clin. Endocrinol. Metab.* **94**, 157–163 (2009).
116. Chazenbalk, G. *et al.* Regulation of adiponectin secretion by adipocytes in the polycystic ovary syndrome: role of tumor necrosis factor-α. *J. Clin. Endocrinol. Metab.* **95**, 935–942 (2010).
117. Manneras-Holm, L. *et al.* Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. *J. Clin. Endocrinol. Metab.* **96**, E304–E311 (2011).
118. Ek, I., Arner, P., Bergqvist, A., Carlstrom, K. & Wahrenberg, H. Impaired adipocyte lipolysis in nonobese women with the polycystic ovary syndrome: a possible link to insulin resistance? *J. Clin. Endocrinol. Metab.* **82**, 1147–1153 (1997).
119. Rosenbaum, D., Haber, R. S. & Dunaif, A. Insulin resistance in polycystic ovary syndrome: decreased expression of GLUT-4 glucose transporters in adipocytes. *Am. J. Physiol.* **264**, E197–E202 (1993).
120. Garvey, W. T. *et al.* Pretranslational suppression of a glucose transporter protein causes insulin resistance in adipocytes from patients with non-insulin-dependent diabetes mellitus and obesity. *J. Clin. Invest.* **87**, 1072–1081 (1991).
121. Carvalho, E., Jansson, P. A., Nagaev, I., Wenthzel, A. M. & Smith, U. Insulin resistance with low cellular IRS-1 expression is also associated with low GLUT4 expression and impaired insulin-stimulated glucose transport. *FASEB J.* **15**, 1101–1103 (2001).
122. Carlson, C. J., Koterski, S., Sciotti, R. J., Poccard, G. B. & Rondinone, C. M. Enhanced basal activation of mitogen-activated protein kinases in adipocytes from type 2 diabetes: potential role of p38 in the downregulation of GLUT4 expression. *Diabetes* **52**, 634–641 (2003).
123. Chen, Y. H. *et al.* miRNA-93 inhibits GLUT4 and is overexpressed in adipose tissue of polycystic ovary syndrome patients and women with insulin resistance. *Diabetes* **62**, 2278–2286 (2013).
124. Ciaraldi, T. P. Molecular defects of insulin action in the polycystic ovary syndrome: possible tissue specificity. *J. Pediatr. Endocrinol. Metab.* **13** (Suppl. 5), 1291–1293 (2000).
125. Ciaraldi, T. P. *et al.* Cellular insulin resistance in adipocytes from obese polycystic ovary syndrome subjects involves adenosine modulation of insulin sensitivity. *J. Clin. Endocrinol. Metab.* **82**, 1421–1425 (1997).
126. Chuang, T. Y. *et al.* MicroRNA-223 expression is upregulated in insulin resistant human adipose tissue. *J. Diabetes Res.* **2015**, 943659 (2015).
127. McAllister, J. M., Legro, R. S., Modi, B. P. & Strauss, J. F. 3rd. Functional genomics of PCOS: from GWAS to molecular mechanisms. *Trends Endocrinol. Metab.* **26**, 118–124 (2015).
128. Yildiz, B. O. & Azziz, R. The adrenal and polycystic ovary syndrome. *Rev. Endocr. Metab. Disord.* **8**, 331–342 (2007).
129. Deeks, A. A., Gibson-Helm, M. E. & Teede, H. J. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil. Steril.* **93**, 2421–2423 (2010).
130. Moran, L., Gibson-Helm, M., Teede, H. & Deeks, A. Polycystic ovary syndrome: a biopsychosocial understanding in young women to improve knowledge and treatment options. *J. Psychosomat. Obstetr. Gynaecol.* **31**, 24–31 (2010).
131. Gibson-Helm, M. E., Lucas, I. M., Boyle, J. A. & Teede, H. J. Women's experiences of polycystic ovary syndrome diagnosis. *Fam. Pract.* **31**, 545–549 (2014).
