Published in final edited form as:
Fertil Steril. 2012 January ; 97(1): 18–22. doi:10.1016/j.fertnstert.2011.11.036.

All Women With PCOS Should Be Treated For Insulin Resistance

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Polycystic ovarian syndrome (PCOS) while clinically heterogeneous, commonly exhibits hyperandrogenism, ovulatory dysfunction and is associated with obesity, insulin resistance, and subfertility (1, 2). Overall, insulin resistance and the compensatory hyperinsulinemia affects some 65–70% of women with PCOS (3,4), with 70–80% of obese (BMI >30) and 20–25% of lean (BMI<25) women exhibiting these characteristics. Part of the insulin resistance appears to be independent of obesity and related specifically to PCOS, with abnormalities of cellular mechanisms of insulin action and insulin receptor function having been documented (5,6).

The hyperinsulinemia appears to be an important factor in maintaining hyperandrogenemia, acting directly to induce excess androgen production by theca cells and also as a co-gonadotropin, augmenting the effect of the increased LH stimulus seen in a majority of women with PCOS (7). The elevated insulin may exert other actions having been implicated in the central actions of androgen in impairing progesterone inhibition of the GnRH pulse generator (9,10). In vitro, insulin increased mRNAs for adrenal steroidogenic enzymes (11) and acutely enhanced adrenal secretory responses to ACTH (12).

In accord with the high prevalence of insulin resistance and obesity, glucose intolerance, type 2 diabetes, dyslipidemia and increased evidence of inflammation are more common in women with PCOS (4). Similarly many women demonstrate features consistent with the metabolic syndrome and elevated triglycerides, LDL and decreased HDL are well recognized (14).

The above outlines the importance of insulin resistance, compensatory hyperinsulinemia and its consequences, the majority of which have negative effects on both metabolic and reproductive health. Options for treating insulin resistance/hyperinsulinemia include life style modifications, exercise, dieting and weight loss, or administration of the thiazolidinediones (TZDs) or metformin. Given the high prevalence of obesity in women with PCOS, efforts to achieve weight reduction are an important component of treatment of the disorder. When effective, often as part of an organized program of lifestyle modification together with exercise and diet, weight loss has been shown to reduce hyperandrogenism, increase ovulation and rates of conception, together with improving the metabolic pertubations (15,16). The main limitations to this mode of therapy reflect the difficulties of

maintaining changes over a prolonged period of time, and recedivism is unfortunately all to common in the absence of ongoing organized programs. The thiazolidinediones, (pioglitazone and rosiglitazone are presently available) have been shown to be effective in controlled trials, reducing plasma androgens and improving insulin sensitivity and glucose tolerance (17,18). While effective, TZDs have significant practical limitations in that they induce weight gain, and more recently have been associated with increased coronary artery disease and myocardial infarction. World wide, we have over 40 years experience using the biguanide metformin, which is FDA approved for managing type 2 diabetes mellitus. Present understanding of the mechanism of metformin action is incomplete, but it activates the adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway (19). AMPK activation appears to be a mechanism reducing hepatic glucose production and increasing insulin sensitivity in peripheral tissues, with additional effects of lowering plasma free fatty acids.

Metformin has been demonstrated to be effective in normalizing several parameters in women with PCOS. Meta analyses (21,22) reviewed some 30 trials and revealed that ovulation was enhanced compared to placebo alone, and resulted in fewer multiple pregnancies while being less effective than clomiphene citrate per se. Other data suggest that metformin is effective in improving ovulation rates in women with clomiphene resistance. Further support for the effectiveness of metformin is seen from a large meta analysis of subjects at risk for diabetes mellitus, including those with and without PCOS and those with and without obesity (23). Overall, treatment with metformin for at least 8 weeks reduced weight, fasting glucose, triglycerides and LDL by 4.5–5.6%, fasting insulin by 14%, calculated insulin resistance (HOMA-IR) by 22% and reduced new onset diabetes by 40%. Importantly in PCOS metformin for up to 6 months reduced hirsutism and in most studies significantly reduced androgen levels, with reductions in testosterone being between 25–50% (24,25). Other studies have not revealed as great a reduction in testosterone and metformin alone is not as effective as a combined oral contraceptive, though the combination may enhance responses (26).

Thus in women without evidence of renal or hepatic disease, metformin appears effective in reducing the negative effects of PCOS on both reproductive and metabolic health. A main limitation can be side effects, which are predominantly gastroenterological consisting of bloating, abdominal discomfort, nausea and diarrhea. The latter is usually dose dependant and can be minimized by gradually building up the dose of metformin, starting at 250–500mg per day taken just before the main meal and increasing over a period of 1–2 months, reaching doses of 2,000–2,500mg per day. If GI side effects intervene, reducing the dose to the prior symptom free level for a period of 7–10 days, can often be followed by a resumption of the dosage increase.

