The Link between Polycystic Ovarian Syndrome and Type 2 Diabetes: Preventive and Therapeutic Approach in Israel

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KEY WORDS: polycystic ovarian syndrome (PCOS), type 2 diabetes, insulin resistance, hyperinsulinemia, hyperandrogenism

IMAJ 2012; 14: 442-447

Polycystic ovarian syndrome is the most common endocrinopathy, affecting 6%–10% of women of reproductive age [1]. It is the major cause of female anovulatory infertility and affects women across their lifespan. It is characterized by disturbed ovarian function, usually manifests as oligomenorrhea or amenorrhea, infertility and enlarged polycystic ovaries, and is associated with clinical and/or biochemical evidence of hyperandrogenism [2]. Endocrine abnormalities may include increased free testosterone levels, low sex hormone binding globulin, and high luteinizing hormone/follicle-stimulating hormone ratio [2,3].

PCOS was originally thought to affect solely women of child-bearing age because of the presence of infertility. However, current evidence has shown that insulin resistance and the compensatory hyperinsulinemia is a central feature of PCOS [4,5]. Women with PCOS have a high incidence of insulin resistance [4], which is accompanied by compensatory hyperinsulinemia and therefore presents an increased risk for type 2 diabetes [4-6]. In vitro and in vivo studies have shown that in women with PCOS the sensitivity of glucose metabolism to insulin is subnormal and modest hyperinsulinemia prevails [3]. Insulin resistance affects approximately 65–80% of women with PCOS and appears to play an important pathogenic role in the hyperandrogenism of both obese and lean women with PCOS [5]. The recognition that the disorder is associated with insulin resistance has provided insight not only into the pathogenesis of PCOS but also into its related short and long-term complications, with significant risk for the development of obesity, metabolic syndrome, impaired glucose tolerance, type 2 diabetes, dyslipidemia, hypertension and atherosclerosis [3,5,6].

PCOS = polycystic ovarian syndrome

PATHOPHYSIOLOGY OF INSULIN RESISTANCE IN PCOS

Specific abnormalities of insulin metabolism identified in women with PCOS include impaired suppression of hepatic gluconeogenesis and abnormalities in insulin receptor signaling that adversely affect the insulin-mediated glucose transport into the muscles, being reduced by 35–40% in PCOS women independent of obesity [3,5,7]. Pancreatic β-cell dysfunction with an increased basal secretion of insulin and inadequate postprandial response has also been described in PCOS women even when, as a result of weight loss, an improvement in glucose tolerance was observed [6].

Adipose tissue, stored mainly in the abdominal fat in PCOS women, has an aberrant morphology and produces less adiponectin than matched controls. This may further aggravate the insulin resistance. Furthermore, activity of the enzyme lipoprotein lipase is low, which can also affect fat metabolism [8].

In PCOS, the insulin receptor defect adversely affects the insulin-mediated glucose transport into the muscles [3,7]. As a result, the glucose in blood remains elevated for a longer time and further stimulates pancreatic beta cells, which in order to improve muscular glucose uptake increase their secretion of insulin in a compensatory manner [3] [Figure 1].

This compensatory hyperinsulinemia of PCOS directly stimulates testosterone production by ovarian thecal cells, promoting the hyperandrogenic state [9] that is responsible for hirsutism, acne, alopecia, higher waist to hip ratio, and the detrimental effects on follicular growth, leading to the anovulatory state, menstrual disturbances and the microcystic appearance of the ovaries that characterize this syndrome [3,5,9]. Insulin stimulates the ovarian production of androgen by activating its homologous receptor [9] in the ovaries of PCOS women that appear to remain sensitive to insulin, or perhaps hypersensitive to it, even when classic target tissues such as muscle and fat manifest resistance to insulin action [10]. In addition, hyperinsulinemia inhibits the hepatic production of sex hormone binding globulin [5], further increasing circulating free testosterone levels. Finally, insulin impedes ovulation, either by directly affecting follicular development, or by indirectly increasing intraovarian androgen levels or altering gonadotropin secretion [5].

The molecular mechanism of insulin resistance in PCOS is controversial. However, several studies have shown that insulin resistance in PCOS is due to post-binding defects in signal transduction and that there are multiple defects in insulin action in PCOS that affect metabolism [7,11,12]. Insulin action is initiated when insulin binds to the insulin receptors-1 and 2. Insulin binding induces autophosphorylation of the insulin receptors on specific tyrosine residues and increases the intrinsic kinase activity of its β-subunit. One pathway proceeds through IRS-1 and IRS-2 and depends on activation of phosphatidylinositol 3-kinase to mediate the insulin actions on glucose metabolism, antilipolysis and protein synthesis.

