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Lifestyle Choices, Diet, and Insulin Sensitizers in Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is significantly affected by environmental regulators impacting on genetic predisposition. Lifestyle changes can significantly modulate the phenotype of this disease. Diet, exercise, smoking, stress, and other factors adversely affect reproductive outcomes in PCOS. These influences can be modulated by structure change in an individual or group. Lifestyle choices should be discussed in this group of patients. The role of insulin sensitizers, including metformin, has still to be determined in this condition.

Key Words: Lifestyle; PCOS; insulin sensitizer; diet.

Introduction

There is an expanding body of research relating to the role that individual lifestyle choices play in successful reproduction and polycystic ovary syndrome (PCOS) in particular *(1)*. Lifestyle modification may often assist couples to conceive spontaneously or optimize their chances of conception with medical treatment while reducing the risk of well-known complications of PCOS.

Lifestyle Factors Affecting Reproduction and Health

Age

The average age of childbearing has increased over the past three decades largely for social reasons. The adverse effects of female aging on fertility are well documented and become clinically relevant at approx 35 yr of age *(2–4)*. Women undergoing assisted reproductive technology treatment also demonstrate a decline in pregnancy rate with increasing age *(3,5,6)* as well as an increased risk of spontaneous abortion *(7)*. The age-associated decline in fertility is associated largely with abnormalities of the oocyte *(8,9)*.

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Women with PCOS may actually develop more regular periods as they get older because of the extra oocytes they possess. Whether fertility improves or not is hard to determine with the current data. However, women with PCOS should be counselled regarding available alternatives and the chance of success in relation to their age, so that they can make informed decisions.

Weight (Table 1)

Weight gain and obesity are becoming increasingly prevalent in Western society and are partially attributable to lack of exercise and inappropriate diet. It is well documented that being overweight or underweight can adversely affect reproductive function *(1,10,11)*. A BMI of ≥25 and <20 kg/m^2 in women is associated with a reduction in fecundity *(12–14)*. The effect of weight on the prevalence of diabetes mellitus, cardiovascular disease, musculoskeletal problems, and other associated conditions is well known. Women with PCOS are more likely to be obese and therefore at greater risk of weight-related disorders. With regard to reproduction, Rich-Edwards et al. *(11)* found an increased risk of ovulatory infertility for women with a BMI < 20 or >24 kg/m^2. Another study found a significantly increased time to conception for women with a BMI of >25 kg/m^2 *(13)* and a large study of women from five countries *(15)* also found a negative association with increased BMI and the time taken to conceive.

Weight also affects the outcomes of assisted-reproduction cycles *(16)* with the fecundity of a very obese group being half that of the normal BMI group. High BMI has also been associated with an increased risk of early pregnancy loss *(10,17)* as well as other adverse pregnancy outcomes *(18,19)*.

Weight-control programs have the potential to influence fertility and relatively small amounts of weight loss have been shown to be effective in improving reproductive performance *(20–22)*. Increasing physical fitness is a useful and effective means of assisting with weight loss *(23)* and lifestyle-modification programs have utilized this principle to assist women to lose weight and become fitter to improve reproductive functioning *(24)*. Exercise may reduce insulin

Table 1
Effect of Weight on Fecundity

Author	Study	Results	Main findings
Rich-Edwards et al. (2002) *(11)*	Comparison of prospectively collected data for 830 cases of ovulatory infertility & 26,125 pregnancies.	A ∪ shaped association between BMI and risk of ovulatory infertility. Increased risk for BMI <20 and >24. Increase in vigorous activity was associated with a lower relative risk—after adjusting for BMI 5% (95% CI: 2–8%) reduction in RR per hour of weekly activity.	High and low BMI associated with increased risk of ovulatory infertility.
Hassan et al. (2004) *(13)*	Observational study of lifestyle habits of 2112 pregnant women and their partners.	Time to pregnancy was significantly longer if the woman's BMI >25 ($p < 0.001$), the woman or her partner smoked >15 cigarettes/d ($p < 0.001$ and 0.04), the partner drank >20 units of alcohol/wk ($p < 0.001$), coffee and tea consumption >6 cups /d ($p = 0.04$). Couples with >4 negative lifestyle factors—the chance of conception decreased by 60%.	Significant association of weight and other lifestyle factors on time taken to conceive.
Bolumar (2000) *(15)*	Population-based survey of 4035 pregnant women from five countries.	An association between high BMI ≥ 30 and delayed conception (OR 11.54, 95% CI: 3.68–36.15). Also with low BMI < 20 (OR 1.70, 95% CI: 1.01–2.83). (This association was only seen in smokers.)	Significant association between delayed conception and high or low BMI in women smokers.

