

# Defining prediabetes in polycystic ovarian syndrome

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## ABSTRACT

**Objective:** The article will review the associations between Prediabetes (PD) and Polycystic Ovarian Syndrome (PCOS) and present factors that decrease the progression of PD into type 2 diabetes mellitus (T2DM). Metformin will also be examined for its role in ovulation induction, pregnancy and ameliorating the metabolic syndrome. **Study Design:** Medline search. **Methods of study:** Keyword search: Prediabetes (PD), Polycystic Ovarian Syndrome (PCOS), Metformin, Glucose Tolerance Test (GTT), Type 2 Diabetes Mellitus. **Results:** As the most common endocrinopathy during the reproductive years, PCOS has a genetic multifactorial inheritance and is associated with a high risk of insulin resistance. The use of metformin has shown mixed results in this patient population as a therapy to improve ovulation function and the metabolic syndrome and showed no definitive reduction in the rate of miscarriage. PCOS patients are significantly predisposed to PD and T2DM. **Conclusion:** Lifestyle changes such as weight loss and physical activity reduce the progression of PD into T2DM in PCOS patients. The new AACE and ADA guidelines establish simplified methods of screening and treating PD. The role of metformin remains undefined in the infertile PCOS patient.

**Keywords:** Polycystic Ovarian Syndrome; Prediabetes; Impaired Glucose Tolerance; Impaired Fasting Glucose; Type 2 Diabetes

## 1. INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most prevalent endocrinopathy during the reproductive years, affecting 5% - 10% of women [1]. PCOS is classically associated with ovulatory dysfunction and hyperandrogenism. In 2003, an expert conference was organized in Rotterdam in May of 2003, co-sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive

Medicine (ASRM) resulting in revised criteria for making the diagnosis of PCOS using two of the following three features: 1) oligo- or anovulation (*i.e.* cycle interval >35 d or <8 cycles/yr); 2) clinical or biochemical signs of hyperandrogenism (*i.e.*, demonstrated by elevated total or free testosterone, DHEAS, free androgen index [2] or signs of hirsutism or acne); 3) ultrasound evidence of polycystic ovaries (12 or more follicles in each ovary (2 mm - 9 mm), and/or increased ovarian volume (>10 mL)—all at the exclusion of other etiologies (hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors, non-classic adrenal hyperplasia) [3,4]. Despite its prevalence, PCOS remains an enigma resulting in significant patient frustration and physician confusion for the most appropriate method of diagnosis and management.

In addition to the reproductive health issues of abnormal uterine bleeding, anovulation, infertility, and endometrial hyperplasia, PCOS patients are at higher prevalence for the metabolic syndrome, namely abdominal obesity, dyslipidemia, hypertension, and prediabetes (PD). The National Cholesterol Education Program Adult Treatment Panel (NCEPATP) defined the metabolic syndrome as the presence of three of the five following factors: waist circumference greater than 88 cm in females; fasting serum glucose 110 mg/dl or more; fasting serum triglycerides greater than 150 mg/dl; serum HDL-cholesterol less than 50 mg/dl; and blood pressure greater than 130/85 mm Hg [5]. The metabolic syndrome occurs at an increased overall prevalence rate of 43% - 47% in women with PCOS [6]. One of metformin's actions is 5-AMP-activated protein kinase (AMPK) pathway. While obesity, type 2 diabetes mellitus (T2DM), and the metabolic syndrome are all disorders of energy balance and AMPK appears to regulate this system, perhaps the role of metformin in improving the metabolic syndrome is through this mechanism [7]. To date, there is no definitive evidence demonstrating the benefit of metformin in PCOS patients as a treatment or prevention for metabolic. As a result, lifestyle modifications remain the mainstay for patients with the metabolic syndrome.

While all medical issues should be addressed in PCOS patients, particularly those trying to conceive, PD can be elusive and requires vigilance with formal testing. Furthermore, there is an indolent but clear progression of PD to T2DM unless intervention is applied early. This article will serve to elucidate the morbid association of PCOS with PD by examining the insulin resistance connection, and presenting new guidelines from the American Association of Clinical Endocrinologists and American Diabetes Association to simplify methods of diagnosing and treating PD as well as to decrease the progression into T2DM.