132. Kitzinger, C. & Willmott, J. 'The thief of womanhood': women's experience of polycystic ovarian syndrome. *Soc. Sci. Med.* **54**, 349–361 (2002).
133. Shroff, R., Syrop, C. H., Davis, W., Van Voorhis, B. J. & Dokras, A. Risk of metabolic complications in the new PCOS phenotypes based on the Rotterdam criteria. *Fertil. Steril.* **88**, 1389–1395 (2007).
134. Daan, N. M. *et al.* Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: who is really at risk? *Fertil. Steril.* **102**, 1444–1451.e3 (2014).
135. Daskalopoulos, G. *et al.* Excess metabolic and cardiovascular risk is not manifested in all phenotypes of polycystic ovary syndrome: implications for diagnosis and treatment. *Curr. Vasc. Pharmacol.* **13**, 788–800 (2015).
136. Tehrani, F. R., Rashidi, H., Khomami, M. B., Tohidi, M. & Azizi, F. The prevalence of metabolic disorders in various phenotypes of polycystic ovary syndrome: a community based study in Southwest of Iran. *Reprod. Biol. Endocrinol.* **12**, 89 (2014).
137. Ibanez, L., Lopez-Bermejo, A., Diaz, M., Marcos, M. V. & de Zegher, F. Early metformin therapy (age 8–12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. *J. Clin. Endocrinol. Metab.* **96**, E1262–E1267 (2011).
138. Legro, R. S. *et al.* Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **98**, 4565–4592 (2013).
139. Fauser, B. C. *et al.* Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil. Steril.* **97**, 28–38.e25 (2012).
140. Azziz, R. *et al.* Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J. Clin. Endocrinol. Metab.* **91**, 4237–4245 (2006).
141. Moran, L. J. *et al.* Sleep disturbances in a community-based sample of women with polycystic ovary syndrome. *Hum. Reprod.* **30**, 466–472 (2015).
142. Thomson, R. L. *et al.* Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. *Fertil. Steril.* **94**, 1812–1816 (2010).
143. Moran, L. J., Hutchison, S. K., Norman, R. J. & Teede, H. J. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst. Rev.* **7**, CD007506 (2011).
A meta-analysis of the data reported on lifestyle changes, and summarizes results that may be obtained and problems that arise with this treatment.
144. Carmina, E. PCOS: metabolic impact and long-term management. *Minerva Ginecol.* **64**, 501–505 (2012).
145. Kiddy, D. S. *et al.* Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin. Endocrinol. (Oxf.)* **36**, 105–111 (1992).
146. Moran, L. J. *et al.* Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **88**, 812–819 (2003).
147. Moran, L. J. *et al.* Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. *J. Acad. Nutr. Diet.* **113**, 520–545 (2013).
148. Goss, A. M. *et al.* Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. *Metabolism* **63**, 1257–1264 (2014).
149. Gower, B. A. *et al.* Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. *Clin. Endocrinol. (Oxf.)* **79**, 550–557 (2013).
150. Roessler, K. K., Birkebaek, C., Ravn, P., Andersen, M. S. & Glintborg, D. Effects of exercise and group counselling on body composition and VO2max in overweight women with polycystic ovary syndrome. *Acta Obstetricia Gynecol. Scand.* **92**, 272–277 (2013).
151. Harrison, C. L., Lombard, C. B., Moran, L. J. & Teede, H. J. Exercise therapy in polycystic ovary syndrome: a systematic review. *Hum. Reprod. Update* **17**, 171–183 (2011).
152. Harrison, C. L., Stepto, N. K., Hutchison, S. K. & Teede, H. J. The impact of intensified exercise training on insulin resistance and fitness in overweight and obese women with and without polycystic ovary syndrome. *Clin. Endocrinol. (Oxf.)* **76**, 351–357 (2012).
153. Skubleny, D. *et al.* The impact of bariatric surgery on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes. Surg.* **26**, 169–176 (2016).