Another pathway proceeds through binding of tyrosine-phosphorylated IRS-1 and IRS-2, leading via p21Ras and Raf-1 to activation of the mitogen-activated protein kinase isoforms of extracellular signal-regulated kinase ERK-1 and 2, thus mediating mitogenic and other gene-regulatory actions of insulin. ERK-1 and 2 are members of a family of serine/threonine kinases, including p38 MAPK and c-Jun NH2-terminal kinase, that play important roles in cellular proliferation, differentiation, apoptosis as well as inflammation [13].

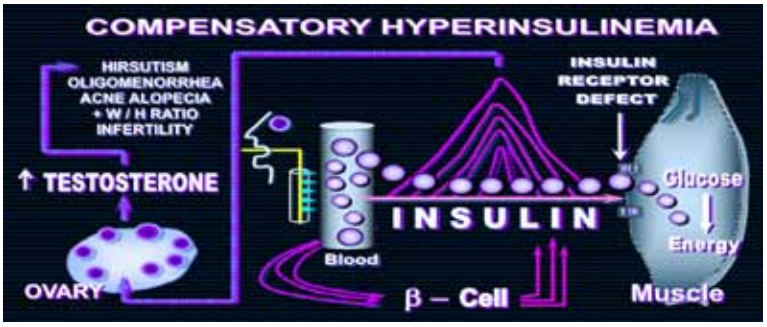
Previous studies have demonstrated that in PCOS there is also a post-binding defect in insulin signaling in adipocyte and decreased activity of PI3 -kinase in muscle biopsies during euglycemic hyperinsulinemic clamps. It was suggested that the impaired action of insulin on glycogen synthesis in cultured skin fibroblasts from POCS women is associated with constitutively increased insulin receptor β-subunit serine phosphorylation and decreased insulin receptor tyrosine kinase activity [7,11,12].

It was also thought that the decreased IRS-1 tyrosine phosphorylation and increased IRS-1 Ser312 phosphorylation seen in women with PCOS may be the initial defect in insulin resistance in PCOS [11,14]. Increased IRS-1 Ser312 phosphorylation would inhibit insulin receptor tyrosine kinase activity and prevent the signal propagation that underlies many biological effects of insulin, leading to decreased activation of the signaling pathway. Evidence for this hypothesis comes from the observed reversal of impaired insulin receptor signaling by serine kinase inhibitors in human fibroblasts from women with PCOS [15].

It was reported that ERK-1 and 2 are responsible for constitutive phosphorylation of IRS-1 Ser312 in women with PCOS, and that Ser312 phosphorylation of IRS-1 is constitutively increased in cultured skeletal muscle cells from PCOS women [14], but the mechanism by which ERK-1 and 2 regulates IRS-1 Ser312 phosphorylation is unknown. Nevertheless, it was found that decreased ERK1/2 activation and IRS-1 Ser312 phosphorylation in PCOS women result in ameliorated insulin resistance [12].

IRS = insulin receptor substrate
MAPK = mitogen-activated protein kinase
PI = phosphatidylinositol

Figure 1. In PCOS the compensatory hyperinsulinemia in response to insulin receptor defect in the muscles directly stimulates testosterone production by ovarian thecal cells, promoting the hyperandrogenic state (original Illustration of the first author, appearing as a poster presentation)



Furthermore, MAPK activity that is constitutively increased in the skeletal muscle of women with PCOS implies that ERK-1 and 2 or ERK-regulated kinases are responsible for the increased Ser312 phosphorylation of IRS-1 [14]. These observations provide strong support for the hypothesis that increased Ser312 phosphorylation is an important mechanism for insulin resistance in PCOS.