## 2. REPRODUCTIVE CONSEQUENCES

Approximately 40% of female infertility is attributed to ovulation dysfunction of which PCOS is the prevailing diagnosis. Multiple regimens (beyond the scope of this article) have been presented for ovulation induction particularly in PCOS patients resistant to clomiphene citrate, including the addition of metformin (see below), yet this latter agent has not been shown to be as effective as clomiphene. The second ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group in 2007 concluded clomiphene citrate is the first line agent for ovulation induction followed by gonadotropins or laparoscopy ovarian diathermy [8]. The expert panel concluded metformin should be limited to PCOS patients with glucose intolerance as current evidence does not support the routine use of metformin in ovulation induction. Metformin appears to be superior to placebo regarding ovulation induction for PCOS patients [9]. Controversy remains when metformin is compared with clomiphene. A recent meta analysis and clinical trial demonstrates improvement in ovulation with metformin [10,11] contrary to a Cochrane Review stating limited improvement of metformin vs. clomiphene [12] and an excellent randomized control trial showing superiority of clomiphene over metformin [13]. It is plausible the disparity in results from these studies may be attributed to patient heterogeneity, *i.e.* BMI, genotype, androgen levels, ethnicity, and racial differences [14].

Aromatase inhibitors such as letrozole and anastrozole have been studied as alternatives to clomiphene. A recent meta-analysis to compare clinical efficacy and safety showed no difference between letrozole and clomiphene regarding miscarriage, pregnancy rates and multiple pregnancy rates and concluded equal effectiveness of the two drugs for ovulation induction in PCOS patients [15]. Anastrozole is inferior to clomiphene and should not be used as a first line for ovulation induction [16]. Both letrozole and anastrozole use for ovulation induction are non-FDA approved applications. Furthermore, weight loss has demonstrated the same efficacy in inducing

ovulation as metformin [17]. Though a patient should strive for a BMI of less than 27 kg/m<sup>2</sup>, to improve ovulation and pregnancy rates, a weight loss of only 2% to 5% may restore normal menstrual function [18-20].

PCOS is not only a common cause of infertility but has been indicated as a risk factor for spontaneous abortions (SAB), particularly among women treated with assisted reproductive technology [21-23]. When controlled for confounding effects of body mass index (BMI), age and PCOS status, insulin resistance significantly increases the risk for SAB [24] estimated to be in the range from 39%-73%, far exceeding the general population [25]. Recent studies have indicated that hyperinsulinemia, obesity, and hyperandrogenemia all may be a source for the increased SAB rate due to adverse affects on the function of the endometrium [26-28].

Though once thought to be a significant enhancement to the treatment of SAB in PCOS patients, the role of metformin is ambiguous. The first double blind placebo controlled trial comparing metformin and clomiphene citrate in non-obese PCOS patients, revealed metformin was superior in terms of achieved pregnancies (15.1% vs 7.2%), lower abortion rate and increased live births [11]. However, a recent meta analysis failed to demonstrate any benefit from metformin use before pregnancy on preventing miscarriage in PCOS patients [29]. The Cochrane Database concluded that current studies did not support the reduction in miscarriage in PCOS patients undergoing IVF while on metformin [30].

## 3. THE INSULIN RESISTANCE CONNECTION

PCOS is well supported to have a genetic multifactorial inheritance. Insulin resistance (IR) is found in 65-70% of PCOS patients when various diagnostic tools are utilized, including the cumbersome hyperinsulinemic euglycemic clamp study [31,32] While the exact etiology of IR remains unclear, the prevailing theory is a post insulin receptor defect affecting signal transduction resulting in an increase in ovarian and adrenal androgens [33-36].

Up to 65% - 70% of PCOS women are obese and often have insulin resistance placing them at risk for overt diabetes [37]. The impact of PCOS on impaired glucose uptake is dramatically shown by lean PCOS demonstrating the same degree of insulin resistance as ovulatory obese women [37]. To further illustrate this point, PCOS patients are more insulin resistant than age- and BMI-matched non-PCOS controls, irrespective of BMI [8]. The relationship of insulin resistance and PCOS underscores the need for performing a 2hr GTT in all PCOS patients since a fasting glucose alone will have a false negative rate of up to 30% in diagnosing PD [38].