concentrations because glucose uptake by the peripheral tissues lowers insulin secretion. A reduction in caloric intake may also contribute to lower insulin secretion, and changes in body fat distribution are also beneficial *(25)*. Lifestyle-modification programs, which have included exercise, have been shown to assist women to lose weight and improve reproductive functioning *(24)*. Including exercise in a weight-reduction program improves insulin sensitivity therefore reducing insulin-resistance independent of weight loss *(26)*. Combining weight loss and exercise also assists with maintenance of a healthy lifestyle *(27,28)*, while the combination of weight loss and physical activity may also enhance psychological well-being *(24,29)*. As there is strong evidence that high and low BMI negatively affect female fertility, particularly in PCOS, women attempting to conceive should be advised to maintain a healthy weight.

Smoking (Fig. 1)

Smoking has been associated with adverse effects on fertility. These effects have been demonstrated in both natural and assisted reproduction, but are not widely recognized *(30)*. The constituents of cigarette smoke may affect the follicular microenvironment in the female and alter hormone levels in the luteal phase *(31)*. Cotinine and cadmium have been detected in the follicular fluid of smokers and women whose partners smoke *(31–33)*, while there is strong evidence of adverse effects of smoking and fertility in the general population. A meta-analysis *(34)* of 12 studies found an OR of infertility for smokers compared to non-smokers of 1.6 (95% CI: 1.34–1.91).

Another population-based study *(114)* found that >50% of women who smoked had a delay of conception >12 mo. A prospective study of 430 Danish couples *(35)* reported that 63% of non-smokers and 51.2% of smokers conceived within 6 mo. Munafo et al. *(36)* found an association with current smoking (within the year prior to conception) and an increase in time taken to conceive. Curtis et al. *(37)* also found an association with smoking and reduced fecundability and a systematic review *(38)* of 12 out of 13 studies demonstrated a negative effect of female smoking on conception. Bolumar et al. *(14)* found a significant negative effect on female fecundity that was dose related. Smoking is also associated with increased risk of early miscarriage as well as adverse obstetric and fetal outcomes *(39–41)*. All of these studies indicate that women with PCOS who smoke should cease in order to improve their reproductive outcomes. In addition, there are many health-related problems that arise from smoking that will be minimized by appropriate intervention. The strong evidence of the negative effects of smoking on fertility mandates that women with PCOS attempting pregnancy should be advised and assisted to stop smoking. Given the impact of PCOS on long-term health risks,

