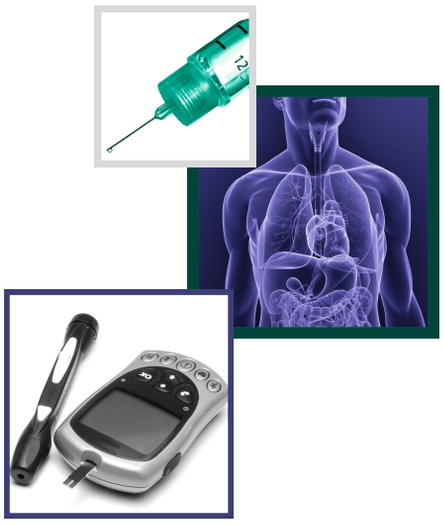
REVIEW

The link between polycystic ovary syndrome and Type 2 diabetes: what do we know today?



Thozhukat Sathyapalan[†1] & Stephen L Atkin[1]

Practice Points

- Polycystic ovary syndrome (PCOS) is identified as a significant nonmodifiable risk factor associated with Type 2 diabetes mellitus (T2DM) by the International Diabetes Federation.
- Approximately 40% of the economic costs of PCOS can be attributed to T2DM, which highlights the need for the prevention of the long-term complications through appropriate screening, diagnosis and intervention.
- The cause of insulin resistance in women with PCOS appears to be, at least in part, related to obesity.
- Women with PCOS have a type of insulin resistance that is independent and additive with that of obesity.
- There is emerging evidence that chronic anovulation as seen by oligo or amenorrhea identifies a group of women at marked increased risk for T2DM.
- A high prevalence of polycystic ovaries has been detected among females of a reproductive age who present with T2DM.
- In PCOS, a family history of diabetes has been found to further magnify the severity of insulin secretory defects compared with PCOS women without a family history.

SUMMARY Polycystic ovary syndrome (PCOS) is a common condition estimated to affect 4–18% of women of reproductive age. PCOS is associated with reproductive and metabolic sequelae. These sequelae include increased risk factors for impaired glucose tolerance, Type 2 diabetes mellitus (T2DM) and cardiovascular disease. Insulin resistance is proposed as a key pathophysiological feature of PCOS contributing to both the reproductive and metabolic disturbances as well as contributing to an increased cardiometabolic risk for women with PCOS. In this article we have discussed the inter-relationship between PCOS, insulin resistance and T2DM as well as various risk factors present in women with PCOS that predisposes them to develop T2DM.

[1]Department of Academic Endocrinology, Diabetes & Metabolism, Hull York Medical School, Hull, UK
[†]Author for correspondence: Michael White Diabetes Centre, 220–236 Analby Road, Hull Royal Infirmary, Hull, HU3 2JZ, UK; Tel.: +44 148 267 5312; Fax: +44 148 267 5385; thozhukat.sathyapalan@hyms.ac.uk

part of future medicine fsg

Populations with a high prevalence of insulin resistance are known to be at increased risk for impaired glucose tolerance (IGT), Type 2 diabetes (T2DM) and cardiovascular disease (CVD) [1,2]. Polycystic ovary syndrome (PCOS) is associated with reproductive and metabolic (IGT, T2DM and CVD) sequelae [3], and there is an increasing focus on the complications associated with metabolic disturbances among women with PCOS as it is a common condition estimated to affect 4–18% of women of reproductive age [4–6]. Approximately 40% of the economic costs of PCOS can be attributed to T2DM in the USA, which highlights the need for the prevention of the long-term complications through appropriate screening, diagnosis and intervention [7].

Currently two definitions of PCOS are in widespread use. According to the 1990 NIH Conference about PCOS, diagnostic criteria should include the evidence of hyperandrogenism and ovulatory dysfunction as an essential part of the diagnosis, without any regard to the morphological diagnosis of polycystic ovaries (PCO) by ultrasonography. However, the Rotterdam consensus statement recommends that the presence of two or three of the following criteria are required for the diagnosis of PCOS:

- Oligo and/or anovulation;
- Clinical and/or biochemical signs of hyperandrogenism;
- Echographic PCO, after the exclusion of other pathologies with a similar clinical presentation such as congenital adrenal hyperplasia, Cushing's syndrome and androgen-secreting tumors [8].

Potential links involving insulin resistance, hyperandrogenism & PCOS

The potential links between hyperinsulinemia and the increased androgen production observed in PCOS includes direct stimulation of ovarian androgen secretion by insulin, possibly through stimulatory effects on the 17α-hydroxylase/17,20-lyase and P_{450}scc enzymes; direct stimulation of luteinizing hormone (LH) secretion by insulin or sensitization of LH-secreting pituitary cells to gonadotropin-releasing hormone stimulation; up-regulation of ovarian IGF-1 receptors with the amplification of IGF-I, IGF-II and insulin actions in the ovary; decreased levels of sex hormone binding globulin (SHBG), with concomitant elevation of free androgens; decreased insulin-like growth factor binding protein-1 production, both in the liver and in the ovary, with concomitant elevation of free IGFs in the circulation and in the ovary; and the synergistic growth- and cyst-promoting action of insulin and LH [9].

It has been proposed that hyperandrogenemia may contribute to insulin resistance in PCOS and that hyperinsulinemia can promote hyperandrogenism [10]. Although androgen levels in PCOS have been reduced and their action blocked by the use of gonadotropin-releasing hormone agonists and androgen receptor blockers, suppression of ovarian or adrenal steroidogenesis has not improved insulin resistance [11], although in some studies antiandrogens such as flutamide and spironolactone have led to partial improvement [12]. Ovarian cautery, which lowers androgen secretion, does not alter insulin resistance [13]. Direct administration of androgens to oophorectomized women has no effect on insulin levels, although it increases circulating levels of IGF-I and suppresses SHBG [9,14]. On the other hand, pharmacological reduction in the level of hyperinsulinemia, either by insulin sensitizers such as metformin or troglitazone, or by insulin secretion inhibitors such as octreotide or diazoxide, has consistently improved circulating androgen levels [9]. In addition, the occurrence of hyperandrogenism in states of extreme insulin resistance other than PCOS [15] and in association with hyperinsulinemia induced by valproate therapy for epilepsy [16] supports a primary role for insulin excess in producing ovarian dysfunction [10].

