

# Polycystic Ovary Syndrome: Insulin Resistance, Infertility, and Treatment

Tricia D. Atkinson

Weber State University

My capstone project is a literature review on polycystic ovary syndrome (PCOS) specifically addressing insulin resistance and infertility, two main issues affecting women with PCOS. My areas of emphasis for my degree are Nutrition, Health Sciences, and Health Promotion. Nutrition and Health Sciences, and in a small part Health Promotion, are integrated in my literature review paper. Health Promotion has been highlighted in my creation of a Facebook page title: Living with PCOS. The Facebook page contains information on the symptoms, possible causes, treatments, definition and diagnosing of PCOS as well as my own experience in dealing with PCOS and is a place for other women with PCOS to discuss their experiences.

, -./0/12\$0&-3)4/&1/#\*4-5 (#####8&  
&

Polycystic ovary syndrome (PCOS) was first identified in 1935 by Drs. Irving Stein and Michael Leventhal, two

, -. /0/12\$0&-3)4/&1/#\*4-5 (%%9&  
&

of metabolic cardiovascular syndrome; abdominal obesity, insulin resistance, dyslipidemia and atherosclerosis (Cemil, Cengiz, & Satiroglu, 2009).

Current diagnosing of PCOS follows the Rotterdam criteria cosponsored by the European Society for Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM). In order for PCOS to be diagnosed, at least two of the following must be present: elevated levels of androgenic hormones, enlarged ovaries containing at least 12 follicles each, and irregular or absent ovulation (Ardabili, Garagari, & Farzadi, 2012). Hyperandrogenism can be clinically diagnosed if the patient displays amenorrhea, hirsutism, acne, androgenic alopecia, and virilization

, -./0/12\$0&-3)4/&1/#\*4-5 (.....&  
&

present in the macro-environment but also in the microenvironment within the ovary. Insulin

(Harrison, Stepto, Hutchinson, & Teede, 2012, p. 351). Other suspected causes for the prevalence of insulin resistance in women with PCOS are, peripheral target tissue resistance, reduced hepatic clearance or increased pancreatic sensitivity (Farshchi, Rane, Love, & Kennedy, 2007).

Many women with PCOS have difficulty losing weight due to the metabolic symptoms and as a result are often over-weight or obese, specifically in the abdominal area. Excess weight is a “major contributor to insulin resistance and exacerbates metabolic and cardiovascular abnormalities in women with PCOS” (Paulil, Raja-Khan, Wu, & Legro, 2011, p.1450). Obesity has significant effects on characteristics of PCOS such as menstrual irregularities tend to be more severe in the obese, androgen levels are higher making hirsutism more severe, and can cause acanthosis nigricans, a condition when certain areas of the skin become darker, thicker, and may smell bad. Overall, fertility is decreased and the rate of spontaneous abortion increases in women who are obese with PCOS (Farshchi, Rane, Love, & Kennedy, 2007). Insulin resistance is commonly thought to only occur in those that are overweight or obese, but it has been found in lean women as well (Paulil, Raja-Khan, Wu, & Legro, 2011). Many women with PCOS are obese or have fat distribution around the abdomen which can be viewed as adipose tissue dysfunction and this contributes to the metabolic abnormalities seen with PCOS (Marino et al, 2012). Adipose tissue of obese people have pro-

, -./0/12\$0&-3)4/&1/#\*4-5 (#####<&  
&

, -./0/12\$0&-3)4/&1/#\*4-5 (#####=&  
&



, -./0/12\$0&-3)4/&1/#\*4-5 ())>&  
&

Therefore, it is of the utmost importance to treat IR to avoid or decrease the aforementioned risks. Treatment options for IR are lifestyle changes, particularly adequate intake of certain vitamins and minerals, and medications such as metformin. Exercise, diet, and insulin sensitizing drugs have proved to be effective in reducing insulin resistance.

Metformin is the first line drug of choice for treating IR in women with PCOS (





androgen production and decreases SHBG in the liver. This then leads to increased free androgens, premature breakdown of ovarian follicles, and anovulation (Misso et al, 2012).