154. Tang, T., Lord, J. M., Norman, R. J., Yasmin, E. & Balen, A. H. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst. Rev.* **5**, CD003053 (2012).
155. Naderpoor, N. *et al.* Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Hum. Reprod. Update* **21**, 560–574 (2015).
156. Du, Q. *et al.* A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. *Curr. Med. Res. Opin.* **28**, 723–730 (2012).
157. Li, X. J. *et al.* Metformin versus thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis. *Clin. Endocrinol. (Oxf.)* **74**, 332–339 (2011).
158. Goodman, N. F. *et al.* American Association Of Clinical Endocrinologists, American College Of Endocrinology, And Androgen Excess And PCOS Society Disease State clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome — part 2. *Endocr. Pract.* **21**, 1415–1426 (2015).
159. Formuso, C., Stracquadanio, M. & Ciotta, L. Myo-inositol versus D-chiro inositol in PCOS treatment. *Minerva Ginecol.* **67**, 321–325 (2015).
160. Nestler, J. E. & Unfer, V. Reflections on inositol(s) for PCOS therapy: steps toward success. *Gynecol. Endocrinol.* **31**, 501–505 (2015).
161. Zhang, Y. Y., Hou, L. Q. & Zhao, T. Y. Effects of acarbose on polycystic ovary syndrome: a meta-analysis. *Exp. Clin. Endocrinol. Diabetes* **122**, 373–378 (2014).
162. Gao, L., Zhao, F. L. & Li, S. C. Statin is a reasonable treatment option for patients with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. *Exp. Clin. Endocrinol. Diabetes* **120**, 367–375 (2012).
163. Sun, J. *et al.* An investigation into the therapeutic effects of statins with metformin on polycystic ovary syndrome: a meta-analysis of randomised controlled trials. *BMJ Open* **5**, e007280 (2015).
164. Khera, R. *et al.* Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA* **315**, 2424–2434 (2016).
165. Diamanti-Kandarakis, E., Katsikis, I., Piperi, C., Alexandraki, K. & Panidis, D. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. *Clin. Endocrinol. (Oxf.)* **66**, 103–109 (2007).
166. Jia, X. Z. *et al.* Effect of vitamin D on clinical and biochemical parameters in polycystic ovary syndrome women: a meta-analysis. *J. Obstetr. Gynaecol. Res.* **41**, 1791–1802 (2015).
167. Mathur, R., Levin, O. & Azziz, R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome. *Ther. Clin. Risk Manag.* **4**, 487–492 (2008).
168. Conway, G. *et al.* The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. *Eur. J. Endocrinol.* **171**, 1–29 (2014).
169. Yildiz, B. O. Approach to the patient: contraception in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **100**, 794–802 (2015).
170. Centers for Disease Control and Prevention (CDC). U. S. medical eligibility criteria for contraceptive use, 2010. *MMWR Recomm. Rep.* **59**, 1–86 (2010).
171. Azziz, R. *et al.* Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J. Clin. Endocrinol. Metab.* **80**, 3406–3411 (1995).
172. Naka, K. K. *et al.* Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study. *Fertil. Steril.* **95**, 203–209 (2011).
173. Donesky, B. W. & Adashi, E. Y. Surgically induced ovulation in the polycystic ovary syndrome: wedge resection revisited in the age of laparoscopy. *Fertil. Steril.* **63**, 439–463 (1995).
174. Farquhar, C., Brown, J. & Marjoribanks, J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database Syst. Rev.* **6**, CD001122 (2012).

175. Abu Hashim, H., Al-Inany, H., De Vos, M. & Tournaye, H. Three decades after Gjonnaess's laparoscopic ovarian drilling for treatment of PCOS; what do we know? An evidence-based approach. *Arch. Gynecol. Obstetr.* **288**, 409–422 (2013).
176. Koulouri, O. & Conway, G. S. A systematic review of commonly used medical treatments for hirsutism in women. *Clin. Endocrinol. (Oxf.)* **68**, 800–805 (2008).