The cause of insulin resistance in women with PCOS appears to be, at least in part, related to obesity, and insulin resistance is not present in all women with PCOS [17]. Whether there is a component of insulin resistance in PCOS independent of the insulin resistance of obesity will be clarified once the specific molecular mechanisms of insulin resistance in both of these conditions are better understood [10]. It has been proposed that the pathogenesis of PCOS is different in obese and nonobese women, with insulin resistance and hyperinsulinemia playing a central role in obese patients and abnormalities of the GH–IGF-I axis being important in PCOS in lean women [10,18].

Risk factors for CVD in PCOS

Risk factors for T2DM and CVD in PCOS include insulin resistance, obesity, abdominal obesity, dyslipidemia and inflammation. Greater

endothelial dysfunction, arterial stiffness, presence of carotid and aortic plaque, carotid intima-media wall thickness and coronary artery calcification [19–21] have all been reported in women with PCOS compared with controls. PCOS is also identified as a significant nonmodifiable risk factor associated with T2DM by the International Diabetes Federation [22] and women with PCOS are also proposed to have a more rapid conversion from IGT to T2DM [23]. Epidemiological studies suggest that T2DM-associated morbidity, estimated over a 20- to 30-year follow-up, is higher [24,25]. Although epidemiological evidence is not yet complete, available evidence indicates more frequent CVD deaths in women with PCOS [26]. Furthermore, women with PCOS have an elevated prevalence of the metabolic syndrome [21,27] and individuals with the metabolic syndrome are at increased risk for T2DM and CVD [28,29]. Even adolescents with PCOS commonly have IGT, T2DM and the metabolic syndrome, suggesting an adverse contribution of PCOS to metabolic health across the female lifespan [30,31]. Therefore, there is an increasing body of literature indicating an elevated prevalence of IGT, T2DM, the metabolic syndrome, risk factors for CVD and potentially CVD in PCOS.

Insulin resistance in women with PCOS is independent as well as additive to the insulin resistance related to obesity [32,33]. With PCOS and obesity together causing the greatest impairment of insulin sensitivity, insulin resistance occurs in approximately 50–70% of women with PCOS and in 95% of obese women with PCOS [34,35]. Consequently, IGT as a predictor of T2DM and premature CVD mortality are highly prevalent in women with PCOS [36]. Girls with PCOS experience a high prevalence of IGT and T2DM during adolescence [30]. Up to 40% of women with classic PCOS develop IGT or T2DM by the fourth decade of life, with age and weight gain worsening glycemic control [23,37,38].

In a systematic review and meta-analysis, women with PCOS presented with a greater prevalence of T2DM than women without PCOS on fixed-effects analysis (odds ratio [OR]: 4.43; 95% CI: 4.06–4.82) **(Figure 1a)** and random-effects analysis (OR: 3.16; 95% CI: 1.87–5.32); however, significant statistical heterogeneity was evident [39]. Women with PCOS had a greater prevalence of T2DM than women without PCOS on fixed-effects analysis (OR: 4.00; 95% CI: 1.97–8.10) **(Figure 1b)** and random-effects analysis (OR: 4.68; 95% CI: 2.29–9.56) [39].

Women with classic PCOS, therefore, have a fivefold increased risk of developing T2DM over 8 years versus age-matched and weight-matched healthy women without PCOS [37], although only 12% of patients with PCOS without obesity developed glucose abnormalities over a period of 6 years [23]. It has been shown that PCOS is associated with a 2.5-fold increased prevalence of IGT and a fourfold increased prevalence of T2DM [39].

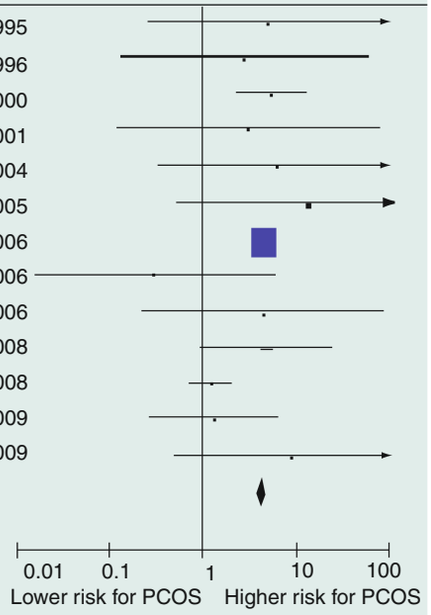
Risk of conversion from normo/impaired glycemia to diabetes in PCOS

Natural history supportive of significant worsening of glucose tolerance would support more aggressive identification and treatment of this disorder in PCOS women. In a follow-up study of 25 women with PCOS, there was a significant increase in the mean 2 h glucose values when oral glucose tolerance was performed at baseline and over a 3-year average period of follow-up [36]. In another small study there was a trend towards worsening glucose tolerance in those who were followed up after an average time of 6.2 years [23]. Conversion rate was high with 9% of normoglycemic women at baseline developing IGT and a further 8% moving directly from normoglycemia to T2DM. For women with IGT at baseline, 54% had T2DM at follow-up. A greater BMI at baseline was an independent significant predictor of conversion risk. These data support a worsening of glucose intolerance over time and the need for periodic screening. Two studies reported either insignificant increases in T2DM incidence [37] or insignificantly higher conversion rates from normal glucose tolerance to IGT or T2DM for women with PCOS compared with women without PCOS [40]. A population attributable risk of 15–35.6% of incident cases of T2DM attributable to PCOS has also been reported [41]. In studies lacking appropriate control groups, IGT and T2DM incidence and conversion from IGT to T2DM are reported as 1.5, 2.6 and 8.7%, respectively (6.2-year follow-up) [23], and 18.9, 8.3 and 11.9%, respectively (2.4-year follow-up) [36]. In the general population in Australian women, the AusDiab study reported 1.3% incidence of IGT, 0.7% incidence of T2DM and 2.9% conversion from IGT to T2DM over 5 years [42]. This supports the concept that risk for IGT and T2DM are increased in women with PCOS. However,