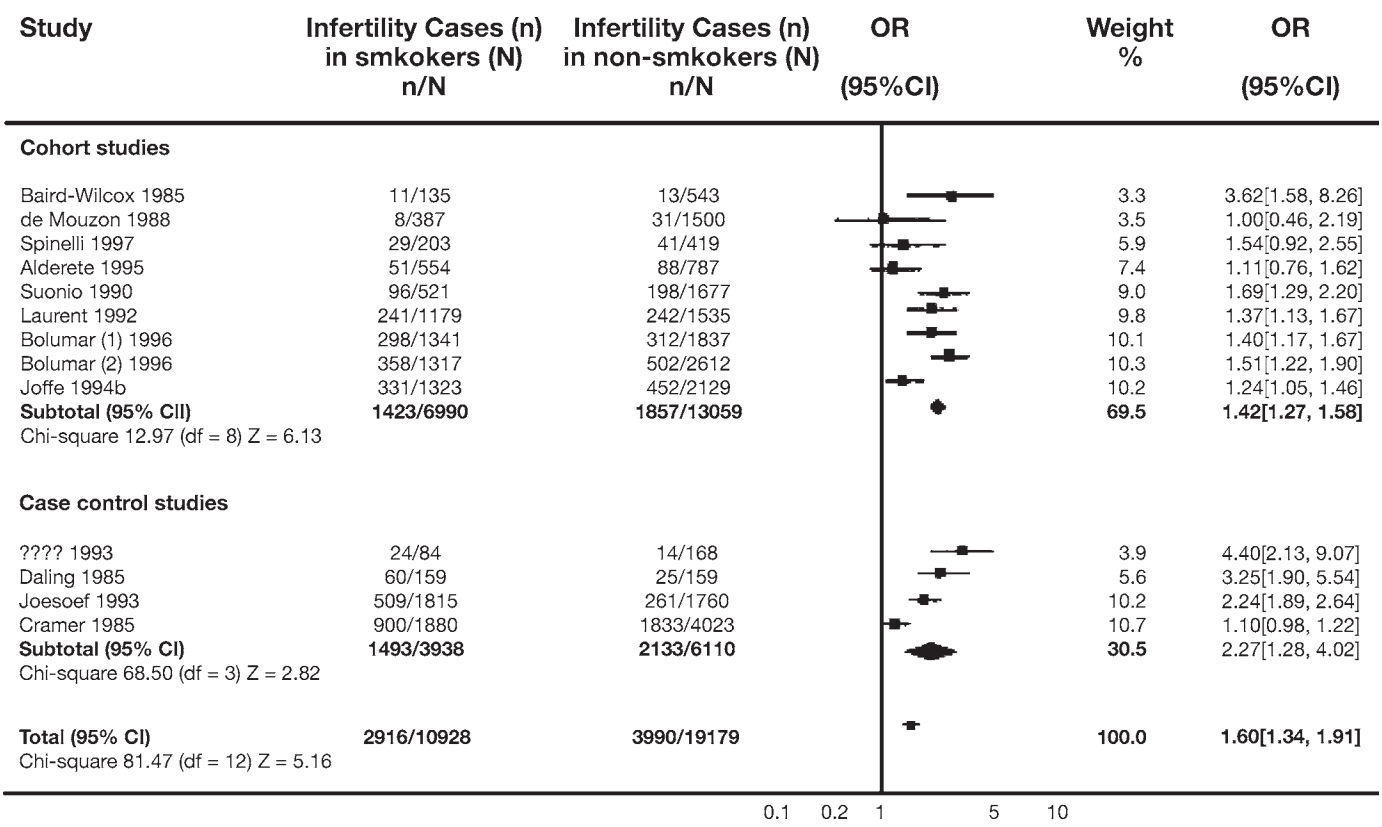

Fig. 1. Meta-analysis of 12 studies of smoking exposure and female infertility. The odds ratio (OR) and 95% confidence interval (CI) for an effect of smoking on fertility are shown on a logarithmic scale.

stopping smoking should be high on the list of priorities for women with this condition.

Psychological Stress

The impact of psychological stress on fertility is unclear although infertility and assisted-reproductive-technology treatment are associated with significant levels of stress *(42–44)*. It is difficult to determine whether psychological stress contributes to infertility or is a symptom of infertility. In addition to this, there is also no consensus as to a definition of psychological stress and the most appropriate way of measuring stress levels *(45)*. Negative effects of psychological stress and fecundity have been found in the general population. A randomized controlled trial of 184 women *(45)* who had been attempting pregnancy for 1–2 yr found significantly higher pregnancy rates in the two intervention groups (55% and 54%) than the control group (20%), indicating that group psychological interventions may be an effective way of improving psychological well being and pregnancy rates. Another study *(46)* of couples attempting to conceive found reduced fecundity in women who were very stressed with long menstrual cycles. A number of studies have shown that stress is associated with poor outcomes on infertility treatment programs and that psychological intervention improves fertility *(47,48)*. A number of studies on quality of life in PCOS have shown that stress is more common in PCOS *(49)* and women with this condition should be assisted to minimize and cope with psychological stress. Indeed some studies *(50)* have shown an improvement in stress-related indices in women undergoing a lifestyle modification program for PCOS.

