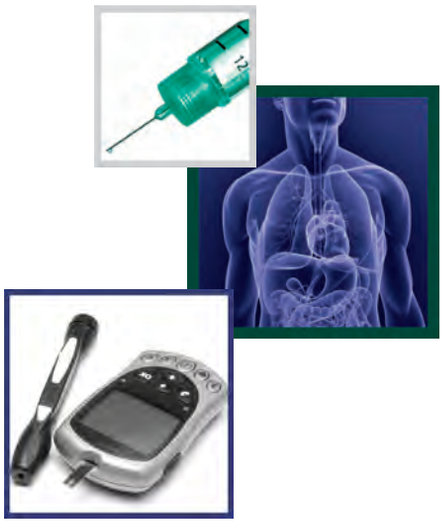
REVIEW

Diabetes advice for women with polycystic ovary syndrome: prevention, prevention, prevention



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Practice Points

- Polycystic ovary syndrome (PCOS) is very common and patients are relatively young at their presentation to the healthcare system.
- There is an increased lifetime risk for Type 2 diabetes mellitus in women with PCOS starting from adolescence to the postmenopausal period. Up to 40% of these women develop either impaired glucose tolerance or Type 2 diabetes mellitus by their fourth decade.
- Considering their generally young age at presentation and high risk status, screening for metabolic complications of PCOS, including diabetes, should form part of the routine work-up for these patients in the healthcare system.
- The best screening test for diabetes in this population is a glucose tolerance test.
- Patients who are found to have abnormal glycemic control or have more than two other risk factors for diabetes (e.g., obesity as defined by ethnicity, waist circumference >80 cm, family history of diabetes in first-degree relatives, personal history of gestational diabetes, sedentary lifestyle, age older than 40 years in white individuals and more than 25 years in other ethnicities, south Asian ethnicity, anovulatory–hyperandrogenic phenotype and acanthosis nigricans) need structured education and lifestyle interventions.
- Those considered at high risk should be reviewed annually and pharmacological interventions should be considered if there is no improvement in risk status after lifestyle intervention.

SUMMARY Polycystic ovary syndrome is the most common endocrine condition in reproductive-age women and is associated with a high risk of long-term metabolic conditions such as diabetes and cardiovascular disease. These patients present at a young age to the healthcare system with a variety of symptoms other than these metabolic conditions and, therefore, it should be embedded in our practice to monitor and prevent these complications. In this article, we review the association of polycystic ovary syndrome with Type 2 diabetes mellitus, identify the high-risk population and recommended interventions to reduce the risk of developing Type 2 diabetes mellitus in this patient group.

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Future Medicine part of fsg

Polycystic ovary syndrome (PCOS) is the most common endocrine problem in women of reproductive age. Over the years, the diagnosis of PCOS has been subject to much debate before we eventually settled on the presence of two out of three major criteria: hyperandrogenism, anovulation and polycystic ovaries [1,2,201]. The importance of PCOS lies in its multidimensional presentation; body image issues such as hirsutism and acne, as well as infertility or anovulatory problems bring these women into contact with the healthcare system [1,2]. These patients are often young [1–3] and emotionally distressed by their condition [4]. Although all these presenting symptoms are important and need addressing, the diagnosis of PCOS has a much bigger and longer lasting impact on a woman's life; higher risk of impaired glucose tolerance (IGT; defined as blood glucose ≥7.8 mmol/l or 140 mg/dl, and <11.1 mmol/l or 200 mg/dl 2 h after 75 g of glucose challenge), Type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, fatty liver disease, hypertension, dyslipidemia, cardiovascular diseases, sleep apnea, gestational problems and depression [1–12,201]. These metabolic complications and the long-term health risks attached to them need to be monitored and treated in these patients in addition to their presenting problems. A cost analysis in the USA reported that approximately 40% of the associated cost of PCOS could be related to T2DM [13] and this is still regarded as an underestimation of the cost [201]. The long-term risks associated with IGT and T2DM, as well as the healthcare cost for these conditions and their complications, make a compelling case to argue for screening and prevention of diabetes in high-risk populations [14–16,202] and there is no doubt that PCOS patients are at a high risk of T2DM [1,7,9,10,16,17,201]. All the associated metabolic complications of PCOS are important and need monitoring. In this article we review the evidence of the association of PCOS with T2DM and IGT, and put forward our recommendation for approaching these complications.

