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Obesity in Polycystic Ovary Syndrome: Insulin Sensitizing Therapy

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Abstract Polycystic Ovary Syndrome (PCOS) is a common reproductive endocrine disorder in women that is highly associated with obesity. Whether obesity is intrinsic to the disorder or is a result of different lifestyle and environmental concerns is unclear, however obesity influences the risks of PCOS with respect to fertility complications, pregnancy complications and cardiovascular risk. Polycystic ovary syndrome is known to be associated with insulin resistance in both lean and obese individuals. Insulin resistance in fact is felt to be a key feature in the reproductive and metabolic dysfunction of PCOS. There are numerous studies reporting the benefits of insulin sensitizing therapy, specifically metformin and thiazolidinediones, on the features of PCOS and emerging evidence on the impact of these agents on the risk and management of obesity. Weight loss and maintenance of weight reduction has been seen in women and adolescents treated with metformin therapy. Most studies indicate a synergy of metformin with lifestyle therapy in the general population but there are limited data in PCOS.

Keywords Obesity · Polycystic ovary syndrome · Weight reduction · Cardiovascular risk · Adolescents · Adolescent obesity · Metformin · Thiazolidinediones · Fertility risk · Pregnancy complications · Insulin resistance · Type 2 diabetes · Insulin sensitizing therapy

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Introduction

The association of obesity with PCOS has been noted since the first description of PCOS in the 1930s [1]. Despite this finding the diagnostic features of PCOS do not include obesity, but rather the diagnostic criteria include clinical or biochemical hyperandrogenism, oligoovulation and presence of polycystic ovaries on ultrasound [2]. There are serious sequelae to PCOS including reproductive dysfunction such as infertility and pregnancy complications, metabolic dysfunction including increased risk of type 2 diabetes and risk factors for cardiovascular disease. As such PCOS represents a major burden on healthcare irrespective of obesity. Obesity however is known to contribute both to the sequelae and the severity of these sequelae.

It is estimated that 40–60 % of women with PCOS are obese although there is widespread variability in the degree of obesity based on geography. Studies range in prevalence from 20 % in Spain to 69 % in the United States [3, 4]. To some degree there is a correlation with the overall prevalence of obesity in the population, with the greatest prevalence in the general population of the United States at more than 30 % [5]. The relative risk of obesity in PCOS is overall increased, with a meta-analysis suggesting a RR of 2.77 (1.80, 4.10). This is variable by race, with Caucasian women demonstrating a RR of 10.79 and Asian women a RR of 2.31 [6]. Obesity worsens the overall clinical picture of PCOS both reproductively and metabolically. Treatment of PCOS therefore must address the obesity as a primary intervention modality in order to adequately address the consequences of PCOS.

Insulin resistance is a major feature of PCOS and is particularly prevalent in those women who are obese with 70–80 % demonstrating insulin resistance and compensatory hyperinsulinemia [7]. Hyperinsulinemia is an important finding associated with the features of PCOS and addressing

the hyperinsulinemia can be critical to the management of the disorder. Currently available insulin sensitizers that have been studied in PCOS include metformin and the thiazolidinedione therapies. With respect to the management of obesity in PCOS, there are studies supporting the use of insulin sensitizer. The majority of available evidence supporting insulin sensitizer use for obesity involves the use of metformin therapy, which will be the insulin sensitizer primarily reviewed in this article. The cornerstone of treatment of obesity in PCOS remains lifestyle therapy with dietary and behavioral changes. This has been previously reviewed [8]. However lifestyle therapy has notoriously low success rates over the long-term. While insulin sensitizing drugs are not considered weight loss agents, there is emerging evidence that they may play a role in the long-term management of weight reduction in both general obese populations and PCOS which will be reviewed.