A

Study or subgroup	PCOS Events	PCOS Total	Control Event	Control Total	Weight (%)	Odds ratio M-H, fixed, 95% CI	Year
dos Reis *et al.* [107]	3	29	0	19	0.1	5.15 [0.25, 105.59]	1995
Rajkhowa *et al.* [108]	2	72	0	39	0.2	2.80 [0.13, 59.82]	1996
Cibula *et al.* [109]	9	28	60	752	0.8	5.46 [2,37, 12.60]	2000
Yarali *et al.* [110]	1	30	0	30	0.1	3.10 [0.12, 79.23]	2001
Sir-Petermann *et al.* [111]	4	146	0	97	0.2	6.16 [0.33, 115.68]	2004
Sawathiparnich *et al.* [112]	3	6	0	6	0.1	13.00 [0.51, 330.48]	2005
Lo *et al.* [113]	988	11035	1136	55175	89.9	4.68 [4.28, 5.11]	2006
Alvarez-Blasco *et al.* [114]	0	32	3	72	0.6	0.31 [0.02, 6.09]	2006
Leibel *et al.* [115]	3	36	0	21	0.1	4.49 [0.22, 91.35]	2006
Marquez *et al.* [116]	6	50	3	70	0.6	3.05 [0.72, 12.82]	2008
Shaw *et al.* [117]	34	104	70	286	6.6	1.50 [0.92, 2.45]	2008
Bhattacharya [118]	6	264	2	116	0.7	1.33 [0.26, 6.67]	2009
Moini *et al.* [119]	4	273	0	276	0.1	9.23 [0.49, 172.33]	2009
Total (95% CI)		**12105**		**56959**	**100.0**	**4.43 [4.06, 4.82]**	
Total events	1063		1274				

Heterogeneity: $\chi^2 = 26.82$, df = 12 (p = 0.008); $I^2 = 55\%$
Test for overall effect: Z = 33.93, (p < 0.00001)



B

Study or subgroup	PCOS Events	PCOS Total	Control Event	Control Total	Weight (%)	Odds Ratio M-H, fixed, 95% CI	Year
Rajkhowa *et al.* [120]	2	72	0	39	9.0	2.80 [0.13, 59.82]	1996
Cibula *et al.* [109]	9	28	60	752	42.3	5.46 [2.37, 12.60]	2000
Yarali*et al.* [110]	1	30	0	30	3.6	3.10 [0.12, 79.23]	2001
Sawathipamic *et al.* [112]	3	6	0	6	6.9	13.00 [0.51, 330.48]	2005
Alvarez-Blasco *et al.* [114]	0	32	3	72	31.1	0.31 [0.02, 6.09]	2006
Moini *et al.* [119]	4	273	0	276	7.1	9.23 [0.49, 172.33]	2009
Total (95% CI)		**441**		**1175**	**100.0**	**4.00 [1.97, 8.10]**	
Total events	19		63				

Heterogeneity: $\chi^2 = 4.27$, df = 5 (p = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 3.84, (p = 0.0001)

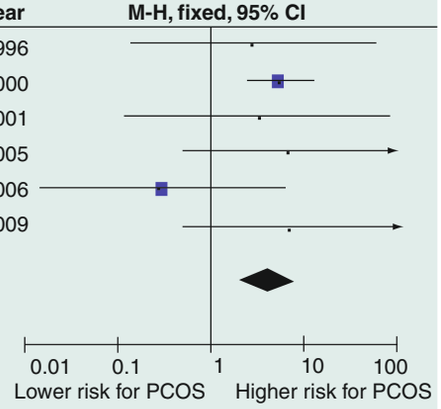


Figure 1. Prevalence of Type 2 diabetes in women with and without polycystic ovary syndrome. Type 2 diabetes prevalence in women with and without PCOS **(A)** and subgroup meta-analysis **(B)** of Type 2 diabetes prevalence in women with and without PCOS in BMI-matched study populations.
PCOS: Polycystic ovary syndrome.
Adapted with permission from [39].

the incidence and/or conversion literature is limited by small numbers or methodological concerns including confounding because of medication use, T2DM diagnosis or family history T2DM status or absence of non-PCOS controls where nonmatched comparisons to population data are extrapolated.

Risk factors for the development of diabetes in women with PCOS

■ Obesity, PCOS & diabetes

Obesity is one of the clearest risk factors for developing diabetes. Even women of average weight (BMI 23–23.8 kg/m^2) were at substantial increased risk for diabetes (relative

risk 3.6) when compared with thinner women (BMI <22 kg/m^2) [43]. It has been estimated that 50% of women with PCOS are obese this can vary greatly between populations. In an English population of PCOS women, approximately 40% of patients were obese [44], whereas in the USA obesity and morbid obesity is much more common – up to 80% [36]. Although approximately 10% of thin women with PCOS can have glucose intolerance, there is a stepwise increase in prevalence as BMI increases [36].

Many studies have also identified a centripetal pattern of obesity in obese PCOS women, that may further contribute to diabetes risks in these women [45]. Simple obesity is associated with a greater deposition of gluteo–femoral fat while centripetal obesity involves greater truncal abdominal fat distribution. Hyperandrogenism is associated with a preponderance of fat localized to truncal abdominal sites [46]. Women with PCOS have a greater truncal abdominal fat distribution as demonstrated by a higher waist:hip ratio [46,47]. The central distribution of fat in these studies was independent of BMI and associated with higher plasma insulin and triglyceride concentrations and reduced high-density lipoprotein cholesterol concentrations [48].

■ Insulin resistance in PCOS

The initial suggestions of the relationship between hyperandrogenism and PCOS were reported in the descriptions of syndromes of extreme insulin resistance in the 1970s, which were subsequently found to be owing to insulin receptor mutations or autoimmune antibodies to insulin receptor [49,50]. In the 1980s it was found that the plasma insulin levels during an oral glucose tolerance test were elevated in eight obese subjects with PCOS, compared with controls [51]. In addition, there was a significant correlation between basal insulin measurements with both serum testosterone and androstenedione concentrations and between insulin response during the oral glucose tolerance test and serum testosterone concentrations. Subsequently it was shown that many women with PCOS have insulin resistance beyond that predicted by their BMI, with 50–70% of these women demonstrating insulin resistance by various measures [35]. Studies have shown that approximately 30–65% nonobese women with PCOS have a mild degree of insulin resistance [52]. Insulin resistance causes compensatory hyperinsulinemia, which drives many of the phenotypic features of PCOS. Most women with PCOS are young and develop compensatory hyperinsulinemia from insulin resistance, with IGT detectable more readily by oral or intravenous glucose testing than by basal glucose measures [53]. Whereas women with PCOS have normal or exaggerated insulin secretory responsiveness, many, particularly those with a family history of T2DM, show impaired β-cell function or a subnormal disposition index (an index of β-cell function that takes insulin resistance into account) [54,55]. A challenge to the assessment of insulin resistance is the imperfect correlation of surrogate measures such as fasting insulin and glucose levels compared with gold standard techniques such as the euglycemic clamp [56].