PCOS & diabetes

■ Epidemiological data

The prevalence of IGT and T2DM in women with PCOS has been reported to be as high as 35 and 10%, respectively [1,10,18–21]. In other studies, the age-specific prevalence of T2DM has been shown to be even higher than this: 11.1% in 45–54 year olds; 15.7% in 55–64 year olds; and 45.5% in those over 65 years old [3]. Compared with the control group or general female population, the overall prevalence of diabetes has been reported to be 2–3-times higher in women with PCOS [3,7,10,22,23]. In a multi-ethnic population, prevalence of T2DM in women with PCOS aged 15–44 years was sixfold higher than the age-matched general female population [3]. A recent meta-analysis of epidemiological studies reported that women with PCOS had an increased prevalence of IGT (odds ratio: 2.48; 95% CI: 1.63–3.77) and T2DM (odds ratio: 4.43; 95% CI: 4.06–4.82) even when they were matched for BMI [7]. The increased risk of diabetes has been shown in postmenopausal women with PCOS [3,24–26] as well as adolescents [27,28]. Women with PCOS have a much higher chance of gestational diabetes as well as other gestational complications associated with insulin resistance such as spontaneous abortion [1,9,10,29,30], and they carry a higher risk of abnormal glucose metabolism after the pregnancy and gestational diabetes [31]. In other words, there is a lifetime high risk of T2DM in women with PCOS from adolescence to the post-menopausal period.

There have been some attempts to calculate the conversion rate from normal to IGT or to T2DM in this patient population. One study reported a 24.1% conversion rate from normal to abnormal glucose tolerance during the 3-year follow-up and annual conversion rates to IGT and T2DM of 6.8 and 2.0%, respectively [32]. It is worth noting that 54% of the population in this study were on insulin sensitizers [32]. Legro *et al.* reported the same annual conversion from IGT to T2DM (2%), while the annual conversion from normal glucose tolerance to IGT was much higher at 16% [33]. Another study reported a 54% conversion rate from IGT to T2DM in a 6.2-year follow-up and 16.6% conversion from normal glucose tolerance to IGT or T2DM in the same period [34]. Ehrmann *et al.* reported 55% conversion from normal glucose tolerance to either IGT or T2DM in a 2.4-year follow-up, and 29% conversion from IGT to T2DM in the same period [20]. In a case–control study, 21.4% of the patients with PCOS developed IGT or T2DM in the 13-year follow-up as compared with 4.5% of the control group, which is almost six-times higher [35]. However, most of these studies either have a short follow-up and/or include a very small

number of women with PCOS (the maximum number was 122) and, therefore, more studies are needed [7]. Evidence from a screening study in the general population shows a conversion rate of 17.0 and 11.8 per 100 person years, respectively, for IGT and impaired fasting glucose (IFG; >6.1 mmol/l or 110 mg/dl and <7 mmol/l or 140 mg/dl) [36]. In a multi-ethnic population, 4.7% of those with normal glucose tolerance developed T2DM after 5 years, while 20.8% of those with IGT and 21.6% of those with IFG in the same period developed T2DM [37]. A meta-analysis of prospective cohort studies reported that, compared with the normoglycemic people, those with IGT had a relative risk of 6.35 (95% CI: 4.87–7.82) for conversion to T2DM [38]. This is not very different from what we have seen in the studies of women with PCOS.

We emphasize the need for long-term high-quality follow-up studies in women with PCOS to calculate their conversion rates to T2DM. However, considering the available data, we can possibly predict high conversion rates in women with PCOS similar to those with IGT in the general population. This conclusion is based on the high rates of underlying insulin resistance and high prevalence of diabetes in women with PCOS.

■ Pathophysiological connection

The specific pathology underlying PCOS remains uncertain. It has a multifactorial and heterogeneous pathophysiology with possible genetic and environmental elements [1,10,39,201]. Although in most cases the diagnosis of PCOS is made after menarche, the origins are believed to have started in childhood or even fetal life [10,17,39–41]. The evidence of familial clustering of the syndrome [39,42,43], as well as the genetic associations [10,39,44], indicate that some women have a predisposition for PCOS. Higher levels of estrogen, sex hormone steroids, androgens and insulin are reported in PCOS, as well as involvement of one or more endocrine glands such as the pituitary, ovaries and adrenals [1,2]. Nevertheless, it seems that epigenetic and environmental factors in the form of hyperandrogenism and insulin resistance play a significant role [10,17,39].