Impact of Obesity on Manifestations of PCOS

There is evidence that obesity, particularly abdominal obesity, worsens both the clinical and endocrine features of PCOS [9]. The prevalence of obesity in PCOS is at least 50 % in most studies. The phenotype of PCOS is strongly influenced by the presence of insulin resistance which is present in the majority of women diagnosed with PCOS by NIH criteria although this may be less so in those diagnosed by Rotterdam criteria [10]. Obesity influences the degree of insulin resistance, with obese women with PCOS demonstrating significantly more insulin resistance than their normal weight counterparts [11, 12]. The converse of this may also be true with those demonstrating more severe insulin resistance also demonstrating a higher propensity to weight gain [13]. It is likely that obesity influences the clinical presentation of PCOS mediated in part through increased insulin resistance, worsening the clinical consequences. As such it is important to consider the impact of obesity on the features of PCOS when treating the condition.

Impact of Obesity on Reproductive Features in PCOS

The impact of obesity on both the reproductive and metabolic features of PCOS has been previously reviewed [14]. There is a clear impact of excess adiposity on the reproductive manifestations of PCOS. Very irregular menses, often associated with menorrhagia, is a complication of PCOS and likely represents oligo-ovulation, with lack of regular progestin withdrawal. Women with PCOS who demonstrate "regular" menstrual cycles, however may also be oligo-ovulatory despite the regular menses [15]. Obesity increases the frequency of anovulatory cycles in these women [16]. There is also an association of persistent anovulation, and continuous estrogen exposure, with endometrial hyperplasia due to lack of progestational changes to the endometrium. This may be associated with an increased risk of endometrial cancer [17]. It is unclear if the degree of menstrual irregularity is influenced by the degree of insulin resistance, but it appears to be influenced by obesity.

Both ovulatory and anovulatory infertility is increased in obesity. The majority of the impact on infertility in PCOS is likely mediated through anovulation however. A large epidemiologic study, the Nurses' Health Study, reported that the relative risk of infertility was significantly increased (1.3 fold higher) with BMI >24–32 kg/m^2 and 2.7 fold higher with BMI >32 [18, 19]. Treatments for infertility in the setting of ovulatory dysfunction frequently involve use of ovulation induction agents. There is good evidence that dosing requirements are increased in women with obesity [20]. Using a calculated model to determine those women with PCOS who were most likely to fail to respond to clomiphene citrate in a large population from the Netherlands, BMI in addition to testosterone concentrations, was the lead predictor of failure to respond [21].

Treatment protocols for infertility may include the use of gonadotropin therapy if clomiphene is unsuccessful in inducing ovulation [22]. Gonadotropin dosing requirement is increased in obesity and there is an increased cancellation rate due to failure to produce adequate follicular development in many women with obesity undergoing gonadotropin stimulation [23]. There is some evidence that treatment with IVF may also be less successful in obese women with PCOS. There is evidence of increased requirements for gonadotropins, lower oocyte yield and fertilization rates, as well as high cycle cancellation rates [24]. Whether these findings are related to the presence of increased insulin resistance is unclear, but these data taken in total indicate obesity clearly influences both the need for and the success of fertility treatments in PCOS.

A defining characteristic of PCOS is excess androgen production associated with symptoms such as hirsutism, which may be exacerbated in the presence of obesity [25]. The degree of insulin resistance is correlated with the degree of hyperandrogenism. Obese women with PCOS have more severe insulin resistance, compared to lean PCOS women [11]. The increased insulin resistance may drive abnormal sex steroid production. Sex hormone binding globulin (SHBG) is the major binding globulin for testosterone and suppression of SHBG that is seen in insulin resistant states is associated with increased concentration of circulating free testosterone resulting in a worse clinical picture [26]. Obese women with PCOS have higher free testosterone concentration compare to normal weight women with PCOS. Hirsutism may also be worse, with obesity acting synergistically with the intrinsic endocrine disturbance in PCOS [16].

Obesity's influence is seen early on in reproductive development. Obese pre-pubertal girls demonstrate higher serum androgen concentrations when compared to normal weight pre-pubertal controls [27]. Puberty enhances insulin

resistance in the natural state with a resultant normal increase in serum androgens. In the setting of obesity however, puberty is associated with a two-fold increase in serum testosterone compared with that seen in lean pubertal girls [28, 29].