The increase in insulin resistance in women with PCOS compared with appropriate controls is of a similar magnitude to that seen in T2DM and is independent of obesity, glucose intolerance, increases in waist:hip:girth ratio as well as differences in muscle mass [15,33]. The synergistic negative effect of obesity and PCOS on hepatic glucose production is an important factor in the pathogenesis of glucose intolerance in PCOS. Insulin resistance is thought to be the primary pathogenetic defect leading to the development of T2DM and prospective population studies have identified it as an independent risk factor for T2DM [57].

■ β-cell dysfunction in PCOS

One of the most common prevailing theories about the etiology of T2DM proposes that the primary pathogenetic defect is peripheral insulin resistance resulting in compensatory hyperinsulinemia. Over time there is β-cell dysfunction leading to inadequate secretion of insulin and ultimately to β-cell exhaustion and the development of frank T2DM. There is now a relatively substantial body of literature confirming β-cell dysfunction in PCOS [57–60]. Basal insulin levels are increased and insulin secretory response to meals has been shown to be reduced in PCOS women [60]. This dysfunction is also independent of obesity [58]. However, β-cell dysfunction *per se* is not thought to be an independent risk factor for CVD.

■ Chronic anovulation, PCOS & T2DM

Chronic anovulation as seen by oligo or amenorrhea has not been traditionally identified as a risk factor for diabetes. However, there is emerging evidence that this symptom alone identifies a group of women at marked increased risk for T2DM. In the Nurses' Health Study II, a largely

non-Hispanic white group, there was a significant increase in the risk for T2DM in women with oligo or amenorrhea. Women with a cycle length of 40 days or greater, including those with complete amenorrhea, had more than twice the risk for developing T2DM compared with women with regular menstrual cycles 21–39 days in length [61]. In studies of insulin-sensitizing agents in women with PCOS, an increase in cycle length at baseline (i.e., decreased menstrual frequency) has been associated with a decreased likelihood of response [62,63]. Thus, fewer menstrual cycles may identify a greater risk for diabetes or failure to respond to insulin-sensitizing therapy within the population of females with PCOS.

■ Hyperandrogenism, PCOS & T2DM

The relationship between hyperandrogenism and diabetes is complex, since there is no linear relationship between the degree of androgen excess and markers of insulin action. Nonetheless there is increasing evidence that hyperandrogenemia *per se* may reflect underlying metabolic dysfunction and a tendency to glucose intolerance. This is not only based on the classic association of diabetes with 'bearded ladies' [64], but also on rare syndromes of marked elevated hyperandrogenemia, marked insulin resistance and acanthosis nigricans, the hyperandrogenism, insulin resistance and acanthosis nigricans syndrome [65]. Sisters of probands with PCOS who have isolated elevated testosterone levels are hyperinsulinemic [66]. Others have shown increased rates of glucose intolerance among first-degree male and female relatives of women with PCOS [66,67].

■ Polycystic ovaries & T2DM

Polycystic ovaries with diabetes are noted in follow-up studies of aging populations with a prior diagnosis of PCOS. PCO have been found in up to 30% of a random female population [68], and their presence does not necessarily signal metabolic abnormalities such as glucose intolerance. Many women with PCO appear to have normal endocrine functions, without hirsutism or irregular menses [69]. Nonetheless more intensive studies of apparently normal females with PCO have detected metabolic and reproductive abnormalities [70,71]. A high prevalence of PCO has been detected among reproductive-aged females who present with T2DM [72]. Although the predictive value of the presence of PCO is unknown, the preliminary data are suggestive that this is a possible sign of metabolic dysfunction.

■ Previous gestational diabetes, PCOS & T2DM

While a history of gestational diabetes is a clear risk factor for T2DM, it is uncertain how much the diagnosis of PCOS increases this risk. Again both disorders involve a marked reduction in peripheral insulin sensitivity [73]. In Latino women with a history of gestational diabetes mellitus (GDM), cumulative conversion rates as high as 80% over 5 years have been reported [74]. Women who present with gestational diabetes have a higher prevalence of PCO detected postpartum [75,76] and this can be associated with persistent postpartum glucose intolerance [77]. The impact of pre-existing glucose intolerance in a woman with PCOS is less certain, but probably increases the risk [77]. Hyperinsulinemia may be an independent risk factor for developing gestational diabetes in women with PCOS [78]. No additional risk of gestational diabetes has been detected by others [79].

In a meta-analysis of pregnancy outcomes in PCOS, women with PCOS demonstrated a significantly higher chance of developing gestational diabetes (OR: 2.94; 95% CI: 1.70–5.08) [80]. However, significant heterogeneity between the studies was detected in this meta-analysis in relation to GDM. However, in this meta-analysis women with PCOS are at increased risk of other pregnancy and neonatal complications including pregnancy-induced hypertension (OR: 3.67; 95% CI: 1.98–6.81), preeclampsia (OR: 3.47; 95% CI: 1.95–6.17) and preterm birth (OR: 1.75; 95% CI: 1.16–2.62). Their babies had a significantly higher risk of admission to a neonatal intensive care unit (OR: 2.31; 95% CI: 1.25–4.26) and a higher perinatal mortality (OR: 3.07; 95% CI: 1.03–9.21), unrelated to multiple births [80]. In another systematic review and meta-analysis evaluating the risk of GDM in PCOS, women with PCOS demonstrated a significantly higher risk for the development of GDM as compared with women without PCOS (OR: 2.89; 95% CI: 1.68–4.98), however, there was significant statistical heterogeneity. In the subgroup of cohort studies, this finding remained robust (OR: 7.11; 95% CI: 2.95–17.12), whereas in the subgroup of case–control studies, it did not (OR: 0.89; 95% CI: 0.38–2.06) [81]. The authors concluded that significant heterogeneity among studies and dependence of the outcome on study type make the higher risk of GDM in women with PCOS a questionable finding [81] and the conduct of

properly designed studies should precede any recommendation to pregnant women with PCOS in regard to the risk of GDM.

■ Family history of T2DM & PCOS

Multiple studies have shown that a family history of T2DM significantly contributes to the risk of T2DM [82,83]. First-degree relatives of patients with T2DM are more likely to suffer stigmata of insulin resistance, including IGT [84]. Diabetes risk is increased according to both the number of relatives affected with T2DM and the closeness of relation. In PCOS, a family history of diabetes has been found to further magnify the severity of insulin secretory defects compared with PCOS women without a family history [55]. A family history of diabetes increases the risk for glucose intolerance in a women with PCOS by two- to three-fold [53].