177. Yildiz, B. O. Assessment, diagnosis and treatment of a patient with hirsutism. *Nat. Clin. Prac. Endocrinol. Metab.* **4**, 294–300 (2008).
178. Swiglo, B. A. *et al.* Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *J. Clin. Endocrinol. Metab.* **93**, 1153–1160 (2008).
179. van Zuuren, E. J., Fedorowicz, Z., Carter, B. & Pandis, N. Interventions for hirsutism (excluding laser and photoepilation therapy alone). *Cochrane Database Syst. Rev.* **4**, CD010334 (2015).
180. Venturoli, S. *et al.* A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *J. Clin. Endocrinol. Metab.* **84**, 1304–1310 (1999).
181. Escobar-Morreale, H. F. *et al.* Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum. Reprod. Update* **18**, 146–170 (2012).
182. Townsend, K. A. & Marlowe, K. F. Relative safety and efficacy of finasteride for treatment of hirsutism. *Ann. Pharmacother.* **38**, 1070–1073 (2004).
183. Moghetti, P. *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* **85**, 89–94 (2000).
This randomized controlled trial clearly demonstrates the positive effect and comparability of androgen blockade on hirsutism in PCOS.
184. Balfour, J. A. & McClellan, K. Topical eflornithine. *Am. J. Clin. Dermatol.* **2**, 197–201; discussion 202 (2001).
185. Lizneva, D., Gavrilova-Jordan, L., Walker, W. & Azziz, R. Androgen excess: investigations and management. *Best Pract. Res. Clin. Obstet. Gynaecol.* http://dx.doi.org/10.1016/j.bpobgyn.2016.05.003 (2016).
186. Boomsma, C. M. *et al.* A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum. Reprod. Update* **12**, 673–683 (2006).
187. Legro, R. S. *et al.* Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N. Engl. J. Med.* **356**, 551–566 (2007).
This is the first large randomized controlled trial to demonstrate the relative inferiority of metformin as a primary ovulatory agent in PCOS.
188. Legro, R. S. *et al.* Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N. Engl. J. Med.* **371**, 119–129 (2014).
189. Zain, M. M., Jamaluddin, R., Ibrahim, A. & Norman, R. J. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial. *Fertil. Steril.* **91**, 514–521 (2009).
190. Sagle, M. A., Hamilton-Fairley, D., Kiddy, D. S. & Franks, S. A comparative, randomized study of low-dose human menopausal gonadotropin and follicle-stimulating hormone in women with polycystic ovarian syndrome. *Fertil. Steril.* **55**, 56–60 (1991).
191. Polson, D. W., Mason, H. D., Saldahna, M. B. & Franks, S. Ovulation of a single dominant follicle during treatment with low-dose pulsatile follicle stimulating hormone in women with polycystic ovary syndrome. *Clin. Endocrinol. (Oxf.)* **26**, 205–212 (1987).
192. Homburg, R. *et al.* Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. *Hum. Reprod.* **27**, 468–473 (2012).
193. Solnik, M. J. in *Te Linde's Atlas of Gynecologic Surgery* (eds Cundiff, G. W., Azziz, R. & Bristow, R. E.) 217–222 (Lippincott Williams & Wilkins, 2013).
194. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil. Steril.* **89**, 505–522 (2008).
195. Api, M. Is ovarian reserve diminished after laparoscopic ovarian drilling? *Gynecol. Endocrinol.* **25**, 159–165 (2009).
196. Nahuis, M. J. *et al.* Long-term outcomes in women with polycystic ovary syndrome initially randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotrophins. *Hum. Reprod.* **26**, 1899–1904 (2011).
197. Cha, K. Y. *et al.* Obstetric outcome of patients with polycystic ovary syndrome treated by *in vitro* maturation and *in vitro* fertilization–embryo transfer. *Fertil. Steril.* **83**, 1461–1465 (2005).