It is likely that a majority of the detrimental reproductive features of obesity in PCOS are mediated in part by insulin resistance that is exacerbated in obese individuals. Both androgen excess as well as ovulatory dysfunction are worse in the setting of obesity. A summary of the impact of obesity in PCOS is shown in Table 1.

Impact of Obesity on Pregnancy Complications in PCOS

Women with PCOS, particularly those who are obese are at significant risk for complications during pregnancy. Pregnancy itself is an insulin resistant state which may be exaggerated in PCOS. A meta-analysis of pregnancy complications in PCOS found that women with PCOS had a significantly higher rate of gestational diabetes mellitus, pregnancy induced hypertension, preeclampsia and preterm birth [30]. Subsequently an updated meta-analysis, was published in 2011 that confirmed these increased risks with a stronger association with PCOS and hypertensive disorders [31].

A recent cross-sectional study of 257 women with PCOS in Norway looked at the incidence of pregnancy complications in the first trimester in a large cohort of women with PCOS [32•]. Women were classified as PCOS by either NIH [33] or Rotterdam criteria. BMI was higher in those diagnosed by NIH criteria which may represent a more severe phenotype and women diagnosed by NIH criteria were more metabolically and endocrinologically abnormal in this study. BMI was an independent predictor for elevated blood pressure in the first trimester and was also correlated to both fasting and 2 h glucose. There was a high prevalence of gestational diabetes by early screen in the first trimester in these PCOS pregnancies, none of whom had known diabetes before conceiving and normal fasting glucose levels.

Table 1 Impact of obesity on PCOS

Endocrine features
↑estrogen
↑androgens
↓SHBG
Reproductive features
↓clinical pregnancy rates
↑miscarriage
↓decreased live birth rate
↑pregnancy complications
Metabolic features
↑insulin resistance
↑diabetes risk
↑inflammatory markers

Cardiovascular Risk in PCOS and the Impact of Obesity

Whether cardiovascular disease is increased in PCOS is a matter of debate [34]. However there is little disagreement that the individual risk factors of cardiovascular disease may be increased in PCOS, particularly in the setting of obesity. The relative independent contributions of obesity and PCOS to cardiovascular risk are still unclear, but likely mediated via increased insulin resistance. Subclinical measures of cardiovascular risk have been studied in PCOS. A recent systematic review summarized the current state of cardiovascular risk in PCOS [35]. Women with PCOS have elevated triglycerides, low HDL-cholesterol and elevated LDL-cholesterol. Increased carotid intima medial thickness, a known predictor of myocardial infarction and stroke, is increased in women with PCOS which may be mediated in part due to obesity [36]. Coronary artery calcification (CAC) is also a known risk factor for cardiovascular disease. CAC is increased in women with PCOS and exacerbated by obesity [37].

Metabolic syndrome is a constellation of cardiovascular risk factors linked via insulin resistance that is associated with increased cardiovascular risk [38]. In the general population, the presence of metabolic syndrome, in the absence of type 2 diabetes, confers a two-fold greater risk of cardiovascular events and five-fold if there is concurrent diabetes [39, 40]. The increased risk of cardiovascular disease seen in metabolic syndrome may be linked to inflammation associated with increased insulin resistance, as evidenced by markers such as increased hs-CRP [41].

Risk of metabolic syndrome may be increased in women with PCOS compared to healthy controls, with reported incidences ranging from 43 % to 47 % [42–44]. Inflammatory markers are linked to increased risk of metabolic syndrome in PCOS, factors that are likely linked to both obesity and insulin resistance [45].

Increased prevalence of metabolic syndrome has also been demonstrated in some studies in adolescents diagnosed with PCOS. A study of adolescent women with PCOS demonstrated a 37 % incidence of metabolic syndrome, which was higher that than reported in a national sample of obese adolescents [46]. Overall diagnosis of PCOS was associated with a four-fold greater risk of metabolic syndrome. However metabolic syndrome may not be independent of obesity in PCOS as other studies did not demonstrate differences when compared to obese non-PCOS adolescents. When compared to a control group matched closely for weight and BMI, PCOS did not seem to infer additional risk independent of obesity [47, 48]. Overall while there is a paucity of data linking PCOS and cardiovascular mortality, the risk factors for cardiovascular disease appear to be increased, beginning in early adolescence in PCOS, and increased in the setting of obesity.