The association between hyperandrogenism and disordered carbohydrate metabolism was initially described in 1921 as 'the diabetes of bearded women' ('diabète des femmes à barbe') or Achard–Thiers syndrome [10,45]. A few decades later, Berghen *et al.* showed that women with PCOS have associated hyperinsulinemia independent of their BMI [46]. Further studies have confirmed the presence of insulin resistance independent of BMI, age or ethnicity in PCOS [10,17,21,39,47–49].

It is clear that insulin resistance plays a major pathologic role in PCOS and explains the multiorgan involvement [9,17,201]. However, it seems that some of the phenotypes are more strongly associated with insulin resistance and, consequently, abnormal metabolic profile. Classically, anovulatory–hyperandrogenic women with PCOS, as described by the National Institute of Child Health and Human Development 1990 criteria [50], are much more likely to show evidence of insulin resistance [10,51,52]. The ovulatory Rotterdam phenotype with hyperandrogenism and polycystic ovaries [53] is not associated with insulin resistance [10,51,52]. Conditions that lead to increased insulin resistance such as obesity may convert these metabolically benign phenotypes into classic anovulatory PCOS [6,10]. Obesity appears to add to the intrinsic insulin resistance in women with PCOS and co-occurrence of obesity and PCOS increases the metabolic complications of PCOS as well as accentuating the signs and symptoms [1,10]. It seems that it is the adipocyte size and BMI rather than the body fat distribution that are associated with insulin resistance in PCOS [54,55]. Insulin stimulates androgen production [56,57] and reduces the hepatic production of sex hormone-binding globulin [58,59] and, therefore, hyperinsulinemia resulting from insulin resistance contributes to the development of signs and symptoms of PCOS. Consequently, there is a cyclic interaction between insulin resistance, hyperandrogenism and anovulation; each contributing to the progress of the condition. In addition, the intrinsic contribution of PCOS to insulin resistance, independent of the underlying BMI, should not be ignored as shown in multiple studies [10,17,49]. It appears that resistance to the peripheral uptake of glucose is a dominant mechanism of insulin resistance in PCOS [10,17,60,61] with a subreceptor defect [10,17] that is slightly different in nature to other insulin resistance states such as obesity and T2DM [10,17]. Some degrees of β-cell dysfunction have also been reported in the spectrum of disease [10,17,62–64]. However, glucose levels may remain normal in some of these patients as a result of

the compensatory hyperinsulinemia secondary to increased β-cell function [17]. Dominant peripheral insulin resistance explains why women with PCOS tend to demonstrate a normal FBG and abnormal postprandial glucose levels [18,19,65,66].

Diabetes & PCOS in clinical practice

Prevention is the best approach to conditions such as diabetes that have expensive, debilitating and sometimes devastating long-term complications [67,202]. Type 2 diabetes is a highly preventable disease and fulfils most of Wilson's criteria as a suitable disease for screening [68]. Identification of the at-risk population with the subsequent introduction of a lifestyle intervention is the most cost-effective approach [69,70,202]. Screening the high-risk population for T2DM has been suggested previously [14,16,202], and considering that PCOS is a high-risk condition for the development of T2DM, these patients might benefit from regular screening for diabetes and lifestyle interventions.

■ Screening

Predictive risk factors

Multiple risk factors have been described for the development of diabetes in the PCOS population. Family history of diabetes [19,21,71], body weight [3,6,71,72], age [3,18,19,72], ethnicity [3,21], waist circumference [19] and hypertension [3] have been associated with risk of diabetes in women with PCOS. Acanthosis nigricans has also been described as an independent predictor of an abnormal glucose tolerance test and metabolic syndrome in Caucasians and south Asian women with PCOS [47,73]. Evidence of hyperandrogenism is the strongest recognized sign and symptom in PCOS that is most closely associated with a high risk of diabetes and insulin resistance, especially when combined with oligomenorrhea [1,10,51]. Some biomarkers have also been recommended as predictors of IGT/T2DM in women with PCOS, including higher levels of glucose, or reduced levels of valine, high-density lipoprotein or alanine [74,75].