Hyperinsulinemia acts synergistically with increased

LH to induce elevated free IGF-1 (insulin-like growth factor) with resultant hyperandrogenemia and ovulatory dysfunction [39]. PCOS also increases the risk for the development of gestational diabetes in 20% - 40% of cases [40]. Several studies have demonstrated the use of metformin in PCOS pregnant patients reduced the risk of gestational diabetes compared to controls [41].

#### 4. TREATMENT OPTIONS

Metformin is an oral biguanide insulin-sensitizing agent, commonly used to maintain blood glucose control in diabetes by augmenting the effects of insulin on glucose uptake without concurrent hyperinsulinemia. Initial enthusiasm for the application of metformin in PCOS patients has waned as the available evidence is inconsistent regarding its beneficence particularly in those trying to conceive and in adolescence [42]. Though its effectiveness may be independent of dosage, metformin may be of benefit in the following groups: 1) clomiphene resistance; 2) normal BMI; 3) PD; and 4) possibly during IVF. Furthermore, ongoing debate carries over to whether metformin reduces miscarriage (as reviewed earlier) and gestational diabetes, both of which are significantly higher risks in PCOS patients [43]. Metformin is a "Class B" drug that has not been shown to increase the incidence of congenital abnormalities [44].

Thiazolidinediones (TZD) are another category of drugs to treat insulin resistance and improve insulin sensitivity and reducing hyperinsulinemia by different mechanisms than metformin, particularly by binding to the PPAR-gamma receptor. Regarding infertility, new TZDs such as rosiglitazone (pregnancy category C) may be more effective than metformin in inducing ovulation [45].

#### 5. PREVENTING PROGRESSION TO DIABETES

By GTT, approximately 30% - 40% of PCOS women have PD, and 12.6% present with T2DM [46-48]. Signs and risk factors in PCOS women for developing PD & T2DM include elevated BMI, acanthosis nigricans (a brown velvety verrucous discoloration in the intertriginous skin area), and a history of gestational diabetes.

The Center for Disease Control estimates there are 57

million persons in the United States with PD [49]. PD is a significant risk factor for the development of T2DM, macrovascular disease and microvascular disease [50]. The complications resulting from the disease are a significant cause of morbidity and mortality and are associated with the damage or failure of various organs such as the eyes, the kidney and the nerves. The progression of PD to T2DM may be retarded by maintaining blood sugar control through lifestyle changes and/or compliance with diabetic medications thereby allowing pancreatic beta cells to maintain functionality.

Since 2003, the American Diabetes Association (ADA) Expert Committee recommended the use of fasting blood glucose levels and/or a 2 hr GTT to diagnose PD (see **Table 1**). HbA1C had been suggested as a diagnostic test but studies had shown weak correlation between A1C and fasting blood glucose and an even weaker correlation between A1C and 2 hour glucose among non-diabetic patients [50]. The ADA has recently revised their clinical practice recommendations for diabetes diagnosis by using Glycosylated Hemoglobin (HbA1C) [51]. A measure of average blood glucose for the preceding three months, HbA1C has now been advocated to diagnosis PD (5.7% - 6.4%) and T2DM (greater than 6.5%). The new application of HbA1c results from improved standardization of assays among different laboratories. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend HgA1C range of 5.5% - 6/4% only as a screen for PD to facilitate formal testing and not for diagnosing type 1 diabetes.

A Department of Health and Human Services supported research showed most people with PD will likely develop diabetes within a decade unless they make modest changes in their diet and level of physical activity to reduce their risk and avoid the debilitating disease [52]. Lifestyle change has consistently demonstrated benefit in prevention or delaying progression to T2DM, delaying onset by 11.1 years. In addition it reduces the incidence of diabetic complication including blindness by 3%, limb amputation by 35%, Stroke by 9% and coronary heart disease by 8%. The Diabetes Prevention Program (DPP) study demonstrated a 58% reduction in

**Table 1.** Defining PD.

	Fasting* Glucose	2hr 75gm GTT <sup>1</sup>	Hemoglobin A1C <sup>2</sup>	Classic symptoms of hyperglycemia or hyperglycemic crisis
<b>Euglycemia</b>	< 100 mg/dL	< 140 mg/dL	4% - 6%	
<b>PD (IFG/IGT)</b>	100 mg/dL - 126 mg/dL	140 - 199 mg/dL	5.7% - 6.4% <sup>3</sup>	
<b>T2DM</b>	≥ 126 mg/dL	> 199 mg/dL	≥6.5% <sup>4</sup>	random plasma glucose ≥200 mg/dl