Insulin Resistance in PCOS

Insulin resistance was first identified in women with PCOS in the 1980s [49]. It is felt to be a common but not universal phenotype in PCOS. Hepatic insulin resistance is seen only in women with PCOS who are obese, suggesting there is a synergy between PCOS and obesity with respect to insulin resistance [50]. Pancreatic β-cell dysfunction is seen in those individuals with other type 2 diabetes risk factors and predisposes to development of diabetes [51].

There is some evidence that women with androgen excess may have increased upper body fat (android obesity) which may predispose to increased rates of hyperinsulinemia and insulin resistance [52]. More recent studies however have challenged the presumption that women with PCOS have increased visceral adiposity [53]. However, there is evidence that adipose tissue in obese women with PCOS may behave differently from women without PCOS. This includes an increase in rates of lipolysis and increased release of free fatty acids, which may predispose to insulin resistance [54].

There is considerable evidence that the hyperinsulinemia, noted in a majority of women with PCOS, contributes to the reproductive and metabolic dysfunction of the condition, but whether insulin resistance is a primary defect in PCOS is not clear. It is possible that the insulin resistance seen in PCOS is a modifying factor rather than causative, given the wide variability in presentations seen. Nonetheless insulin resistance is a potential powerful target for medical management of the syndrome, particularly in the setting of obesity.

Insulin Sensitizing Agents and the Impact on Obesity

While the cornerstone of treatment of obesity should be founded in lifestyle changes in diet and exercise, there are low success rates in achieving and maintaining weight loss. Therefore drug therapy may offer additional benefits to achieving weight reduction [55]. However the traditional drugs used for weight reduction may not be suitable for women attempting conception as they have not been tested in early pregnancy. Insulin sensitizing agents are not traditional weight loss agents or considered antiobesity drugs. There is some evidence, however, that metformin therapy may contribute to weight reduction. Weight reduction in the metformin arm of the diabetes prevention trial was −2.08 % compared to −0.2 % in the placebo arm [56].

Obesity predisposes individuals to type 2 diabetes mellitus. Fasting hyperinsulinemia in insulin resistant states predates the onset of type 2 diabetes by several years and post-prandial rises in glycemia can be present several years before detection of formal diagnosis of diabetes as evidenced by abnormal 2 h glucose tolerance testing prior to development of fasting hyperglycemia. Women with PCOS and obesity have an increased rate of conversion to type 2 diabetes in a recent [57] long term study with an age-standardized prevalence of 39.3 % at the end of the study. Therefore management of insulin resistance before the onset of diabetes is imperative and has been shown to delay the onset of diabetes [56, 58].

Maintenance of weight loss once achieved is also challenging. In a 7–8 year follow up to the diabetes prevention program where metformin was used open label, the initial weight loss was maintained and at the end of a 10 year assessment, weight reduction was 2 % in the metformin group. This was directly related to metformin continuation [59••]. Additionally serum liver function tests are often elevated in obesity associated with nonalcoholic fatty liver disease (NAFLD). Subjects in the DPP randomized to the metformin arm demonstrated reduction in ALT over the first 2 years of the study but this was directly related to weight loss associated with metformin use [60].

Impact in PCOS

An initial systemic review of the effectiveness of metformin in PCOS did not suggest an impact on weight loss [61]. This meta-analysis however was focused on the use of metformin in ovulation induction in PCOS and did find improvement in ovulatory parameters and menstrual cycles with metformin use. Subsequent large randomized trials however have demonstrated modest weight reduction in the metformin arms of treatment. In the Pregnancy in Polycystic Ovary Syndrome Study (PPCOS) which included randomization to clomiphene, clomiphene plus metformin and metformin alone, the metformin arm demonstrated a significant mean reduction in BMI of −0.6 with the combination group demonstrating a decrease in BMI of −0.5. This is compared to the clomiphene arm which demonstrated a significant net increase in BMI of +0.2. Despite the weight reduction, metformin was not better than placebo in inducing pregnancy [62].