Women with PCOS have increased risk factors in pregnancy. They are at an increased risk for miscarriage, gestational diabetes, hypertension, preterm delivery, and perinatal morbidity and mortality (Paulil, Raja-Khan, Wu, & Legro, 2011). Some of these risks are attributed to the altered physiology of the endometrium which can lead to miscarriage and implantation failure (Paulil, Raja-Khan, Wu, & Legro, 2011). Like insulin resistance, lifestyle change is the first-line treatment for managing infertility caused by anovulation particularly for PCOS women that are obese (Costello et al, 2012).

Treatment for women with PCOS experiencing infertility starts first with lifestyle changes such as decreasing BMI, improved diet, and increasing exercise especially if the woman is obese. Aubuchon & Legro (2011) said, "Pre-conceptual weight loss of 5% to 10% is often recommended as first-line therapy to promote ovulation and conception and improve obstetric outcomes for overweight and obese women with PCOS" (p. 677). Pharmaceutical therapy such as clomiphene and metformin are not recommended until lifestyle therapy has been tried and infertility persists (Costello et al, 2012). The optimal medical therapy is one of the more controversial areas in managing the infertility of those with PCOS, and clomiphene citrate and metformin are the most commonly prescribed by health practitioners. There is great debate on which one is more effective in terms of desired outcomes, side effects, and individual situations such as clomiphene citrate resistance (Misso et al, 2012). Metformin and clomiphene are used as second-line therapy, although metformin is often added with lifestyle changes since some research has shown it aids in weight-loss. Metformin is recommended by some as an alternate

first-line therapy for infertility, but studies are conflicted on live birth rates especially when compared to clomiphene citrate (Paulil, Raja-Khan, Wu, & Legro, 2011).

As mentioned metformin is an insulin-sensitizing drug used for type 2 diabetes and glucose intolerance, but is commonly prescribed off-label for ovulation induction, first reported such use was in 1994, in women with PCOS (Aubuchon & Legro, 2011). Metformin decreases circulating androgens, decreases insulin, increases sex hormone binding globulin, and has potential direct effects on the ovary (Aubuchon & Legro, 2011). The common side effect associated with metformin, gastrointestinal upset, can be improved with extended release formulations. Metformin should not be prescribed for those patients with renal or hepatic impairment to avoid lactic acidosis (Aubuchon & Legro, 2011). Usual dosing prescribed starts at 500 mg per day and increases every week until a maximum dose of 1500 to 2000 mg per day is reached (Aubuchon & Legro, 2011). An advantage of metformin over clomiphene is multiple pregnancy rates are not increased. Although ovulation and clinical pregnancies are increased several randomized controlled trials (RCT) have shown it does



, -./0/12\$0&-3)4/&1/#\*4-5 (#####6: &  
&

, -./0/12\$0&-3)4/&1/#\*4-5 ( ; &

need to follow the infants for three years before ruling out congenital defects due to AIs. Initial results have revealed,

The authors concluded that there was no difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments. However, it appears that congenital cardiac anomalies may be less frequent in the letrozole group (Legro et al, 2012, p. 471).

Thiazolidinediones are alternative insulin sensitizers, are commonly used for treatment of type 2 diabetes, and include drugs such as pioglitazone and rosiglitazone. They are not commonly used for ovulation induction due to their unproven benefits for infertility and associated side effects of weight gain, less favorable pregnancy rates, and possible cardiovascular risk (Aubuchon & Legro, 2011).

.

More aggressive methods for treating infertility are laparoscopic ovarian drilling and in vitro fertilization (IVF). These surgeries are -0.2 p6(i) 0.2 (4cm BT 508.2 ( ova) 0.2 (ri) 0.2 (a)m B41.2 (m) 0



, -./0/12\$0&-3)4/&1/#\*4-5 (%%6<&  
&

thought to aid ovulation by decreasing ovarian androgens and make a favorable pituitary  
gonadotropin response (

, -./0/12\$0&-3)4/&1/#\*4-5 (%%6=&  
&

obese, this may further exacerbate pregnancy complication in addition to PCOS (Aubuchon &  
Legro

, -./0/12\$0&-3)4/&1/#\*4-5 (%%6>&  
&

and fat intake. Many women with PCOS experience carbohydrate cravings and this often causes



general advice is it should have 20 – 30% protein with the other groups decreased to compensate for more calories directed toward protein (Toscani, Mario, Radavelli-Bagatini, Wiltgen, Matos, & Spritzer, 2011). Some concerns of high protein diets are increased body stores of iron which have been associated with an increased risk of developing type 2 diabetes (Farshchi, Rane, Love, & Kennedy, 2007).