Screening of T2DM in women with PCOS

The IDF advocates early screening, detection and treatment of T2DM to reduce disease-related morbidity and mortality [22]. It is recognized that patients with glucose abnormalities have a higher conversion to T2DM and it has been suggested that an oral glucose tolerance test should be performed every 2 years for those with normal glucose tolerance and annually if impaired fasting glucose or IGT be present [85]. It has also been suggested that the use of an glycated haemoglobin greater than 6.5% as proposed for diabetes diagnosis [86]. However, caution should be exercised as patients with T2DM may be missed [87] and the utilization of glycated haemoglobin for the diagnosis of diabetes in PCOS needs better definition.

Insulin sensitising agents in PCOS

Several antihyperglycemic agents used in the treatment of T2DM, including biguanides (metformin) and thiazolidinediones (troglitazone, pioglitazone, rosiglitazone) can reduce insulin levels in women with PCOS. These drugs may also reduce ovarian androgen production (and serum-free testosterone concentrations) and restore normal menstrual cyclicity [88–91].

Metformin's major effect is to decrease hepatic glucose production thus reducing the need for insulin secretion; it also decreases intestinal absorption of glucose and modestly improves insulin sensitivity (increases peripheral glucose uptake and utilization). Metformin also has an antilipolytic effect that lowers fatty acid concentrations, thus reducing gluconeogenesis [92]. At a molecular level, metformin increases the activity of the enzyme AMP-activated protein kinase [93]. Metformin appears to work through the Peutz–Jeghers protein, LKB1, to regulate AMP-activated protein kinase [94]. It is used primarily for the treatment of T2DM, but has also been used in women with PCOS [95].

In a trial compared with placebo, the metformin group had improvement in plasma insulin and insulin sensitivity (as measured by glucose clamp studies); a reduction in serum free testosterone; and an increase in mean serum high-density lipoprotein cholesterol. Both the biochemical and clinical changes were independent of changes in bodyweight and were sustained in a follow-up open long-term observational study (mean duration of treatment was 11 months) [62]. A meta-analysis of 13 trials reported that metformin is associated with a reduction in blood pressure, low-density lipoprotein and fasting insulin levels, when compared with placebo [95].

All available thiazolidinedione derivatives have been shown to improve insulin sensitivity and dyslipidemia. The anti-inflammatory and antiatherosclerotic effects of these compounds are due to activation of nuclear peroxisome proliferator-activated receptors, which regulate the expression of numerous genes affecting glycemic homeostasis, lipid metabolism, vascular tone, inflammation and arteriosclerosis [96]. Thiazolidinediones may have androgen-lowering effects owing to inhibition of P450c17 and 3β–hydroxysteroid dehydrogenase, two key enzymes in human androgen synthesis [97]. Insulin and thiazolidinediones independently stimulate expression of PPAR-γ, insulin receptor, IRS-1 and StAR protein in human ovarian cells. Thus, PPAR-γ, insulin receptor with its signaling pathways and StAR protein constitute a novel human ovarian regulatory system with complex interactions among its components [98].

Thiazolidinediones have not been studied to the same level as metformin. Although they appear to improve insulin sensitivity, they are associated with weight gain. Troglitazone (400 mg/day for 3 months) reported an improvement in insulin action and a 20–30% decrease in serum free testosterone concentrations [88,89]. However, troglitazone was removed from the market because of its associated hepatotoxicity. A trial in 40 women with PCOS randomly assigned to pioglitazone (30 mg/day) or placebo for 3 months reported a significant improvement

in insulin sensitivity, a decrease in the free androgen index (owing to an increase in SHBG) and an increase in ovulatory rates in the pioglitazone group when compared with placebo [99]. In a 6 month trial of 52 obese women with PCOS randomly assigned to pioglitazone (30 mg/day) or metformin (850 mg three times daily), insulin sensitivity and hyperandrogenemia improved to a similar degree, in spite of significant weight gain in the pioglitazone group [100]. Because of limited clinical data, the potential weight gain and a possible association with cardiovascular adverse events, the use of thiazolidinediones in women with PCOS who do not have T2DM is controversial.

Incretin mimetics agents in PCOS

The GI tract produces several peptide hormones that participate in regulation of food intake. Ingested nutrients, especially fats and carbohydrates, stimulate glucagon-like peptide-1 (GLP-1) secretion from L cells in the distal small intestine [101]. GLP-1 accentuates glucose-dependent insulin release, inhibits glucagon secretion, increases pancreatic β-cell growth, suppresses appetite and energy intake and delays gastric emptying. GLP-1 receptor is expressed by the gut, pancreas, brainstem, hypothalamus and vagal-afferent nerves [54]. Activation of the hypothalamic GLP-1 receptor decreases food intake [102].

In a 24-week randomized controlled trial in women with PCOS a combination treatment with exenatide (GLP-1 mimetic) and metformin was found to be superior to exenatide or metformin monotherapy alone in reducing weight (mean weight loss of 6 ± 0.5 kg) and improving menstrual cycles, ovulation rate, free androgen index and insulin sensitivity [103]. In a head-to-head comparison study in people with T2DM, 1·8 mg liraglutide daily and 10 µg exenatide twice daily produced similar weight loss (3·2 kg with liraglutide vs 2·9 kg with exenatide). However, liraglutide achieved better glycemic control and was better tolerated than exenatide [104].

Bariatric surgery in PCOS

In subjects with morbid obesity and diabetes bariatric surgery may be considered as an effective therapy [105]. Few studies have shown bariatric surgery to be associated with a significant improvement in weight, hirsutism, insulin resistance and fertility in women with PCOS [106].

Conclusion & future perspective

Polycystic ovary syndrome is a common condition estimated to affect 4–18% of women of reproductive age group. There is an increasing body of literature suggesting that PCOS is associated with an increased prevalence of IGT, T2DM, the metabolic syndrome which are risk factors for CVD. Risk factors for T2DM and CVD in PCOS include insulin resistance, obesity, abdominal obesity, dyslipidemia and inflammation. Long-term metabolic abnormalities, above and beyond obesity, are related to reduce sensitivity to insulin and compensatory hyperinsulinemia in women with PCOS. There is emerging evidence that chronic anovulation as seen by oligo or amenorrhea identifies a group of women at marked increased risk for T2DM.