Weight loss has been seen in a number of studies of insulin sensitizers in women with obesity. A systematic review of use of insulin sensitizers in women of reproductive age included 14 randomized placebo controlled trials and included trials with metformin as well as thiazolidinediones. Comparing all randomized placebo controlled metformin studies, an overall BMI reduction of −0.68 was seen (−1.13, −0.24) favoring metformin use. When analyzed by dose of metformin used in the trials, this difference was only significant for the high dose (>1,500 mg) therapy. Studies of short duration (≤ 8 weeks) also did not demonstrate a benefit [63].

A recent randomized, placebo-controlled trial of metformin in women attempting pregnancy in Finland compared the pregnancy rates after 3 months of treatment. The investigators gave 2,000 mg per day to obese women and 1,500 mg to non-obese women. The pregnancy rate was significantly higher in the obese group treated with metformin compared to placebo, although pregnancy rate was not significantly improved in the

non-obese group. The metformin subjects demonstrated a 1.3 kg weight loss over the 3 months study which was not seen in the placebo group. It is not clear if the improvement in pregnancy rates was related in part to the weight reduction [64•]. Overall this suggests that use of metformin in reproductive aged women with obesity and PCOS leads to a significant but modest weight reduction that is influenced by both dose and duration of treatment. This weight reduction may improve pregnancy rates. Weight loss alone in PCOS produces variable phenotypic changes in PCOS but more than 1/3 will have resolution of PCOS phenotype [65].

There are limited trials utilizing thiazolidinedione therapy alone and in comparison to metformin. Overall there was no evidence of a differential in weight loss seen but these comparative trials were small in size with limited power [66–68]. Thiazolidinedione therapy has been shown in non-PCOS populations to contribute to weight gain [69, 70].

What about the impact of insulin sensitizing agents on metabolic complications associated with obesity in women with PCOS? There are few data in women with PCOS alone, but in those at risk for diabetes, metformin was demonstrated to decrease fasting glucose, triglycerides and LDL significantly. Additionally there is improvement in fasting insulin and reduced insulin resistance as well as reduction in risk of type 2 diabetes mellitus. In a meta-analysis of placebo controlled studies of metformin, with a subanalysis of women with PCOS, women with PCOS had a weight reduction on metformin of −5.3 % compared to placebo. These women had a BMI of 33.9 at baseline [71]. Overall metformin improved triglycerides −5.3 % compared to placebo and LDL was reduced 5.6 %.

With respect to impact of metformin on pregnancy complications in women with PCOS, there is little data to support a benefit of metformin use. A randomized, double-blind, multicenter trial in Norway there was no improvement of risk of pre-eclampsia, gestational diabetes in women randomized to metformin [72••]. Metformin did reduce the amount of weight gained during pregnancy but this did not alter birth weight. The findings were not different in women with BMI >30 kg/m^2 as demonstrated in a subgroup analysis, suggesting that obesity alone is not an indication for metformin use in pregnancy in women with PCOS.

Insulin Sensitizing Agents and the Impact on Adolescents with Obesity and PCOS

PCOS is known to present in the perimenarchal time period. Hyperandrogenism is known to be exacerbated in pubertal girls who are obese [27]. Obese girls with hyperandrogenism are very likely to be at risk for development of PCOS, although long-term studies of this have not been reported. Adolescence is a time of marked insulin resistance that is exaggerated in obese adolescents. It is likely that this group could be a target for management of insulin resistance with potential for improved long-term health.

Metformin has been studied in obese adolescents with and without PCOS. Metformin for 3 months in obese hyperandrogenic adolescents reduced androgenic response to ACTH [73]. Metformin, in combination with oral contraceptives and lifestyle modification, in another small trial in adolescents with PCOS, did not improve weight reduction compared to placebo but did appear to result in decreased waist circumference [74].