Caffeine

Caffeine may affect female reproduction by targeting ovulation and corpus luteal function through alterations to hormone levels *(51)* and has been associated with higher early follicular E2 levels in females *(52)*. Although not all studies have found that the consumption of caffeine is a risk factor for subfertility, the majority of evidence indicates that it is associated with reduced fecundity. One large study *(53)* found a significantly increased risk of subfecundity for women drinking >500 mg of caffeine per day. Another study *(54)* found that non-smoking women who consumed >300 mg of caffeine daily had an OR of 2.65 (95% CI: 1.38–5.07) for delayed conception of more than 1 yr. The time taken to conceive was not increased for women who consumed ≤300 mg of caffeine daily. Another large population-based study *(55)* found a statistically significant relationship only among women who smoked and consumed large quantities of caffeine (≥8 cups of coffee per day) (OR 1.35, 95% CI: 1.02–1.48). Wilcox et al.'s *(56)* prospective study of 104 women attempting pregnancy reported that the

probability of becoming pregnant in a menstrual cycle was significantly reduced for women who drank more than one cup of coffee per day. Women who consumed more than one cup of coffee per day were half as likely to become pregnant as those who drank less and the risk increased with higher consumption. Another study *(57)* found a dose-related effect of caffeine consumption and increased time taken to conceive. Compared to women who did not consume caffeine, the consumption of approximately three cups of coffee per day was associated with an OR for delayed conception of 2.24 (95% CI: 1.06–4.73). Several studies have not found an association between caffeine consumption and fecundity *(58,59)*.

There is evidence of an association between caffeine consumption and increased risk of spontaneous abortion *(60–63)*. A meta-analysis *(63)* of the relevant research reported a modest but significant risk of spontaneous abortion and low birth weight associated with moderate to heavy caffeine consumption during pregnancy. However, not all studies have found an association between caffeine consumption and spontaneous abortion *(64)*. Women with PCOS should seek to reduce their input of caffeine to a minimum.

Alcohol (Table 2)

The widespread use of alcohol extends to those people with subfecundity. Alcohol is a teratogen, and there is a body of research on the toxic effects of alcohol and clinical observation and animal experimentation suggesting that alcohol consumption interferes with reproduction *(59,65)*. Moderate levels of alcohol have been associated with reduced fertility and an increased risk of spontaneous abortion *(66)*. Alcohol may also have a direct effect on the maturation of the ovum, ovulation, blastocyst development, and implantation *(67)*.

A study *(68)* of 430 couples attempting to conceive over a 6 mo period found that female and male alcohol consumption of >10 drinks per week during the week of conception was associated with two to five times the adjusted risk of spontaneous abortion than non-drinkers. Another study *(60)* reported that the consumption of five or more units of alcohol per week was associated with a significantly increased risk of spontaneous abortion (OR 4.84, 95% CI: 2.87–8.16). Shu et al. *(69)* reported that first trimester alcohol consumption (averaging four drinks per week) was associated with a reduction in fetal growth. This observation was stronger in smokers. The results of another large study *(70)* suggested a decrease in birth weight associated with maternal drinking during pregnancy, especially in women who smoked.

Most reports have found alcohol consumption to adversely affect fecundity, although the levels of consumption that may be associated with risk are unclear. There is also conflicting evidence indicating that outcomes of ART may be affected by the amount of alcohol consumed by the woman undergoing IVF procedures. As there is strong evidence linking high levels of alcohol consumption with adverse effects on pregnancy outcome and some evidence of adverse effects on fecundity, it would seem appropriate to advise couples where the woman has PCOS is attempting to conceive against alcohol consumption particularly at high levels.