The above sections emphasize the overall positive action of metformin in reducing signs and symptoms of PCOS. They also bring to mind the question of whether we should be more aggressive in treating younger subjects who are obese and have hyperandrogenemia (HA). Paralleling the marked increase in obesity in the last 30–40 years, HA is relatively common being present in 60–70% of pre and post pubertal girls with marked obesity (BMI >90–95%ile for age) (27,28, 29). Given that hyperandrogenemic syndromes prior to puberty are a risk factor for subsequent development of PCOS (30), and approximately half of HA adolescents have already developed resistance to progesterone inhibition of the GnRH pulse generator (9), efforts to ameliorate the excess androgen production would seem appropriate. Indeed abnormal regulation of GnRH/LH secretion with persistently rapid GnRH pulse secretion is already present in premenarchal adolescent girls with HA (31), suggesting that prepubertal androgen excess may modify hypothalamic set points for steroid feedback during pubertal maturation (32). In adults impairment of progesterone inhibition of GnRH

pulse frequency can be corrected by prior androgen receptor blockade (33), but may not simply reflect the degree or duration of HA. The only significant difference between HA girls resistant to and those who remained sensitive to progesterone feedback, was that fasting insulin levels were elevated in progesterone resistant girls (9, 10). It remains unknown whether blockade of androgen action or reduction in plasma insulin or androgen levels during pubertal maturation will correct these hypothalamic feedback abnormalities. However metformin for 3 months improved glucose intolerance, decreased testosterone and fasting insulin values, and reduced the exaggerated adrenal androgen responses to ACTH stimulation in obese adolescents (34). Additional evidence shows that low sex hormone binding globulin (SHBG) levels, HA and elevated insulin in the early teen years, predict subsequent development of the metabolic syndrome and class 3 obesity by the middle of the third decade (35). This in turn provides support to the concept that adolescent girls with this disorder should receive the earliest possible treatment.

In sum, a majority of women and adolescent girls with PCOS have insulin resistance and consequent hyperinsulinemia. The latter commonly leads to hyperandrogenemia with negative effects on reproductive function, impairing normal regulation of GnRH secretion by steroids during pubertal maturation. Together, the increased LH drive and co-gonadotropin action of insulin on the ovary maintain hyperandrogenemia. The majority of evidence in adult women indicate that treatment of insulin resistance, either by lifestyle changes or metformin, leads to improvement in reproductive and metabolic abnormalities and probably reduces future development of diabetes and arterial disease. It remains unknown whether reducing insulin and thus androgen excess over a period of months to years, will allow reversal of abnormal hypothalamic steroid feedback and restoration of normal LH secretion. However present evidence would support every effort to reduce hyperinsulinemia and its consequences both before and during puberty in hyperandrogenemic girls. In addition to treating adults perhaps we should be more aggressive and take the lead of our pediatric colleagues, many of whom have already adopted metformin as a standard treatment in light of the difficulties of maintaining diet and life style restrictions in the younger age group.

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CON

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I do not support the use of insulin sensitizing drugs (ISDs) in all women with PCOS. First, insulin resistance is a common but not universal feature of PCOS, even when diagnosed using the NIH criteria (1). It is a less common finding in the additional PCOS phenotypes diagnosed using the Rotterdam criteria (2). Many studies have shown that both lean and obese women with PCOS have insulin resistance (1). However, from the first studies to assess insulin sensitivity in PCOS using the “gold standard” method, the hyperinsulinemic euglycemic clamp (4), it was evident that some women with PCOS diagnosed by NIH criteria had insulin sensitivity that was well within the range of that in reproductively normal control women of comparable age, weight and ethnicity(3). Further, studies using the euglycemic clamp have found no evidence for insulin resistance (for example 5) in some populations of lean women with PCOS.

Insulin sensitivity varies by PCOS phenotype(6, 7). Studies stratifying affected women according to the Rotterdam diagnostic criteria have shown that women with the most marked metabolic abnormalities are those with hyperandrogenism and chronic anovulation (i.e. NIH criteria), independent of polycystic ovaries (PCO)(2). Other Rotterdam phenotypes, PCO and hyperandrogenism with ovulatory cycles or anovulation and PCO without hyperandrogenism, have much milder metabolic dysfunction or are metabolically normal (8, 9). Moreover, women with PCO morphology according to Rotterdam criteria and regular cycles are metabolically normal, although they may have subtle hormonal abnormalities (10).

Second, ISDs are not a panacea, even for classic NIH PCOS (11). Meta-analyses of metformin (12) indicate that it improves menstrual regularity and ovulation rates in PCOS. Thiazolidinediones (TZDs) appear to have similar efficacy but there are fewer RCTs(12). A large RCT (13) showed that clomiphene citrate was superior to metformin when the relevant fertility endpoint, live births, was examined. Metformin is not recommended as a first-line therapy for infertility in PCOS (14). Further, a recent RCT showed that metformin treatment from the first trimester through pregnancy did not reduce pregnancy complications or alter birthweight in PCOS (15). Metformin and other ISDs reduce hirsutism but appear to be inferior to antiandrogens and contraceptive steroids (16). ISDs are also not recommended as first-line therapy for hirsutism (17).