A diabetes risk score that was tested in this population showed that women with PCOS, irrespective of their age and BMI, had a higher risk of diabetes compared with the control group [76]. Larger follow-up studies are needed to understand the causative mechanism of these potential risk factors and also to determine an accurate risk score for diabetes in these women.

Blood test for the identification of the at-risk population & those with diabetes

There are broadly three options for a blood test: fasting blood glucose (FBG), HbA1c and oral glucose tolerance test (OGTT). However, the choice of blood test to monitor PCOS patients needs further research.

It has been established in multiple studies that FBG is not a good indicator of insulin resistance in these women [10,17,65,77] and normal levels of FBG do not exclude those women with PCOS who have IGT and T2DM [18,19,78]. Chronic hyperinsulinemia may contribute to the normalization of the FBG. In one study, over 50% of the patients with diabetes could not be diagnosed by using FBG alone [19]. One recent study has used this test as an initial step to identify those with IFG and T2DM [79]. However, by using FBG, there is a chance that we miss a large portion of those women at risk of diabetes who have IGT.

The use of HbA1c in screening for diabetes has been discussed extensively. Recent guidelines and expert statements recommend the use of HbA1c to screen for T2DM in the general public [80–82,203]. They recommend the cut-off point of HbA1c ≥6.5% (48 mmol/mol) for the diagnosis of diabetes (emphasizing that a second test is necessary in asymptomatic patients) [80–82,203]; however, there is no agreement on the issue of the use of HbA1c for the diagnosis of the population at risk of diabetes. International expert committees recommend that the HbA1c ranges from 6.0 to 6.4% (42–47 mmol/mol) to identify those at high risk [81,82], while the American Diabetes Association (ADA) lowers the HbA1c level to 5.7% (39 mmol/mol) [80].

The evidence for the use of HbA1c in the screening and diagnosis of T2DM and risk of diabetes in women with PCOS is scarce, and the few studies that are emerging have shown inconclusive results. In one study [83] in women with PCOS (n = 111), using the ADA classification for diagnosis of diabetes and those at risk of diabetes, HbA1c classified 44% of the subjects as normal when they had a high-risk status according to OGTT and evidence of insulin resistance using the homeostasis model assessment (HOMA) [80]. In the same study, 24% of subjects were classified as high risk according to their HbA1c while their OGTT was normal and HOMA indicative of insulin resistance [83]. Another study in a larger population (208 women with PCOS) reported a

sensitivity of 35% and specificity of 99% for the cut-off point of HbA1c ≥6.5% (48 mmol/mol) for diagnosis of T2DM when compared with OGTT [84]. A much larger study [85] (n = 671), again using the ADA cut-off points for HbA1c in the diagnosis of the high-risk population, reported a sensitivity of 25% and specificity of 100% for the identification of those women with IFG and IGT. The sensitivity for the diagnosis of T2DM using HbA1c was 66.7% with 100% specificity [85]. Another study in Turkey (252 PCOS and 117 controls) confirmed these finding, showing a 52.4% sensitivity and 74.4% specificity for a HbA1c of >5.6% (39 mmol/mol) as a cut-off point for diagnosing the high-risk population [86]. Interestingly, in this study, using OGTT detected 14.3% of women with PCOS and 8.5% of the control group as IGT, while HbA1c categorized 7.9% of PCOS women and 8.5% of the control group as high risk [86]. These discrepancies in identifying patients with T2DM and those at risk of diabetes using HBA1c or OGTT are not unique to PCOS and have been shown in the general population in diabetes screening studies [87]. There is also evidence in the general population of the independent effect of ethnicity on glycemic indices and HbA1c cut-off points for diagnosing T2DM and the at-risk population [88]. These effects are yet to be investigated further in the PCOS population.

Obviously, while there is a need for further data to support a scientific decision about the use of HbA1c in screening for diabetes and a high risk of diabetes in women with PCOS, current data show a very low sensitivity, especially in the search for those who are at high risk of diabetes (those with IFG and IGT).