There are a few reports showing that there is an increased incidence of IGT and diabetes mellitus in women with PCOS, with an increased rate of conversion from normal glucose tolerance/IGT to T2DM; however, further well-controlled studies are required owing to address the limitations of previous data owing to small subject numbers and methodological concerns including confounding. There is also some evidence to show that women with PCOS have a significantly higher chance of developing gestational diabetes, but well-designed studies need to be performed to allow any recommendations to be made to pregnant women with PCOS in regard to the risk of GDM. Since PCOS is considered as a higher risk population for developing T2DM, it has been suggested that an oral glucose tolerance test should be performed every 2 years for those with normal glucose tolerance and annually if impaired fasting glucose or IGT be present.

Several antihyperglycemic agents used in the treatment of T2DM, including biguanides, thiazolidinediones and incretin-mimetics, can reduce insulin levels in women with PCOS. These drugs may also reduce ovarian androgen production and restore normal menstrual cyclicity. However, further studies on their application to clinical practice, particularly for the thiazolidinediones and incretin-mimetics, need to be undertaken.

The risk of developing CVD and T2DM is related to insulin resistance and obesity needs to be further explored, although it is more difficult to prove a causal link between PCOS *per se* and disease events.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Lehto S, Ronnemaa T, Pyorala K, Laakso M. Cardiovascular risk factors clustering with endogenous hyperinsulinaemia predict death from coronary heart disease in patients with Type II diabetes. *Diabetologia* 43(2), 148–155 (2000).

2 Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. *Diabetes* 54(11), 3252–3257 (2005).

3 Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J. Clin. Endocrinol. Metab.* 92(2), 405–413 (2007).

4 Diamanti-Kandarakis E. Current aspects of antiandrogen therapy in women. *Curr. Pharm. Des.* 5(9), 707–723 (1999).

5 Diamanti-Kandarakis E, Bartzis MI, Zapanti ED *et al*. Polymorphism T–>C (-34 bp) of gene *CYP17* promoter in Greek patients with polycystic ovary syndrome. *Fertil. Steril.* 71(3), 431–435 (1999).

6 March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum. Reprod.* 25(2), 544–551 (2009).

7 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(8), 4650–4658 (2005).

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(1), 19–25 (2004).

9 Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory system in health and disease. *Endocr. Rev.* 20(4), 535–582 (1999).

10 Poretsky L, Bhargava G, Saketos M, Dunaif A. Regulation of human ovarian insulin receptors *in vivo*. *Metabolism* 39(2), 161–166 (1990).

11 Dunaif A, Green G, Futterweit W, Dobrjansky A. Suppression of hyperandrogenism does not improve peripheral or hepatic insulin resistance in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 70(3), 699–704 (1990).

12 Moghetti P, Tosi F, Castello R *et al*. The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. *J. Clin. Endocrinol. Metab.* 81(3), 952–960 (1996).

13 Tiitinen A, Tenhunen A, Seppala M. Ovarian electrocauterization causes LH-regulated but not insulin-regulated endocrine changes. *Clin. Endocrinol. (Oxf)* 39(2), 181–184 (1993).

14 Azziz R, Deal CL, Potter HD, Gargosky SE, Rosenfeld RG. Regulation of extragonadal insulin-like growth factor-binding protein-3 by testosterone in oophorectomized women. *J. Clin. Endocrinol. Metab.* 79(6), 1747–1751 (1994).

15 Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr. Rev.* 18(6), 774–800 (1997).

16 Isojarvi JI, Rattya J, Myllyla VV *et al*. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann. Neurol.* 43(4), 446–451 (1998).

17 Meirow D, Yossepowitch O, Rosler A *et al*. Insulin resistant and non-resistant polycystic ovary syndrome represent two clinical and endocrinological subgroups. *Hum. Reprod.* 10(8), 1951–1956 (1995).

18 Insler V, Shoham Z, Barash A *et al*. Polycystic ovaries in non-obese and obese patients: possible pathophysiological mechanism based on new interpretation of facts and findings. *Hum. Reprod.* 8(3), 379–384 (1993).

19 Meyer C, McGrath BP, Cameron J, Kotsopoulos D, Teede HJ. Vascular dysfunction and metabolic parameters in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 90(8), 4630–4635 (2005).

20 Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. *J. Clin. Endocrinol. Metab.* 90(10), 5711–5716 (2005).

21 Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 90(4), 1929–1935 (2005).

22 Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabet. Med.* 24(5), 451–463 (2007).

23 Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum. Reprod.* 16(9), 1995–1998 (2001).

24 Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. *J. Clin. Epidemiol.* 51(7), 581–586 (1998).

25 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(5), 595–600 (2000).

26 Shaw LJ, Bairey Merz CN, Azziz R *et al*. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health – National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J. Clin. Endocrinol. Metab.* 93(4), 1276–1284 (2008).

27 Bhattacharya SM. Metabolic syndrome in females with polycystic ovary syndrome and International Diabetes Federation criteria. *J. Obstet. Gynaecol. Res.* 34(1), 62–66 (2008).

28 Isomaa B, Almgren P, Tuomi T *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24(4), 683–689 (2001).

29 Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE. The metabolic syndrome in Australia: prevalence using four definitions. *Diabetes Res. Clin. Pract.* 77(3), 471–478 (2007).

30 Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 87(3), 1017–1023 (2002).

31 Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels

independent of obesity and insulin resistance. *J. Clin. Endocrinol. Metab.* 91(2), 492–497 (2006).

32 Corbould A. Insulin resistance in skeletal muscle and adipose tissue in polycystic ovary syndrome: are the molecular mechanisms distinct from Type 2 diabetes? *Panminerva Med.* 50(4), 279–294 (2008).

33 Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38(9), 1165–1174 (1989).

34 Carmina E, Lobo RA. Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome. *Fertil. Steril.* 82(3), 661–665 (2004).

35 DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. *Fertil. Steril.* 83(5), 1454–1460 (2005).

36 Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 22(1), 141–146 (1999).

37 Boudreaux MY, Talbott EO, Kip KE, Brooks MM, Witchel SF. Risk of T2DM and impaired fasting glucose among PCOS subjects: results of an 8-year follow-up. *Curr. Diab. Rep.* 6(1), 77–83 (2006).

38 Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J. Clin. Endocrinol. Metab.* 90(6), 3236–3242 (2005).

39 Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, Type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum. Reprod. Update* 16(4), 347–363 (2010).

40 Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 91(1), 48–53 (2006).

41 Talbott EO, Zborowski JV, Rager JR, Kip KE, Xu X, Orchard TJ. Polycystic ovarian syndrome (PCOS): a significant contributor to the overall burden of Type 2 diabetes in women. *J. Womens Health (Larchmt)* 16(2), 191–197 (2007).