Alcohol is also a potent calorigenic agent and its use increases the problems faced by women trying to control their weight. Overall, alcohol use should be avoided or reduced where possible in women with PCOS.

Environmental Pollutants

Decreased fertility has been associated with occupational exposure to chemicals and pollutants. This is not surprising as environmental and lifestyle factors are said to be key factors in human disease such as cancers *(71)*. There have been reports suggesting that exposure to pesticides, cosmetics, and chemicals within the home and workplace have been associated with infertility *(72)*. An increased risk of intrauterine growth retardation has been associated with the use of video display terminals *(73)*. However, the overall results of studies in relation to risks associated with this type of exposure during pregnancy have been inconsistent.

There is strong evidence of an adverse effect of some pollutants and chemicals on human reproduction and of an association with exposure to other environmental factors. Couples where the female has PCOS and is attempting pregnancy should be individually counselled regarding any potentially harmful exposures.

Diet

An association between maternal nutritional status and adverse pregnancy outcomes has been demonstrated *(74–77)*. However, although early pregnancy is a vulnerable period for embryo and fetal development, the effect of the women's nutritional status prior to pregnancy has rarely been studied *(78,79)*. The environment at the time of conception can impact on the developing embryo and subsequent long-term health of the child *(78)* and it would therefore seem reasonable to assume that fecundity is positively influenced by the consumption of a healthy varied diet. Women with PCOS may have appetite problems whereby they are less satiated after a meal *(80)* and tend to obesity. Adequate dietary advice would therefore be appropriate for women with PCOS attempting pregnancy or concerned about long-term side-effects.

Exercise

The overall physical, emotional, and increased general well-being benefits of being physically fit are well documented *(81–85)*. Kull *(82)* found that even low levels of physical activity positively related to women's mental health and well being. It is therefore reasonable to assume that a moderate level of physical fitness would be beneficial to reproductive functioning. However, there is a need for further research regarding the effects that moderate levels of

Table 2
Effect of Alcohol Consumption on Fecundity

Author	Study	Results	Main findings
Hakim (1998) *(59)*	Prospective observational study of 124 healthy women—followed for 2 yr. (Daily diary, urine specimens, monthly interviews.)	During a menstrual cycle when more than one alcoholic beverage was consumed—conception rate 10.6% compared with 17.6% when no alcohol consumed.	Association with the consumption of alcohol at any level and reduced incidence of conception.
Jensen (1998) *(115)*	Prospective study of 430 couples—followed for 6 cycles. (Initial and monthly lifestyle questionnaire. Daily diary kept, monthly S/A.)	Fecundability OR decreased with increased alcohol intake for women. Consumption of 1–5 drinks/wk OR 0.61 (95% CI: 0.40–0.93). Consumption of 11–15 drinks/wk OR 0.34 (95% CI: 0.22–0.52). No affect of alcohol consumption on male fecundity.	Alcohol intake in women (not men) associated with reduced fecund ability.
Eggert (2004) *(67)*	Prospective study of 7393 healthy women. (Tracked for 18 yr for number of hospitalizations.)	High alcohol consumers (>140 gm/wk) at increased risk of infertility examinations RR 1.59 (95% CI: 1.09–2.31). (Limitations—data on alcohol consumption only collected once, data not adjusted for confounders.)	An association with high alcohol consumption and infertility.
Juhl (2003) *(116)*	Telephone interview of 29,884 pregnant women.	Wine drinkers had slightly shorter waiting time to pregnancy than non-wine drinkers. A higher proportion of women waited >12 mo to conceive among those with the highest alcohol intake; 18% of women drinking an average of >7 drinks/wk took >12 mo to conceive in comparison with 16% in the no alcohol group.	Suggested that wine drinking may have a positive effect on conception.
Olsen (1997) *(117)*	Population-based random sample of women + women ≥20 wk pregnant (>4000 in each group). Interviews.	No strong association between alcohol intake and subfecundity. Some association between alcohol consumption of >8 drinks/wk.	No association between low-level intake of alcohol and subfecundity.
Juhl (2001) *(118)*	Retrospective study of self reported data from 39,612 pregnant women.	A small association between high intake of alcohol per week (>14 drinks) and longer waiting time to pregnancy for parous women. Subfecundity OR 1.3. (95% CI: 1.0–1.7). No effect for nulliparous women with high to moderate intake compared to low intake. Women consuming no alcohol had a slightly longer waiting time. OR 1.2 (95% CI: 1.1–1.3)	No significant association of alcohol consumption and reduced time taken to conceive.