Meta-analyses (12, 18) of metabolic endpoints in women with PCOS indicate that metformin has modest efficacy for reducing circulating glucose and insulin levels as well as for reducing systolic blood pressure. However, the results of recent meta-analyses differ with those limited to women with PCOS showing no benefit of metformin on lipid parameters or body weight (12). The meta-analysis of Salpeter and colleagues (18) that contained RCTs in women with PCOS as well as in other groups of subjects, found a beneficial effect of metformin on body weight and lipid parameters. There are limited RCTs of metabolic endpoints with TZDs. There is significant heterogeneity in many of the endpoints examined in the meta-analyses, most likely because of differences in diagnostic criteria and body weight as well as other potential differences, such as ethnic/racial differences in the PCOS cohorts studied(12). Further, many of the RCTs limited to PCOS examining metabolic endpoints have been small and/or metabolic parameters have not been the primary endpoints of the trial(12, 18).

What can be extrapolated from large RCTs of ISDs for metabolic endpoints in other cohorts? The efficacy of ISDs, both metformin and TZDs, for diabetes prevention has been demonstrated in individuals with prediabetes(19), which, given the high risk of glucose intolerance in women with PCOS(2), likely contained more than the 7% population prevalence of affected women among the younger female participants. In the Diabetes Prevention Program (DPP)(20), metformin both reduced incident metabolic syndrome and reversed prevalent metabolic syndrome in individuals with prediabetes but this effect was less pronounced in women. Metformin also resulted in modest weight loss that was greatest at one year of therapy but was maintained at 10 years (21, 22). Hyperinsulinemia is an independent risk factor for cardiovascular disease (CVD) (23). However, there is no evidence to support treating insulin resistance *per se*to reduce CVD events. The PRO active Study (24), a large RCT examining standard T2D therapy compared to standard therapy with TZD in patients with T2D, who are at very high risk for CVD, found no significant reduction in the primary endpoint of mortality from any cause, non-fatal myocardial infarction, acute coronary syndrome, coronary revascularization, stroke, leg amputation or revascularization of the leg.

Third, isolated insulin resistance cannot be reliably diagnosed with surrogate markers (25, 26). Fasting insulin levels reflect insulin secretion and clearance as well as insulin resistance (26) and not sufficiently predictive of euglycemic clamp measures of insulin action to be used for the diagnosis of insulin resistance in individuals patients (25). Other fasting measures, such ashomeostatic model assessment (HOMA) (27), fasting glucose:insulin ratio (G:I ratio) (28), and quantitative insulin sensitivity check index (QUICKI) (29), are all based on fasting glucose and insulin levels and essentially provide identical information (26). As discussed above, even when insulin resistance is assessed using the euglycemic glucose clamp, it is clear that some women with PCOS have normal insulin sensitivity (3). Therefore, in clinical practice, treatment of should be directed to the presumed sequelae of insulin resistance, metabolic syndrome, dysglycemia (impaired fasting glucose [IFG],

fasting glucose ≥100 mg/dl and/or impaired glucose tolerance [IGT], 2 h post-glucose ≥140 mg/dl) or prediabetes and type 2 diabetes (T2D)(30–32)and/or to those features of PCOS shown to improve with ISD therapy (11, 33)

The increased cardiovascular disease risk (34, 35) and more recent concerns about increased risk for bladder cancer (36)substantially constrain the use of TZDs in otherwise healthy young women (11). The remaining ISD, metformin, appears to be quite safe (18, 32). Metformin is appropriate as a first-line therapy for T2D or combined glucose intolerance (IFG and IGT)in women with PCOS, as it is in the general population (31, 32). Metformin is a reasonable treatment option for affected women who have impaired glucose tolerance. Metformin may also beneficial for women with PCOS with metabolic syndrome and/or obesity(18, 20, 37). Contraceptive steroids and antiandrogens are superior to metformin for the treatment of hirsutism (38). Clomiphene citrate is the recommended first-line therapy for ovulation induction in PCOS (14).

In summary, there are no data to support treating all women with PCOS with metformin on the assumption that they are insulin resistant. Further, fasting insulin and glucose levels as well as calculations based on these parameters are not sensitive and specific for the diagnosis of insulin resistance (26, 39). This fact coupled with the lack of data to support treating insulin resistance *per se* indicates that the metabolic evaluation of women with PCOS should focus on detecting conditions for which intervention may be warranted: IFG, IGT, metabolic syndrome and LDL levels. Moreover, RCTs are needed in women with PCOS to assess the efficacy of ISDs in ameliorating metabolic endpoints since much of the current information comes from studies investigating non-metabolic primary endpoints in PCOS or from studies in non-PCOS populations.

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