42 Magliano DJ, Barr EL, Zimmet PZ *et al*. Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 31(2), 267–272 (2008).

43 Colditz GA, Willett WC, Stampfer MJ *et al*. Weight as a risk factor for clinical diabetes in women. *Am. J. Epidemiol.* 132(3), 501–513 (1990).

44 Goldzieher JW. Polycystic ovarian disease. *Fertil. Steril.* 35(4), 371–394 (1981).

45 Wild RA. Obesity, lipids, cardiovascular risk, and androgen excess. *Am. J. Med.* 98(1A), 27S–32S (1995).

46 Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J. Clin. Endocrinol. Metab.* 57(2), 304–310 (1983).

47 Holte J, Bergh T, Berne C, Berglund L, Lithell H. Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. *J. Clin. Endocrinol. Metab.* 78(5), 1052–1058 (1994).

48 Talbott E, Guzick D, Clerici A *et al*. Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler. Thromb. Vasc. Biol.* 15(7), 821–826 (1995).

49 Flier JS, Kahn CR, Roth J, Bar RS. Antibodies that impair insulin receptor binding in an unusual diabetic syndrome with severe insulin resistance. *Science* 190(4209), 63–65 (1975).

50 Kahn CR, Flier JS, Bar RS *et al*. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N. Engl. J. Med.* 294(14), 739–745 (1976).

51 Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. *J. Clin. Endocrinol. Metab.* 50(1), 113–116 (1980).

52 Falcone T, Finegood DT, Fantus IG, Morris D. Androgen response to endogenous insulin secretion during the frequently sampled intravenous glucose tolerance test in normal and hyperandrogenic women. *J. Clin. Endocrinol. Metab.* 71(6), 1653–1657 (1990).

53 Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for Type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J. Clin. Endocrinol. Metab.* 84(1), 165–169 (1999).

54 Ehrmann DA, Kasza K, Azziz R, Legro RS, Ghazzi MN. Effects of race and family history of Type 2 diabetes on metabolic status of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 90(1), 66–71 (2005).

55 Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS. Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* 96(1), 520–527 (1995).

56 Diamanti-Kandarakis E, Kouli C, Alexandraki K, Spina G. Failure of mathematical indices to accurately assess insulin resistance in lean, overweight, or obese women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 89(3), 1273–1276 (2004).

57 Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of Type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340(8825), 925–929 (1992).

58 Dunaif A, Finegood DT. β-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 81(3), 942–947 (1996).

59 O'Meara NM, Blackman JD, Ehrmann DA *et al*. Defects in β-cell function in functional ovarian hyperandrogenism. *J. Clin. Endocrinol. Metab.* 76(5), 1241–1247 (1993).

60 Pimenta W, Korytkowski M, Mitrakou A *et al*. Pancreatic β-cell dysfunction as the primary genetic lesion in NIDDM. Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *JAMA* 273(23), 1855–1861 (1995).

61 Solomon CG, Hu FB, Dunaif A *et al*. Long or highly irregular menstrual cycles as a marker for risk of Type 2 diabetes mellitus. *JAMA* 286(19), 2421–2426 (2001).

62 Moghetti P, Castello R, Negri C *et al*. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J. Clin. Endocrinol. Metab.* 85(1), 139–146 (2000).

63 Azziz R, Ehrmann D, Legro RS *et al*. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* 86(4), 1626–1632 (2001).

64 Jeffcoate W, Kong MF. Diabete des femmes a barbe: a classic paper reread. *Lancet* 356(9236), 1183–1185 (2000).

65 Barbieri RL. Hyperandrogenism, insulin resistance and acanthosis nigricans. 10 years of progress. *J. Reprod. Med.* 39(5), 327–336 (1994).

66 Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 88(5), 2031–2036 (2003).

67 Colilla S, Cox NJ, Ehrmann DA. Heritability of insulin secretion and insulin action in women with polycystic ovary syndrome and their first degree relatives. *J. Clin. Endocrinol. Metab.* 86(5), 2027–2031 (2001).

68 Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. *Clin. Endocrinol. (Oxford)* 51(6), 779–786 (1999).

69 Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries – a common finding in normal women. *Lancet* 1(8590), 870–872 (1988).

70 Carmina E, Wong L, Chang L *et al.* Endocrine abnormalities in ovulatory women with polycystic ovaries on ultrasound. *Hum. Reprod.* 12(5), 905–909 (1997).

71 Chang PL, Lindheim SR, Lowre C *et al.* Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary-ovarian responses to gonadotropin-releasing hormone-agonist testing. *J. Clin. Endocrinol. Metab.* 85(3), 995–1000 (2000).

72 Conn JJ, Jacobs HS, Conway GS. The prevalence of polycystic ovaries in women with Type 2 diabetes mellitus. *Clin. Endocrinol. (Oxf.)* 52(1), 81–86 (2000).

73 Kjos SL, Buchanan TA. Gestational diabetes mellitus. *N. Engl. J. Med.* 341(23), 1749–1756 (1999).

74 Kjos SL, Peters RK, Xiang A, Henry OA, Montoro M, Buchanan TA. Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. *Diabetes* 44(5), 586–591 (1995).

75 Anttila L, Karjala K, Penttila RA, Ruutiainen K, Ekblad U. Polycystic ovaries in women with gestational diabetes. *Obstet. Gynecol.* 92(1), 13–16 (1998).

76 Kousta E, Cela E, Lawrence N *et al*. The prevalence of polycystic ovaries in women with a history of gestational diabetes. *Clin. Endocrinol. (Oxf.)* 53(4), 501–507 (2000).

77 Harris MI. Gestational diabetes may represent discovery of preexisting glucose intolerance. *Diabetes Care* 11(5), 402–411 (1988).

78 Lanzone A, Caruso A, Di Simone N, De Carolis S, Fulghesu AM, Mancuso S. Polycystic ovary disease. A risk factor for gestational diabetes? *J. Reprod. Med.* 40(4), 312–316 (1995).

79 Vollenhoven B, Clark S, Kovacs G, Burger H, Healy D. Prevalence of gestational diabetes mellitus in polycystic ovarian syndrome (PCOS) patients pregnant after ovulation induction with gonadotrophins. *Aust. NZ J. Obstet. Gynaecol.* 40(1), 54–58 (2000).

80 Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum. Reprod. Update* 12(6), 673–683 (2006).

81 Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I. Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Fertil. Steril.* 92(2), 667–677 (2009).

82 Fernandez-Castaner M, Biarnes J, Camps I, Ripolles J, Gomez N, Soler J. β-cell dysfunction in first-degree relatives of patients with non-insulin-dependent diabetes mellitus. *Diabet. Med.* 13(11), 953–959 (1996).