Metformin has been studied more extensively in adolescents with general obesity. In a 2009 systematic review of five randomized controlled trials of metformin in obese children and adolescents suggested that metformin appeared to be efficacious for weight reduction. Overall metformin treatment of at least 6 months duration reduced BMI by 1.42 kg/m^2 [75]. In a subsequent trial using metformin or placebo, in combination with lifestyle modification, was initiated after initial unsuccessful lifestyle intervention for 6 months. There was no significant reduction in BMI in the metformin group compared to placebo although insulin resistance improved. The subjects received 1,000 mg per day of metformin in this study [76•].

In a 12 week study of 1,500 mg of metformin or placebo or comprehensive lifestyle therapy in 203 overweight or obese young women, metformin was not effective in reducing body weight whereas lifestyle modification demonstrated a mean of −4.2 kg in weight reduction [77•].

The impact of metformin may be related to timing of the start as well as the dose. In a 6-month study of children aged 6–12 with severe obesity, children randomized to 2,000 mg of metformin daily reduced weight by −3.38 kg during the placebo controlled phase of the study. The study was then extended in an open label protocol. No additional weight reduction was seen in the metformin group, but a significant reduction in BMI was noted in those previously treated with placebo who were then given metformin [78•]. In a longer 48 week

Table 2 Clinical Impact of Insulin Sensitizers on obese PCOS

Feature	Impact of insulin sensitizer
Weight loss	Consistent weight reduction of 2-3 % with metformin, dose and time dependent
Menstrual frequency	Improved in majority of trials
Ovulation	Improved in majority of trials
Pregnancy	Variable in large trials
Miscarriage	No impact in majority of trials
Pregnancy complications	No impact
Glucose tolerance	Improved
Cardiovascular risk markers	Some evidence of improved lipids, inflammatory markers
Mortality	No data

randomized placebo controlled trial of obese adolescents with obesity, an escalating dose of metformin up to 2,000 mg was used. Metformin use was associated with a significant impact on body weight over a period of 52 weeks with a reduction in BMI of −0.9. The placebo group did not demonstrate a reduction in BMI despite lifestyle advice. The BMI reduction persisted in the metformin group for 12–24 weeks after discontinuation of study drug after which body weight increased toward that in the control group [79]. A summary of the impact of insulin sensitizers in PCOS is shown in Table 2.

Conclusions

PCOS is associated with insulin resistance in the majority of cases with or without obesity but insulin resistance is increased in obese individuals. As obesity is present in a majority of individuals with PCOS, with a significant risk of developing type 2 diabetes mellitus, insulin resistance is a reasonable therapy target in PCOS treatment paradigms. Studied insulin sensitizing agents in PCOS include metformin and thiazolidinediones. As thiazolidinedione therapy has been associated with weight gain as well as other potential cardiovascular risks, the majority of trials of insulin sensitizing therapy in PCOS have focused on the use of metformin. While lifestyle modification is the cornerstone of therapy for obesity related concerns in PCOS, there is overall low compliance with therapy and difficulty with sustaining lifestyle changes over time. There is reasonable evidence that metformin is associated with a sustained and reproducible weight loss in obese individuals. Data specifically in PCOS are limited but are consistent with this finding. Data from the general population are encouraging.

The success of metformin with respect to weight loss may be related to both duration of treatment and the dose, with doses <1,500 mg not demonstrating a significant weight impact. Studies suggest longer duration may be of more benefit but that maximal benefit may be seen by 6 months into therapy. The age of metformin start may also be relevant to its success. Data in children and adolescents with obesity are remarkably consistent for weight reduction and this may be a significant tool in the early management of PCOS in adolescents. There are limited data on metformin's impact on metabolic parameters in PCOS but overall there is significant impact on conversion to type 2 diabetes in the general population as well as improvement in triglycerides and LDL in obese individuals.

Use of any drugs in reproductive aged women has to consider the impact on pregnancy. Although metformin has not been demonstrated to improve pregnancy outcomes in obese women with PCOS, there is a generally good safety profile compared to other insulin sensitizing agents. Overall the role for metformin in obesity in PCOS is evolving but data suggest favorable impact on both weight and metabolic indices. Early treatment in adolescence is intriguing and deserving of further large scale trials in adolescents at risk for PCOS.

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- • Of importance
- •• Of major importance

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