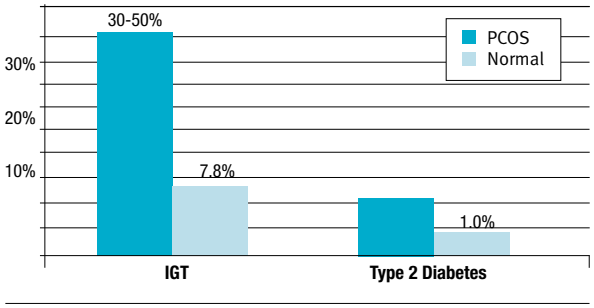
It was previously reported that obese women have lower levels of insulin receptor, IRS and PI3-kinase than non-obese women [16]; however, a recent study showed that the levels of activated ERK-1 and 2, Ser312-phosphorylated IRS-1, tyrosine-phosphorylated IRS-1, IR β-subunit, PI3-kinase and GLUT-4 were similar in both obese and non-obese PCOS women and lower than in controls, suggesting that non-obese and obese PCOS women have a similar risk of developing insulin resistance or type 2 diabetes [12]. The decrease of compensatory hyperinsulinemia in PCOS via a reduction in IRS-1 Ser312 phosphorylation may therefore be an effective tool for reducing the risk of type 2 diabetes in women with PCOS.

In PCOS, the compensatory hyperinsulinemia directly stimulates ovarian testosterone production promoting the hyperandrogenic state

Clinical studies have shown that lowering circulating insulin levels resulted in reduction of serum testosterone levels and increased frequency of ovulation and fertility in PCOS women. Those trials include the inhibition of insulin release with diazoxide [17] and improvement of insulin sensitivity with diet-induced weight loss [18] by administration of metformin, which resulted in decreases in ovarian 17,20-lyase activity and ovarian secretion of androgens [19,20], and of other insulin sensitizers, i.e., rosiglitazone [10]. In women with the syndrome, long-term treatment with metformin

MAPK = mitogen-activated protein kinase
IR = insulin receptor

Figure 2. Prevalence rates of impaired glucose tolerance in PCOS is 30–40% and the prevalence of type 2 diabetes 5–10%, which is substantially higher than found in a major population-based study (Second National Health and Nutrition Survey) of U.S. women of similar age and BMI (7.8% IGT and 1.0% type 2 diabetes). Original picture, based on Legro at al., 1999 [4].



resulted in increased ovulation, improved menstrual cyclicity, and reduced serum androgen levels [9,19,20].

PCOS AND METABOLIC SYNDROME

The prevalence of the metabolic syndrome is two to threefold higher among women with PCOS compared to normal women matched for age and body mass index, while 20% of women with PCOS under 20 years old have the metabolic syndrome [21].

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), the prevalence of metabolic syndrome has been reported to be between 33% and 46% in women with PCOS, compared to 6% in normal women aged 20–29 years and 15% in women aged 30–39 [21,22] Furthermore, the metabolic syndrome is present in 80% of PCOS women who are also obese. Hence, the prevalence of the metabolic syndrome is two to threefold higher in women with PCOS compared to age- and BMI-matched non-PCOS controls, regardless of BMI [4,6,22].

Obese PCOS and non-obese PCOS women are at high risk of metabolic syndrome and type 2 diabetes

RISK FOR TYPE 2 DIABETES IN PCOS WOMEN

The prevalence of type 2 diabetes is tenfold higher among young women with PCOS than among normal women, and impaired glucose tolerance or overt type 2 diabetes develops by the age of 30 years in 30–50% of obese women with PCOS [4,6,22,23] [Figure 2]

Insulin resistance in PCOS appears to be responsible for this predisposition to develop type 2 diabetes [24]. In fact, in PCOS women the prevalence of IGT is 30–50%, and that of type 2 diabetes 5–10%. In addition, the conversion from IGT to type 2 diabetes is increased [4,23]. A recent study showed that PCOS women have twofold higher odds for subsequent development of type 2 diabetes: 23.1% in PCOS woman versus 13.1% in non-PCOS women [25].

Women with PCOS and normal glucose tolerance at baseline have a 16% conversion rate per year to type 2 diabetes. Thus by the age of 30 years, 30–50% of obese PCOS women develop IGT or overt type 2 diabetes. This is a three to sevenfold greater risk than in an age-comparable population [23].

More recently a systematic review and meta-analysis [26] show that women with PCOS have an elevated prevalence of IGT, type 2 diabetes and metabolic syndrome in both BMI and non-BMI-matched studies.

SHOULD WOMEN WITH PCOS RECEIVE METFORMIN THERAPY?

Metformin, a biguanide, is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to inhibit hepatic glucose production, but it also increases the sensitivity of peripheral tissues to insulin [27]. The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in non-diabetic women with PCOS [24].