\* fasting = no caloric intake for at least 8 h; <sup>1</sup>2003 ADA guidelines; <sup>2</sup>2010 ADA guidelines; <sup>3</sup>AACE/ACE supports HgA1C range 5.5%-6.4%; <sup>4</sup>AACE/ACE considers HgA1C an optional criteria, not primary

progression from PD to T2DM with intense lifestyle changes [52]. In the study, these changes included a weight loss of 7% and at least 150 minutes of physical activity per week. The DPP study also demonstrated metformin 850 mg twice daily in PD patients reduced the progression to T2DM by 31%. The DPP study did not evaluate the effect of combination of lifestyle modifications and pharmacotherapy but computer modeling has determined no additional benefit with combination of lifestyle modification and metformin [50].

## 6. GUIDELINES

The American Association of Clinical Endocrinologist (AACE) released a consensus statement in July of 2008 establishing two goals for the treatment of pre-diabetes:

1) Aggressive lifestyle management. The ADA further recommends lifestyle modifications to include a sustained weight loss goal of 5% - 10% combined with moderate to intense physical activity of 30 - 60 minutes daily, at least 150 minutes weekly [53].

2) Avoid cardiovascular complications associated with elevated glucose levels with pharmacotherapy in PD refractory to lifestyle modification.

All patients 45 years or older and overweight should be screened for PD [54]. The ADA recommendations to screen for PD are shown in **Table 2**. The Food and Drug Administration (FDA) has yet to approve pharmacotherapy as a treatment for PD. Therefore, any physician considering starting a patient on medications for this condition must consider the available evidence and a risk-benefit analysis. Metformin and acarbose have strong evidence for reduction in progression of PD to T2DM. Both drugs are relatively safe and may be acceptable pharmacotherapy for prevention [55].

Recommendations for monitoring patients with PD

**Table 2.** Screen for PD/T2DM in all patients >45 yrs or in patients <45 years and overweight (BMI  $\geq$  25 kg/m<sup>2</sup> with any of the following risk factors.\*

Hypertension ( $\geq$ 140/90mm Hg)
First degree relative with T2DM
A history of gestational diabetes or delivered an infant weighing >9 lbs.
PCOS
HgA1C $\geq$ 5.7% or PD
High blood triglycerides (>250 mg/dl) and/or low HDL cholesterol (<35mg/dl)
Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
History of Cardiovascular disease
Native American, African American, Hispanic American, Asian American and Pacific Islander

\*if normal results, re-screen every three years.

**Table 3.** Monitoring patients with PD.

Semi-annual	Annual
Fasting glucose	
Hb A1C	2 hr - GTT <sup>1</sup>
Fasting lipids	
Urine for microalbumin	

<sup>1</sup>2003 ADA guidelines

are shown in **Table 3**. Patients at highest risk should be followed more carefully. These patients include those with greater than one risk factor: impaired glucose tolerance, impaired fasting glucose level, or the metabolic syndrome. Patients with PD should also have the same target blood pressure less than 130/80 mmHg and target LDL less than 100 mg/dL as those with diabetes. If the results of monitoring reveal worsening hyperglycemia or CV parameters, intensified lifestyle and pharmacotherapy must be considered.

The CDC estimates \$107 billion of the health budget is used each year to care for patients with diabetes [49,56]. Identifying and treating patients with PD potentially has several benefits: the onset of type 2 diabetes and its subsequent complications can be prevented or delayed decreasing morbidity and mortality; and billions of dollars can ultimately be saved in health care expenditure.

## 7. CONCLUSIONS

Prediabetes (PD) is ubiquitous with the potential for severe morbidity and mortality. Given the association with the metabolic syndrome, all PCOS patients should be screened for PD by either a 2hr GTT or HgA1C because a fasting glucose alone will miss up to 30%. Behavioral modification for weight loss including aggressive lifestyle management may avoid cardiovascular complications. Furthermore, while metformin appears to reduce the progression of PD to Diabetes (T2DM), the role of metformin remains undefined in the infertile PCOS patient.

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