Considering the inaccuracies associated with the use of FBG and HbA1c in a population such as women with PCOS who have a very high risk of developing T2DM, OGTT remains the best choice to maximize identification of patients with T2DM and those at high risk for diabetes. However, arguably, the one limitation of OGTT (the time and the labor needed to perform the test), which has been highlighted repeatedly in the past [81,82,89,90], may be more applicable in the case of PCOS, which is a common condition and patients present at a very young age. A stepwise approach and the use of risk scores in screening for diabetes have been recommended in the general population [202]. Stepwise screening has also been used in PCOS by using insulin level, free androgen index, low levels of sex hormone-binding globulin [75,78], FBG [32,79] and/or diabetes risk scores [76] as the initial step. However, each of these initial steps has its own limitation; measuring insulin levels is not practical in routine clinical practice and impossible in the community set up, and the accuracy of FBG levels in women with PCOS has long been debated.

Numerous international organizations have made recommendations for the screening for T2DM and a high risk of diabetes in women with PCOS **(Table 1)** [1,18,91–95]. OGTT is the most recommended test of the three guidelines that have been published after the initial proposal of the use of HbA1c to screen diabetes [1,94,95]. These guidelines acknowledge the need for further evidence for the use of HbA1c in women with PCOS. One important item in common between all of these recommendations and those from the experts in the field of diabetes [14,16,80,81,202] is the need to identify the high-risk population and prevent the development of diabetes.

In summary, there is a need for further large population-based studies in women with PCOS to make better and pragmatic recommendations to identify those who would benefit from a blood test to screen for diabetes. Until then, and while waiting for further clarification on the use of HbA1c in diagnosing diabetes and a high risk of diabetes in women with PCOS, OGTT remains the best option.

■ Interventions

Identification of the high-risk population is justified if there is an intervention available to reduce the incidence and, consequently, the cost of the diseases and related complications. In other words, prevention needs to be cost effective to be able to justify the implementation of a screening program [96].

There has been no cost–effectiveness analysis specific to PCOS and diabetes, but there is good evidence from modeling studies in diabetes to show that identification of the high-risk population followed by an intervention is cost effective [97]. Interestingly, lifestyle interventions are likely to be more cost effective than pharmacological interventions in the prevention of future diabetes [97,202]. Lifestyle interventions in high-risk populations have been successful [98–103] and have shown their legacy effect long after the active trial is stopped [67,104,105].

Table 1. Recommendations by international organizations for the evaluation of glycemic status in women with polycystic ovary syndrome.

Organization	Publication year	Recommended test	Frequency	Additional risk factors identified[†]	Ref.
American Association of Clinical Endocrinologists	2005	Measurement of glucose (and possibly insulin) levels. OGTT may be considered, particularly in obese women and those with a family history of T2DM	Not specified	Not specified except for the metabolic syndrome as a general risk for diabetes and cardiovascular diseases	[91]
Royal College of Obstetrics and Gynaecology	2007	Fasting (if any of the additional risk factors then OGTT)	Annually	Fasting blood glucose is ≥5.6 mmol/l, BMI >30 or a strong family history of diabetes	[93]
Androgen Excess and PCOS Society	2007/2010	OGTT	Every 2 years Annually if IGT or risk factors	Advanced age (>40 years), family history of T2DM, personal history of GDM, BMI >30	[18,94]
American College of Obstetricians and Gynecologists	2009	OGTT	Not specified	Age, high BMI, high waist:hip ratio, family history of diabetes	[92]
Australian PCOS Society	2011	OGTT	Every second year in all women. Annually in those with an additional risk factor	Age, ethnicity, family history, history of hypertension, use of antihypertensive drugs, smoking, physical inactivity, waist circumference	[95]
European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine	2012	OGTT	Not specified	Screening should be performed in the following conditions: hyperandrogenism with anovulation; acanthosis nigricans; obesity (BMI >30 or >25 in Asian populations); women with a family history of T2DM or GDM	[1]

[†]Additional to PCOS itself.
GDM: Gestational diabetes mellitus; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test; PCOS: Polycystic ovary syndrome; T2DM: Type 2 diabetes mellitus.

Lifestyle interventions in PCOS

A systematic review of randomized lifestyle interventions in PCOS [106] has shown that they can be beneficial in reducing; weight (mean difference [MD]: -3.47 kg; 95% CI: -4.94 to -2.00; $p < 0.00001$), waist circumference (MD: -1.95 cm; 95% CI: -3.34 to -0.57; $p = 0.006$) and fasting insulin levels (MD: -2.02 μU/ml; 95% CI: -3.28 to -0.77; $p = 0.002$). These studies were either supervised physical activity or mixed activity and diet interventions and only included a small number of patients (164 patients in the systematic review) [106].