198. Siristatidis, C. *et al. In vitro* maturation in women with versus without polycystic ovarian syndrome: a systematic review and meta-analysis. *PLoS ONE* **10**, e0134696 (2015).
199. Walls, M. L. *et al. In vitro* maturation as an alternative to standard *in vitro* fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. *Hum. Reprod.* **30**, 88–96 (2015).
200. Shi, Y. *et al.* Live birth after fresh embryo transfer versus elective embryo cryopreservation/frozen embryo transfer in women with polycystic ovary syndrome undergoing IVF (FreFro-PCOS): study protocol for a multicenter, prospective, randomized controlled clinical trial. *Trials* **15**, 154 (2014).
201. Tang, T., Glanville, J., Orsi, N., Barth, J. H. & Balen, A. H. The use of metformin for women with PCOS undergoing IVF treatment. *Hum. Reprod.* **21**, 1416–1425 (2006).
202. Tso, L. O., Costello, M. F., Albuquerque, L. E., Andriolo, R. B. & Freitas, V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database Syst. Rev.* **2**, CD006105 (2009).
203. McHorney, C. A. Health status assessment methods for adults: past accomplishments and future challenges. *Annu. Rev. Public Health* **20**, 309–335 (1999).
204. Li, Y. *et al.* Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil. Steril.* **96**, 452–458 (2011).
205. Cronin, L. *et al.* Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J. Clin. Endocrinol. Metab.* **83**, 1976–1987 (1998).
The authors of this article developed the first PCOS-dedicated health-related QOL questionnaire for PCOS.
206. Barnard, L. *et al.* Quality of life and psychological well being in polycystic ovary syndrome. *Hum. Reprod.* **22**, 2279–2286 (2007).
207. Hahn, S. *et al.* Metformin treatment of polycystic ovary syndrome improves health-related quality-of-life, emotional distress and sexuality. *Hum. Reprod.* **21**, 1925–1934 (2006).
208. Ladson, G. *et al.* The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. *Fertil. Steril.* **95**, 1059–1066.e7 (2011).
209. Harris-Glocker, M., Davidson, K., Kochman, L., Guzick, D. & Hoeger, K. Improvement in quality-of-life questionnaire measures in obese adolescent females with polycystic ovary syndrome treated with lifestyle changes and oral contraceptives, with or without metformin. *Fertil. Steril.* **93**, 1016–1019 (2010).
210. Cinar, N., Harmanci, A., Demir, B. & Yildiz, B. O. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study. *Hum. Reprod.* **27**, 1840–1845 (2012).
211. Deeks, A. A., Gibson-Helm, M. E., Paul, E. & Teede, H. J. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? *Hum. Reprod.* **26**, 1399–1407 (2011).
212. Elsenbruch, S. *et al.* Determinants of emotional distress in women with polycystic ovary syndrome. *Hum. Reprod.* **21**, 1092–1099 (2006).
213. Liu, D. M. *et al.* Evidence for gonadotrophin secretory and steroidogenic abnormalities in brothers of women with polycystic ovary syndrome. *Hum. Reprod.* **29**, 2764–2772 (2014).
214. Coviello, A. D., Sam, S., Legro, R. S. & Dunaif, A. High prevalence of metabolic syndrome in first-degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. *J. Clin. Endocrinol. Metab.* **94**, 4361–4366 (2009).
215. Recabarren, S. E. *et al.* Metabolic profile in sons of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **93**, 1820–1826 (2008).
216. Baillargeon, J. P. & Carpentier, A. C. Brothers of women with polycystic ovary syndrome are characterised by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. *Diabetologia* **50**, 2424–2432 (2007).
217. Fraser, G. L., Ramael, S., Hoveyda, H. R., Gheyle, L. & Combalbert, J. The NK3 receptor antagonist ESN364 suppresses sex hormones in men and women. *J. Clin. Endocrinol. Metab.* **101**, 417–426 (2016).