83 Alford FP, Henriksen JE, Rantzau C *et al.* Impact of family history of diabetes on the assessment of β-cell function. *Metabolism* 47(5), 522–528 (1998).

84 Stewart MW, Humphriss DB, Berrish TS *et al*. Features of syndrome X in first-degree relatives of NIDDM patients. *Diabetes Care* 18(7), 1020–1022 (1995).

85 Wild RA, Carmina E, Diamanti KE *et al.* Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome AE-PCOS Society. *J. Clin. Endocrinol. Metab.* 95(5), 2038–2049 (2010).

86 Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33(Suppl. 1), S62–S69 (2010).

87 Lorenzo C, Wagenknecht LE, Hanley AJ, Rewers MJ, Karter AJ, Haffner SM. A1C between 5.7 and 6.4% as a marker for identifying pre-diabetes, insulin sensitivity and secretion, and cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes Care* 33(9), 2104–2109 (2010).

88 Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R. The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 81(9), 3299–3306 (1996).

89 Ehrmann DA, Schneider DJ, Sobel BE *et al.* Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 82(7), 2108–2116 (1997).

90 Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. *N. Engl. J. Med.* 340(17), 1314–1320 (1999).

91 Sepilian V, Nagamani M. Effects of rosiglitazone in obese women with polycystic ovary syndrome and severe insulin resistance. *J. Clin. Endocrinol. Metab.* 90(1), 60–65 (2005).

92 Patane G, Piro S, Rabuazzo AM, Anello M, Vigneri R, Purrello F. Metformin restores insulin secretion altered by chronic exposure to free fatty acids or high glucose: a direct metformin effect on pancreatic β-cells. *Diabetes* 49(5), 735–740 (2000).

93 Hawley SA, Gadalla AE, Olsen GS, Hardie DG. The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. *Diabetes* 51(8), 2420–2425 (2002).

94 Shaw RJ, Lamia KA, Vasquez D *et al.* The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 310(5754), 1642–1646 (2005).

95 Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst. Rev.* (3), CD003053 (2003).

96 Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. *Drugs* 62(10), 1463–1480 (2002).

97 Arlt W, Auchus RJ, Miller WL. Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450c17 and 3β-hydroxysteroid dehydrogenase. *J. Biol. Chem.* 276(20), 16767–16771 (2001).

98 Seto-Young D, Avtanski D, Strizhevsky M *et al*. Interactions among peroxisome proliferator activated receptor-γ, insulin signaling pathways, and steroidogenic acute regulatory protein in human ovarian cells. *J. Clin. Endocrinol. Metab.* 92(6), 2232–2239 (2007).

99 Brettenthaler N, De Geyter C, Huber PR, Keller U. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 89(8), 3835–3840 (2004).

100 Ortega-Gonzalez C, Luna S, Hernandez L *et al*. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 90(3), 1360–1365 (2005).

101 Brubaker PL, Anini Y. Direct and indirect mechanisms regulating secretion of glucagon-like peptide-1 and glucagon-like peptide-2. *Can. J. Physiol. Pharmacol.* 81(11), 1005–1012 (2003).

102 Drucker DJ. The biology of incretin hormones. *Cell Metab.* 3(3), 153–165 (2006).

103 Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 93(7), 2670–2678 (2008).

104 Buse JB, Rosenstock J, Sesti G *et al*. Liraglutide once a day versus exenatide twice a day for Type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 374(9683), 39–47 (2009).

105 Buchwald H, Estok R, Fahrbach K *et al*. Weight and Type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am. J. Med.* 122(3), 248–256 (2009).

106 Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J. Clin. Endocrinol. Metab.* 90(12), 6364–6369 (2005).

107 dos Reis RM, Foss MC, de Moura MD, Ferriani RA, Silva de Sa MF. Insulin secretion in obese and non-obese women with polycystic ovary syndrome and its relationship with hyperandrogenism. *Gynecol. Endocrinol.* 9, 45–50 (1995).

108 Rajkhowa M, Talbot JA, Jones PW, Clayton RN. Polymorphism of glycogen synthetase gene in polycystic ovary syndrome. *Clin. Endocrinol.* 44, 85–90 (1996).

109 Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J. Increased riskof non-insulin dependent diabetes mellitus, arterial hypertension andcoronary artery disease in perimenopausal women with a history ofthe polycystic ovary syndrome. *Hum. Reprod.* 15, 785–789 (2000).

110 Yarali H, Yildirir A, Aybar F *et al*. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. *Fertil. Steril.* 76, 511–516 (2001).

111 Sir-Petermann T, Angel B, Maliqueo M *et al*. Insulin secretion in women who have polycystic ovary syndrome and carry the Gly972Arg variant of insulin receptor substrate-1 in response to a high-glycemic or low-glycemic carbohydrate load. *Nutrition* 20, 905–910 (2004).

112 Sawathiparnich P, Weerakulwattana L, Santiprabhob J, Likitmaskul S. Obese adolescent girls with polycystic ovary syndrome (PCOS) have more severe insulin resistance measured by HOMA-IR score than obese girls without PCOS. *J. Med. Assoc. Thai.* 88(Suppl. 8), S33–S37 (2005).

113 Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 91, 1357–1363 (2006).

114 Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Arch. Intern. Med.* 166, 2081–2086 (2006).

115 Leibel NI, Baumann EE, Kocherginsky M, Rosenfield RL. Relationship of adolescent polycystic ovary syndrome to parental metabolic syndrome. *J. Clin. Endocrinol. Metab.* 91, 1275–1283 (2006).

116 Marquez JL, Pacheco A, Valdes P, Salazar LA. Association between CAPN10 UCSNP-43 gene polymorphism and polycystic ovary syndrome in Chilean women. *Clin. Chim. Acta. Int. J. Clin. Chem.* 398, 5–9 (2008).

117 Shaw LJ, Bairey Merz CN *et al*. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J. Clin. Endocrinol. Metab.* 93, 1276–1284 (2008).

118 Bhattacharya SM. Polycystic ovary syndrome and abnormalities in glucose tolerance. *Int. J. Gynecol. Obstet.* 105, 29–31 (2009).

119 Moini A, Eslami B. Familial associations between polycystic ovarian syndrome and common diseases. *J. Assist. Reprod. Genet.* 26, 123–127 (2009).

120 Rajkhowa M, Talbot JA, Jones PW, Clayton RN. Polymorphism of glycogen synthetase gene in polycystic ovary syndrome. *Clin. Endocrinol.* 44, 85–90 (1996).