With regard to diabetes, two major randomized clinical trials – the Indian Diabetes Prevention Programme (IDPP-1) [28] and the U.S. Diabetes Prevention Program (DPP) [29] – have shown that the use of metformin decreases the relative risk for progression to type 2 diabetes (by 26% and 31%, respectively) among patients with IGT at baseline. Furthermore, after the discontinuation of metformin in the U.S. Diabetes Prevention Program, diabetes developed in fewer subjects than would have been expected [30]

In an uncontrolled retrospective study of 50 women with the polycystic ovary syndrome treated with metformin for an average of 43 months at an academic medical center, there was no progression to type 2 diabetes even though 11 women (22.0%) had IGT at baseline [31]. The annual conversion rate from normal glucose tolerance to impaired glucose tolerance was only 1.4%, as compared to 16–19% reported in the literature [4,6] for women with PCOS who were not taking metformin. Metformin may actually retard progression to glucose intolerance in affected women [31].

Furthermore, lifestyle intervention together with the use of metformin can prevent IGT progression to type 2 diabetes

BMI = body mass index

IGT = impaired glucose tolerance

and reduce the risk of cardiovascular events in patients with PCOS, strengthening the argument for early detection of IGT, especially in this group of women who are at high risk of type 2 diabetes [25].

Metformin may decrease circulating androgen levels and improve menstrual cyclicity, and is of benefit in improving clinical pregnancy and ovulation rates as well as addressing the traditional goals of glucose metabolism in long-term treatment. However, there is no evidence that metformin improves live birth rates, whether used alone or in combination with clomiphene or when compared with clomiphene. Therefore, the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited [32]

PREVALENCE OF DIABETES IN ISRAEL

Diabetes is one of the most frequent chronic diseases in the modern word and is associated with striking comorbidities and serious health implications for patients, health care systems, and society. In Israel as in other countries, the prevalence of diabetes has risen over the last few decades, reaching a prevalence of 6.4% in adults over 18 years old, with an annual increase of 0.2%. The prevalence of diabetes increases with age, reaching 15% among people aged 30–40, while among those aged 65 or above the prevalence is 25% [33].

In Israel, with an estimated population of 7 million, there are more than 490,000 diabetics. Recent epidemiological evaluation also reported that there are an additional 200,000 diabetics who have the disease but were not diagnosed [34]. Since diabetes decreases life expectancy and is a health-threatening condition, all measures to prevent the development of diabetes are of pivotal importance, especially in those groups with a high predisposition like PCOS.

CUES IN THE PREVENTION OF TYPE 2 DIABETES IN PCOS WOMEN IN ISRAEL

In Israel, the incidence of type 2 diabetes is markedly high and is a leading cause of morbidity, particularly in those over age 40. As described above, there is a strong association of PCOS, the metabolic syndrome and type 2 diabetes [6,23].

When considering the prevention of such a debilitating condition as diabetes, it should be remembered that PCOS will almost invariably express itself soon after menarche. When the diagnosis of PCOS is made, this should serve as a beacon flashing a warning signal that diabetes may well be encountered later in life and that its prevention should be considered when PCOS is initially diagnosed. However, in Israel, it would seem that these warning signals are often ignored due to a failure in making the connection between PCOS and diabetes type 2 – and the opportunity for true preventive medicine is missed.

Gynecologists tend naturally to concentrate on the gynecologic symptoms of irregular periods and infertility, whereas diabetologists often fail to make the connection between the two conditions. In addition, dermatologists encountering adolescents with hirsutism or persistent acne will sometimes treat symptomatically with medication that may further worsen the insulin resistance [35] without recognizing that they have PCOS – and another opportunity to prevent diabetes in later life is missed. In view of the long-term consequences associated with insulin resistance and impaired glucose tolerance related to the development of type 2 diabetes and subsequently cardiovascular disease, it is crucial that young girls with this disorder be diagnosed and treated.

PCOS often manifests around the time of menarche as irregular and often lengthy menstrual cycles [36]. Unfortunately, PCOS is often unrecognized and undiagnosed at this time because most adolescents do not have regular menstrual cycles [37]. In adolescent girls with irregular menstrual cycles for more than 2 years after menarche, it is highly likely that the underlying cause is not physiological but PCOS. This is especially true if the irregular periods are accompanied by persistent acne or hirsutism. Although the prescribed treatment for irregular menstrual cycles is oral contraceptive pills, particularly those containing progestins with anti-androgenic actions if the diagnosis of PCOS has been correctly made, this treatment will have no effect on the potential for developing diabetes.