A recent systematic review of dietary interventions in PCOS did not recommend any specific diet and only emphasized the beneficial effects of weight loss [107]. Exercise has been beneficial in women with PCOS in improving insulin resistance, weight, waist circumference and reproductive outcomes [108,109], and the effects are independent of the type, frequency and length of the exercise session [108]. In a small group of women with PCOS (n = 12), an increase in walking activity reduced fasting insulin and lipids without any change in BMI [110]. There is no age limitation on the beneficial effects of these lifestyle interventions; however, there are limited studies on adolescents and post-menopause in women with PCOS [1,111].

With few randomized controlled trials, and most consisting of a small number of patients, there is a need for further evidence. However, the limited available evidence indicates the beneficial effects of the intervention on indices of insulin resistance.

■ Pharmacological

There are no large-scale randomized controlled trials to compare the effects of lifestyle and pharmacological interventions to prevent diabetes in women with PCOS at a high risk of diabetes. A meta-analysis of these types of interventions in the general population at risk of diabetes showed that lifestyle intervention was more effective in prevention of diabetes [98]; however, we cannot directly extrapolate these results to the women with PCOS and similar modeling studies are needed in this population. In women with PCOS, a combination of the lifestyle interventions and metformin has had more impact on the weight and insulin indices compared with lifestyle alone or placebo [112,113].

Insulin sensitizers and metformin, in particular, have been successful in improving

insulin resistance in women with PCOS [114]. There is a reported reversion of 55% from IGT to normal glucose tolerance over the 43-month study period [115]. A meta-analysis of randomized controlled trials of the effects of metformin in women with PCOS and at high risk of diabetes showed improvements in FBG, insulin and HOMA, as well as a reduction in the incidence of diabetes [116]. The use of metformin for prevention of diabetes has been recommended in multiple expert statements [1,94,95], but always with an added caution that there is a need for further studies.

Thiazolidinediones are another class of insulin sensitizers and have been effective in ameliorating hyperinsulinemia and lowering FBG in women with PCOS [117]. Pioglitazone is superior to metformin in these effects [118]; however, by increasing weight, thiazolidinediones have fewer beneficial effects on body weight and BMI compared with placebo [117] and metformin [118,119]. In a large population of people at high risk of diabetes, rosiglitazone was demonstrated to be very effective in inducing regression to normoglycemia [120]. Unfortunately, associated complications such as liver failure with troglitazone or cardiovascular problems with rosiglitazone resulted in their withdrawal from the market. Pioglitazone also causes complications and recent reports about the increased risk of bladder cancer following its long-term use have resulted in concerns [121]. There are also doubts about the safety of thiazolidinediones in pregnancy (see British National Formulary) and, therefore, it is recommended that they were used with contraceptives in reproductive-age women if needed.

Incretin-based therapies in the form of tablets (DPP-4 inhibitors) or injection (GLP-1 agonists) are new classes of medication with promising outcomes in patients with T2DM particularly regarding weight profile and glycemic control. Studies of incretin-based therapies in women with PCOS are limited; in a three-arm randomized controlled study, the combination of exenatide and metformin proved superior to either therapy alone for weight loss and body fat composition [122]. A recent study presented the same results for a combination of liraglutide and metformin [123]. There are ongoing studies of these medications in people without diabetes that will hopefully help us to better understand their effects independently of diabetes, and these drugs may find their ways into the treatment options for PCOS.

Further studies are needed for all groups of medications, and a comparison with lifestyle intervention would allow direct comparisons of their effects.

Recommendations

We acknowledge that there is a lack of convincing evidence, such as from well-performed prospective randomized controlled trials, to make conclusive recommendations for screening and prevention of diabetes in women with PCOS. There is a need to conduct long-term and prospective studies to investigate the risk factors associated with a higher chance of diabetes in this patient population. There is also a need for pragmatic and cost-effective lifestyle interventions to be implemented in the system for those identified as high-risk patients. Having acknowledged these gaps we can take a lead from studies in the general population and take into account that PCOS is a well-established risk factor for T2DM, there is a very high prevalence of IGT in women with PCOS, there is a possible high conversion rate to T2DM in this patient population and there is some evidence that lifestyle interventions are helpful in women with PCOS.