Glycemic index is a measurement of how quickly a food affects blood glucose levels compared to consumption of pure glucose. Low glycemic diets are typically prescribed for those with type 2 diabetes to help control their blood sugar levels although they have gained popularity as diets such as the Zone Diet and Nutrisystem. Foods with a high GI deliver glucose quickly after eating. Consuming large amounts of foods with high glycemic loads is related to an increased risk of type 2 diabetes (Farshchi, Rane, Love, & Kennedy, 2007). A low GI diet can be accomplished by consuming whole grains, legumes, and vegetables and some fruits. Examples of food with low glycemic index are oatmeal, peanuts, carrots, kidney beans, skim milk, most vegetables, and most fruits. Benefits that have been found using a low GI diet are improved insulin sensitivity, a lower postprandial insulin response, an increase in HDL, and overall decrease in triglycerides (Farshchi, Rane, Love, & Kennedy, 2007).

A low-

carbohydrate diet is the Atkins diet. Low-carbohydrate diets are usually for short-term weight loss since there are negative effects when carried out past six months such as higher cholesterol due to higher protein being obtained from fatty meats, possible kidney problems from eating too much protein, and ketosis (Farshchi, Rane, Love, & Kennedy, 2007). Benefits observed with a low-carbohydrate diet management in women with PCOS are improved adipokine levels that are closer to normal, improved insulin sensitivity, and an improvement in the cardiovascular risk profile (Farshchi, Rane, Love, & Kennedy, 2007). Gower et al (2013) explained why a low-carbohydrate diet aids in improved insulin and glucose levels by saying a

...reduction in dietary carbohydrate (CHO) would decrease the glucose stimulus to the beta-cell and may thereby reduce the amount of insulin secreted on an acute basis. It is also possible that, on a chronic basis, a lower-CHO diet may reduce beta-cell responsiveness to a fixed glucose stimulus (p. 550).

In their study Gower et al (2013) found, after 16 days of a low-carbohydrate diet, that subjects had a lower fasting insulin concentration and a lower acute insulin response to glucose when compared to other diets. After eight weeks studying two different diets, one at 41% carbohydrates and the second at 55%, the lower-carbohydrate diet resulted in decreased fasting glucose, decreased fasting insulin, decreased levels of testosterone, and an improvement in insulin resistance. They concluded a low-carbohydrate diet may have numerous benefits on the metabolic and reproductive health of women with PCOS (Gower et al, 2013).

A reduction in overall fat intake, specifically saturated fat, has been studied and shown to have benefits as well for those with PCOS. Fat is the most energy-rich nutrient of the diet with 9

kcal/g compared to protein and carbohydrate at 4 kcal/g. “Furthermore, the body has a virtually infinite capacity to store fat, particularly in hyper-insulinaemic individuals (Farshchi, Rane, Love, & Kennedy, 2007, p. 764). The quality of fatty acids is important and an increased intake of unsaturated fatty acids has been shown to improve insulin sensitivity particularly the longer chain polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil (Farshchi, Rane, Love, & Kennedy, 2007). In a regular diet, fat should be 25-35% of the total calorie content with a maximum of 7% coming from saturated fat. Trans-fats should be avoided as they have been linked with an increased risk of anovulatory infertility (Farshchi, Rane, Love, & Kennedy, 2007). Those with PCOS need to pay particular attention to the fats in their diet since dyslipidemia is an important factor of long-term cardiovascular risk. Most commonly dyslipidemia manifests as low HDL levels and an increase in LDL levels which may contribute to the susceptibility to cardiovascular disease (Farshchi, Rane, Love, & Kennedy, 2007).