physical fitness may have on fecundity. Exercise in PCOS would be expected to reduce stress, increase burning of calories and improve weight control.

Recreational Drugs

Recreational drugs such as marijuana, cocaine, barbiturates, and heroin can impact on female and male fertility. Marijuana is used by many young adults *(86,87)* and should therefore be considered when consulting couples attempting conception. The effect of marijuana on human reproduction is uncertain as the published evidence is small and inconsistent *(88)*. One study *(89)* found that women who smoked marijuana had a slightly increased risk for infertility due to an ovulatory abnormality (RR = 1.7, 95% CI:

1.0–3.0). Another study *(90)* reported that the average time taken to conceive was significantly shorter for women who had used marijuana regularly and for women who had ever used cocaine than for women who had never used these drugs.

Although the evidence of taking marijuana in relation to human reproduction is unclear, couples with PCOS in the woman attempting to conceive should be advised of the possibility of adverse effects on reproduction as well as in relation to their general health and well being.

Summary of Lifestyle Modification

There is abundant evidence that lifestyle impacts on fecundity and long-term health and disease and most lifestyle factors are modifiable. It is strongly recommended that couples with PCOS attempting to conceive should be counselled and advised regarding their lifestyle choices. A structured program of education, support, and access to specialist health professionals should back counselling to encourage and facilitate appropriate lifestyle changes.

Diet and PCOS

A low fat, moderate protein, and high carbohydrate intake diet (30:15:55%) with a restricted caloric input is the standard recommended diet in most countries. Concomitant exercise is essential for weight maintenance and contributes to reducing stress and improves the sense of well-being. Weight loss is maintained more effectively and compliance is increased when an *ad libitum* low-fat high-carbohydrate dietary pattern is followed over longer periods of time, compared to fixed-energy diets. There has also been increased community interest in a dietary protocol advocating a moderate increase in protein (to approx 30% of total energy intake) and concomitant reduction in dietary carbohydrates. Furthermore, altering the type of carbohydrate to produce a lower glycemic response (low glycemic index or low GI) is also proposed to improve satiety and metabolic parameters.

High-protein diets range from the medically acceptable 30% protein, 40% carbohydrate, 30% fat to the Atkins-type diet, which is much higher in protein (50%) and is high in fat. High-protein diets are more likely to reduce *ad libitum* intake, increase subjective satiety, and decrease hunger compared to high-carbohydrate diets. Weight loss may be more substantial in the short term, but is no better in other diets in the longer term. The evidence for improved insulin sensitivity with high-protein diets is debatable and metabolic improvements are not better in PCOS when caloric intake is matched for low-protein diets *(80)*. Indeed there is some concern that metabolic changes and cardiovascular risk may increase with high-protein diets, particularly with large amounts of red meat. Overall it appears as if dietary composition is not a key component of diets for PCOS provided caloric intake is reduced substantially. Ultimately, weight loss will result from a decrease in energy intake or increase in energy expenditure and this should be the key approach.

The potentially detrimental effects of a high-carbohydrate diet might also be minimized through modifying the source of the dietary carbohydrate, achieved practically through changing the glycemic index of the carbohydrate. The glycemic index (GI) is a classification index of carbohydrate foods based on postprandial glucose response and is defined as the incremental area under the blood glucose curve produced by a standard amount of carbohydrates in a food relative to the incremental area produced by the same amount of carbohydrate from a standard source. Claims have been made that low GI foods reduce postprandial insulin demand and thereby reduce hyperinsulinemia. There are no studies on the role of GI and diets for women with PCOS.