In Israel, the incidence of type 2 diabetes is markedly high and is a leading cause of morbidity, particularly in those over age 40

Women with PCOS are often diagnosed at a much later stage, usually when they seek treatment for infertility. Again, the treatment for infertility in this case will be the primary concern of the gynecologist, while any thoughts of the future consequences of PCOS and the metabolic syndrome are disregarded.

Two main factors must be considered regarding PCOS women. The first involves cyclic control of irregular menstruation cycles, fertility, acne and hirsutism and other hyperandrogenic symptoms. The second involves avoidance of the long-term sequelae that are associated with obesity, insulin resistance, glucose intolerance, subsequent dyslipidemia, hypertension, and type 2 diabetes, all known to be significant risk factors for the development of cardiovascular disease [37]. Because of the connection between insulin resistance and PCOS, it is recommended that all adolescents suspected of having the disorder be screened by fasting blood glucose levels. If fasting blood glucose levels are elevated, the next step is to order a 2 hour 75 g oral glucose tolerance test

to confirm glucose intolerance or type 2 diabetes [38]. In fact, most authorities recommend the OGTT as a screening test in all obese adolescent females. Whereas the testing for insulin resistance by the gold standard of the insulin clamp is not recommended because of the time-consuming nature of the test and the expense [36], HOMA-IR (homeostasis model assessment-estimated insulin resistance) may give a much simpler indication of the presence of insulin resistance. However, the OGTT is probably the test of choice for pragmatic diagnosis. The most cost-effective predictor for insulin resistance and cardiovascular risk is probably a waist circumference of > 88 cm [21]. If the adolescent is found through laboratory testing to have glucose intolerance or type 2 diabetes, testing should probably be repeated at yearly intervals. Since disturbances in glucose metabolism can cause lipid abnormalities, particularly increased total cholesterol, decreased high density lipoprotein and increased low density lipoprotein, it is recommended that lipid assays be performed as well. Determining baseline lipid levels is also important because many of the treatments, specifically combined oral contraceptive pills, can also alter these values and may impact on the therapeutic management of PCOS women.

As for the actual prevention of diabetes in the woman with PCOS, lifestyle changes, diet and exercise under expert supervision, especially for those who are obese, is the treatment of choice. As mentioned above, metformin may also be used in the long term but more evidence on the efficiency of this treatment is still required. With long-term metformin there should also be awareness that homocysteine levels may increase and that multivitamin therapy may be necessary to control the levels [39]. A revealing study from the Diabetes Prevention research group [40] showed that lifestyle changes reduced the cumulative incidence of diabetes by 58% compared to 31% with metformin.

In conclusion, the purpose of this article is to increase the awareness of physicians, whether gynecologists, fertility experts, diabetologists, endocrinologists or others, of the strong link between PCOS, insulin resistance, metabolic syndrome, and the incidence of diabetes. It is hoped that this increased awareness will bring about a concerted effort in Israel to reduce the incidence of diabetes.

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OGTT = oral glucose tolerance test

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Capsule

Aspirin helps to control metabolism, polarity, autophagy, and the restraint of cell proliferation

The protein kinase AMPK (adenosine monophosphate-activated protein kinase) directly monitors cellular energy stores as reflected by changes in cellular concentrations of AMP, adenosine diphosphate (ADP), and adenosine triphosphate (ATP). Through phosphorylation of its targets, it helps to control metabolism, polarity, autophagy, and the restraint of cell proliferation. Activation of AMPK is also proposed to be beneficial for the treatment of diseases, including cancer and diabetes. Hawley et al. report that AMPK can be activated by high concentrations of salicylate, a compound derived from the very commonly used drug aspirin. In mice, salicylate promoted fatty acid and carbohydrate metabolism in an AMPK-dependent fashion

Science 2012; 336: 918

Eitan Israeli

Capsule

Cancer cells need more glycine

To better characterize metabolic properties of cancer cells, Jain et al. systematically measured the concentrations of hundreds of metabolites in cell culture medium in which 60 different cancer cell lines were growing. The fastest growing cancer cells tended to consume glycine, whereas more slowly growing cells excreted some glycine. The rapidly growing cancer cells appeared to need glycine for synthesis of purine nucleotides required for continued synthesis of DNA. Interfering with glycine metabolism slowed growth of the rapidly proliferating cancer cells. Thus, an increased dependence on glycine by rapidly growing cancer cells could potentially provide a target for therapeutic intervention.

Science 2012; 336: 1040

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