Two other diets that may be beneficial to those with PCOS are the My Plate diet and Therapeutic Lifestyle Changes (TLC) diet. Although there is no research with these two diets and PCOS specifically, they have been extensively researched with diabetes and lowering LDL cholesterol levels, two risk factors those with PCOS face. The My Plate diet was developed by the U.S. federal government to aid consumers in making healthier eating choices. The icon, a plate divided into 4 sections with a glass on the side, emphasizes fruit, vegetables, grains, protein, and dairy groups (2014, [www.choosemyplate.gov](http://www.choosemyplate.gov)). The My Plate website is very helpful in determining the daily amounts needed from each food group depending age and gender and has helpful BMI calculators and weight management tools to help a person lose weight. This is

beneficial to those with PCOS in helping to choose healthier foods, how much they should be eating, and what they need to do in order to lose weight. The TLC diet was developed by the National Institutes of Health's National Cholesterol Education Program. It was designed as a regimen to reduce the risk of cardiovascular disease which is one of the higher risk factors a woman with PCOS faces. The key to the TLC diet is to cut back on fat, especially saturated fat. The diet is to be high in soluble fiber, 7% or less of daily calories in saturated fats, and consume no more than 200 milligrams of cholesterol daily. The TLC diet is in high fresh fruits and vegetables, whole grains, low-fat/non-fat dairy products, fish and poultry (Turley & Thompson, 2013).

Specific nutrient deficiencies have been linked to PCOS, specifically



, -./0/12\$0&-3)4/&1/#\*4-5 (7: &  
&

Spedding, & Buckley, 2012). Foods which contain vitamin D are some varieties of fish, cod liver oil, oysters, caviar,



no studies to show a difference or similarity between lean and obese women with PCOS and vitamin D (Thomson, Spedding, & Buckley, 2012). More studies are needed in order to establish what exactly is needed from vitamin D in improving symptoms of women with PCOS.

Two other nutrients linked to insulin resistance are folate and vitamin B<sub>12</sub>. Folate is essential for numerous bodily functions such as creating and repairing DNA, help cell division, and produce red blood cells. It is most well-known for pregnancy and if deficient can cause spina bifida or anencephaly in the fetus which lead to the fortifying of cereals and breads 50 years ago. Common food sources for folate are fruits, vegetables, whole grains, beans, and fortified cereals and breads. Vitamin B<sub>12</sub> is an important vitamin specifically for keeping nerve and blood cells healthy, aids in making DNA, and helps prevent anemia. Food sources for vitamin B<sub>12</sub> are beef liver, clams, fish, meat, poultry, milk, and fortified cereals. Plasma homocysteine (Hcy) is a biomarker of folate deficiency and insulin resistance in women with PCOS is associated with high plasma Hcy (Palomba et al, 2010). In a study by Cemil, Cengiz, & Satiroglu (2009), it was demonstrated that folate and vitamin B<sub>12</sub> treatment improved insulin resistance in patients with metabolic syndrome (Palomba et al, 2010). Another study's results mentioned by Cemil, Cengiz, & Satiroglu (2009), found obesity was associated with lower serum concentrations of vitamin B<sub>12</sub> in PCOS. Although the studies by Cemil, Cengiz, & Satiroglu (2009), found a possible correlation between folate, vitamin B<sub>12</sub>, insulin resistance, and PCOS, further studies need to be done.