Dietary Intervention and Insulin-Sensitising Agents

Given the key etiological role of insulin resistance in some subsets of PCOS, the use of insulin-sensitizing agents is a logical treatment strategy in PCOS. This may be particularly relevant where non-pharmacological approaches to reducing insulin resistance are unsuccessful or not feasible, for example, in women with PCOS who are lean but insulin resistant. Insulin sensitizers commonly used in the treatment of PCOS are metformin (a biguanide) and rosiglitazone and pioglitazone (thiazolidinediones). Metformin lowers blood glucose levels primarily by reducing hepatic glucose production, while the thiazolidinediones improve the peripheral action and utilization of insulin *(91,92)*. There may also be a direct role for thiazolidinediones in regulation of ovarian steroidogenesis *(93)*, while it is unclear whether metformin directly inhibits ovarian steroidogenesis *(94–96)*.

Use of insulin sensitizers reduces both the complications of hyperinsulinemia and hyperandrogenemia in PCOS. Metformin (at doses ranging from 500 to 2500 mg/d) reduces insulin resistance, hyperinsulinemia, and hyperandrogenism in PCOS *(97)* and may also improve lipid profiles, endothelial function *(98)*, inflammatory state *(99)*, and reduce gestational diabetes *(100)*. Improvements in fertility outcomes including menstrual cyclicity, ovulation rates, and pregnancy have also been shown with use of metformin alone or with clomiphene citrate *(101)* and in non-overweight adolescents with PCOS *(102)*.

There has been some suggestion that metformin may lead to weight loss *(103)*, although a previous meta-analysis of the existing studies did not observe this *(101)*.

It is also unclear whether metformin confers additional benefits to dietary therapy. In a randomized controlled trial of diet with or without metformin (850 mg twice daily) in PCOS, dietary therapy in addition to metformin use resulted in a greater loss of weight and reduction in visceral

fat, weight circumference, and testosterone, although there were no significant differences in the reduction in fasting insulin between the groups *(97)*. In comparison, significant weight reductions occurred for both lifestyle treatment and lifestyle treatment with metformin (850 mg twice daily) (6.8 ± 3.8 kg vs 8.9 ± 2.9 kg). While significant reductions in androgens occurred only for the combination of metformin and dietary advice, ovulation rates were not different between the treatment groups *(104)*.

Troglitazone was the first thiazolidinedione used in treatment of PCOS (removed from clinical use due to hepatotoxicity) and was associated with decreases in insulin sensitivity and improvements in hyperandrogenism and ovulation rate *(105,106)*. Rosiglitazone and pioglitazone use improves insulin sensitivity *(107)* despite commonly observed increases in weight and BMI *(108)*. Reductions in androgen levels (through decreases in testosterone, androstenedione, and DHEA and increases in SHBG) and improvements in insulin sensitivity and ovulation rate in isolation *(108,109)* or in combination with clomiphene *(110,111)* have also been reported.

It is unclear as to whether one treatment is more effective than the other for obese or lean women or insulin-resistant or insulin-sensitive women with PCOS. In studies comparing the use of metformin or rosiglitazone in PCOS, equivalent improvements in insulin sensitivity and menstrual cyclicity were observed in lean women with PCOS. However, reductions in serum androgens were only observed for the rosiglitazone-treated group *(112)*. Conversely, hyperandrogenism was improved equally in lean insulin-sensitive women with PCOS treated with metformin or rosiglitazone, while greater improvements in ovulation rates and insulin sensitivity were observed for metformin treatment *(113)*.

We propose that metformin should be the first medication prescribed after lifestyle intervention. It is inexpensive, relatively free of side effects, and effective. Rosiglitazone and proglitazone tend to increase weight and have less safety features than metformin.

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