Considering the previous guidelines published for the women with PCOS **(Table 1)** and recommendations for identification of the high-risk population followed by preventive measures [202], we recommend that **(Figure 1)**:

- OGTT stays the gold-standard test for evaluation of glucose metabolism in women with PCOS until we have conclusive evidence for the use of HbA1c in this population. More studies need to look into the use of HbA1c tests in this population;

- Known risk factors in the general population associated with increased risk of diabetes are obesity (BMI ≥30 in white and ≥27.5 in south Asians and black and minor ethnicities) [204], waist circumference >80 cm, a first-degree relative with a history of T2DM, personal history of gestational diabetes, age >40 years in white and >25 years in south Asians and other minor ethnicities, some of the ethnic origins (e.g., south Asians, African–Caribbean and black African descent), hypertension defined as blood pressure >140/90 mmHg, and a

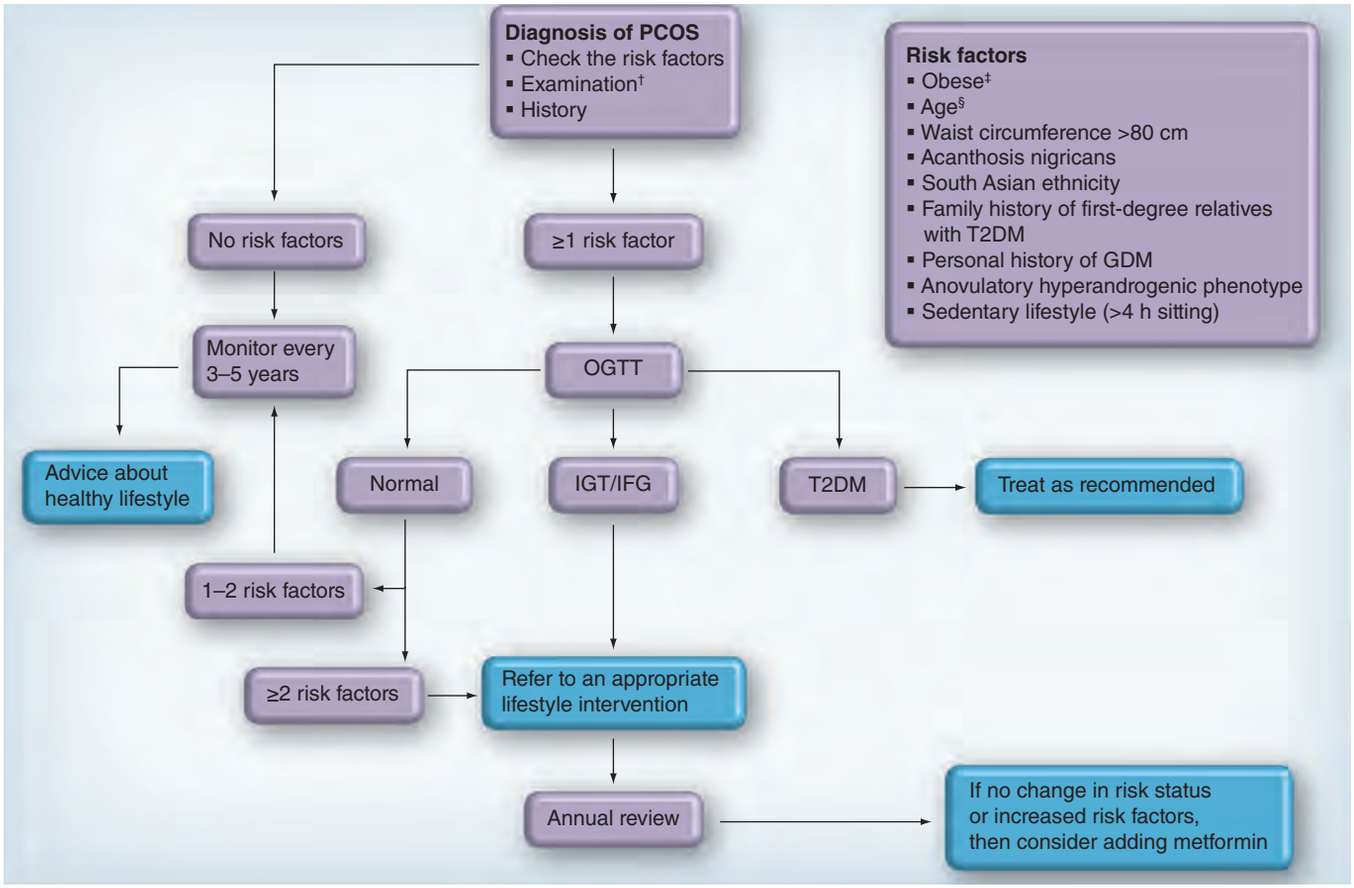

Figure 1. Pathway for screening and intervention for Type 2 diabetes mellitus in women with polycystic ovary syndrome.