218. Azziz, R., Dumesic, D. A. & Goodarzi, M. O. Polycystic ovary syndrome: an ancient disorder? *Fertil. Steril.* **95**, 1544–1548 (2011).
219. Sir-Petermann, T. *et al.* Early metabolic derangements in daughters of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **92**, 4637–4642 (2007).
220. Sir-Petermann, T. *et al.* Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **94**, 1923–1930 (2009).
221. Maliqueo, M. *et al.* Adrenal function during childhood and puberty in daughters of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **94**, 3282–3288 (2009).
222. Battaglia, C. *et al.* Polycystic ovaries in childhood: a common finding in daughters of PCOS patients. A pilot study. *Hum. Reprod.* **17**, 771–776 (2002).
223. Ibanez, L. *et al.* Postpubertal outcome in girls diagnosed of premature pubarche during childhood: increased frequency of functional ovarian hyperandrogenism. *J. Clin. Endocrinol. Metab.* **76**, 1599–1603 (1993).
224. Meas, T. *et al.* Endocrine consequences of premature pubarche in post-pubertal Caucasian girls. *Clin. Endocrinol. (Oxf.)* **57**, 101–106 (2002).
225. McCartney, C. R. *et al.* The association of obesity and hyperandrogenemia during the pubertal transition in girls: obesity as a potential factor in the genesis of postpubertal hyperandrogenism. *J. Clin. Endocrinol. Metab.* **91**, 1714–1722 (2006).
226. van Hooff, M. H. *et al.* Predictive value of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at age 15 years for oligo-amenorrhoea at age 18 years. *Hum. Reprod.* **19**, 383–392 (2004).
This study demonstrates the predictive nature of the degree of menstrual dysfunction, particularly for persistent menstrual dysfunction in adolescents.
227. Wiksten-Almstromer, M., Hirschberg, A. L. & Hagenfeldt, K. Prospective follow-up of menstrual disorders in adolescence and prognostic factors. *Acta Obstetricia Gynecol. Scand.* **87**, 1162–1168 (2008).
228. Fanelli, F. *et al.* Androgen profiling by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in healthy normal-weight ovulatory and anovulatory late adolescent and young women. *J. Clin. Endocrinol. Metab.* **98**, 3058–3067 (2013).
229. Villarroel, C. *et al.* Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents. *Gynecol. Endocrinol.* **31**, 625–629 (2015).
230. Ibanez, L. *et al.* Polycystic ovaries in nonobese adolescents and young women with ovarian androgen excess: relation to prenatal growth. *J. Clin. Endocrinol. Metab.* **93**, 196–199 (2008).
231. Cresswell, J. L. *et al.* Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet* **350**, 1131–1135 (1997).
232. DeFronzo, R. A., Bonadonna, R. C. & Ferrannini, E. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care* **15**, 318–368 (1992).

Acknowledgements
The authors thank Y.-H. Chen, Augusta University, Georgia, USA.

Author contributions
Introduction (R.A.); Epidemiology (R.A.); Mechanisms/pathophysiology (R.A., E.C., Z.-J.C., A.D., J.S.E.L., H.J.T. and B.O.Y.); Diagnosis, screening and prevention (R.A. and H.J.T.); Management (R.A., E.C., Z.-J.C., R.S.L., D.L. and B.O.Y.); Quality of life (E.C. and B.O.Y.); Outlook (R.A., B.N.-H., D.L. and R.S.L.); Overview of Primer (R.A.).

Competing interests
R.A. has a consulting agreement with KinDex Pharmaceutical Inc., is on the advisory board of Global PET Imaging, and has a consulting appointment with Selge Holdings and Ventures. J.S.E.L. has received unrestricted research grants from Ferring, Merck-Serono, MSD, Schering Plough, Serono and Okganon. R.S.L. is a consultant for Takeda, KinDex, Euroscreen and Ferring, and has received research funding from and is a consultant for Ferring. All other authors declare no competing interests.