†Plus any other necessary blood test as needed for diagnosis.

‡Ethnic definition (white: normal BMI: <25, overweight: 25 to <30 and obese: ≥30; black, South African and minor ethnicities: normal BMI: <23, overweight: 23 to <27.5 and obese: ≥27.5).

§>40 years for white and >25 years in south Asians and other ethnicities.

GDM: Gestational diabetes mellitus; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test; PCOS: Polycystic ovary syndrome; T2DM: Type 2 diabetes mellitus.

sedentary lifestyle [202,205]. Evidence of an association between a sedentary lifestyle and increased risk of diabetes comes from observational studies and is summarized in a meta-analysis showing that increased diabetes risk correlates with longer sitting times [124]. It is difficult to define the exact duration of sedentary time that increases the risk of diabetes; however, there are some studies that have suggested 2 or 4 h of television watching time increases the rates of diabetes compared with 1 h of watching television [125,126]. Acanthosis nigricans and the classic oligomenorrhic-hyperandrogenic phenotype can be added to the list for the women with PCOS [1,10,47,51,73,127]. Considering the current lack of definitive evidence for a specific risk score for this population and bearing in mind their high risk of diabetes as discussed before, we can use the available risk scores from the general population as well as specific known risk factors such as the classic phenotype to identify those who would benefit from a definitive blood test;

- Every woman with PCOS needs an assessment for the risk of diabetes at the time of diagnosis. This will help with the planning of further action if necessary. Those without any extra risk factors need a reassessment every 3–5 years. The presence of any risk factor from the above list is an indication for

further assessment with an OGTT **(Figure 1)**. Those identified as being at high risk of diabetes (as determined by IGT and IFG) as well as those who have more than two additional risk factors (more than three risk factors for T2DM including PCOS status) will benefit from an available, quality-assured intensive lifestyle intervention, as recommended for high-risk individuals in the general population [202]. In the absence of an established program tailored for PCOS, these patients might benefit from referral to other available diabetes prevention programs [128]. If there is no benefit from lifestyle intervention in the annual review, pharmacological interventions should be considered.

Identification of the 'high-risk' population is the most important initial step in the prevention of T2DM and should be followed by an intervention to modify the risks. Most of the modeling and intervention studies for the prevention of diabetes have been based on an initial risk score assessment using one of the variety of available risk scores as summarized in the National Institute for Health and Care Excellence (NICE) guidelines [202]. These risk scores generally use weighted risk factors associated with diabetes, and, therefore, some of the risk factors have a higher impact on the diagnosis of diabetes [129]. Every individual can be assessed according to the combination of risk factors that they have and those with the highest score will be identified as high risk [130]. There is a lack of risk assessment studies in women with PCOS and, therefore, we can either do nothing and just wait for evidence before making a decision, or we can cautiously extrapolate from the available data to reduce the long-term risk of diabetes in this high-risk and young patient group while waiting for the emergence of the evidence. In the case of women with PCOS and considering the lack of any risk score, each risk factor is treated equally in its effect on the outcome of diabetes. The recommendations for PCOS patients have been adapted from recent UK guidelines [202].

Conclusion & future perspective

Risk prediction and prevention are the future of medicine [131]. There is an emerging epidemic of young patients with T2DM [132] who have shown an early onset of diabetes and high rates of complications [133–135]. This underlines the need to introduce lifestyle interventions to the younger 'at-risk' population. Women with PCOS are a recognized high-risk group who are typically young and have their life in front of them. They would benefit from an early intervention to reduce their risk for the development of T2DM. There is a paucity of evidence for intervention specific to this group, but that should not put us off from extrapolating from the available evidence to plan for future risk reduction in this patient group. There is a need for epidemiologic studies in women with PCOS as well as tailored structured education programs to address their cardiovascular risks.

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