The essential trace minerals, zinc, manganese, magnesium, and copper, have not been specifically linked to insulin resistance, but have been thought to cause increased oxidative stress in women with PCOS. These minerals have four major functions: 1) stabilizers, 2) elements of structure, 3) essential for hormonal function, and 4) cofactors in enzymes. Food sources for zinc and manganese are seafood, spinach, seeds (pumpkin and squash), nuts, cocoa, bread, and chocolate. Magnesium is found in dark leafy greens, nuts and seeds, fish, beans, and avocados. Copper can be found in seafood, kale, seeds and nuts, and mushrooms. Recent studies have indicated increased oxidative stress in the patients with PCOS (Kurdoglu, Kurdoglu, Demir, & Sahin, 2012). Oxidative stress is an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants. Free radicals can damage cell components and cause disruptions in cellular signaling. Oxidative stress is attributed to many diseases such as Parkinson's and Alzheimer's as well as the development of cancer. High levels of reactive oxygen species (ROS), which are attributed to oxidative stress, are found in women with PCOS (Kurdoglu, Kurdoglu, Demir, & Sahin, 2012). Manganese (Mn) is important in protecting the body against oxidative stress by being a cofactor in MnSOD which neutralizes the highly reactive superoxide ions to less reactive hydrogen peroxide ( $H_2O_2$ ), which is then converted to  $H_2O$ . Zinc is important as a catalytic, structural, and regulatory ion as well as an antioxidant in which it contributes to the structure of the Cu-Zn SOD another component for redox reactions. Copper (Cu) is important in many ways: as a cofactor of many enzymes involved in redox reactions, enzymatic roles, and electron transport within cells. It can also induce oxidative stress by catalyzing the formation of reactive oxygen species and decreasing glutathione (GSH) levels (Kurdoglu, Kurdoglu, Demir, & Sahin, 2012). GSH is an important antioxidant which prevents damage by reactive oxygen species to

cellular components (Wu, Fang, Yang, Lupton, & Turner, 2004). Kurdoglu, Kurdoglu, Demir, & Sahin (2012) found in their study that women with PCOS had higher levels of copper and half the levels of manganese which they attributed to the increased need for MnSOD which is needed as an antioxidant defense due to the higher levels of copper. They also found that copper levels were negatively correlated with BMI in the PCOS group. Chromium is another important essential trace element for teeth and normal body functions, such as the digestive system. It helps to move glucose from the bloodstream to cells to be utilized as energy. It is found in many foods such as brewer's yeast, meats, cheeses, spices, molasses, cereal, fresh fruits and vegetables. Studies involving PCOS and chromium are limited, but there have been several studies with chromium and type 2 diabetes. Some evidence suggests increasing chromium consumption by mouth can lower fasting blood sugar levels, decrease insulin levels, and improve insulin efficiency in those with type 2 diabetes (Johnson, 2013). More research, particularly with those with PCOS, is needed to establish the benefits chromium may have.

## A

Another factor in lifestyle changes is physical activity. Adults who are physically active have numerous health benefits over those adults that live a sedentary lifestyle. Those benefits are: a decreased risk cardiovascular disease, hypertension, lower risk of osteoporosis, type 2 diabetes, colon cancer, and better mental health (Eleftheriadou et al, 2012). In fact a single bout



Healthy People 2020 was released on December 2, 2010 and is a United States government health initiative. The missions of Healthy People 2020, as stated on the [www.healthypeople.gov](http://www.healthypeople.gov) (2014) website, are:

- Identify nationwide health improvement priorities.
- Increase public awareness and understanding of the determinants of health, disease, and disability and the opportunities for progress.
- Provide measurable objectives and goals that are applicable at the national, State, and local levels.
- Engage multiple sectors to take actions to strengthen policies and improve practices that are driven by the best available evidence and knowledge.
- Identify critical research, evaluation, and data collection needs (United States Department of Health and Human Services [USDHHS], 2014).

PCOS is a multi-faceted syndrome affecting millions of women of childbearing age. It represents a significant burden on health care systems due to the many symptoms and risk factors it presents. Just in the United States





Harrison, C. L., Lombard, C. B., Moran, L. J., & Teede, H. J. (2011). Exercise therapy in polycystic ovary syndrome: a systematic review. *Human Reproduction Update*, 17(2), 171-183.

Harrison, C. L., Stepto, N. K., Hutchison, S. K., & Teede, H. J. (

, -./0/12\$0&-3)4/&1/#\*4-5 (.....8: &  
&

Moran, L. J., Ko, H., Misso, M., Marsh, K., Noakes, M., Talbot, M., Frearson, M., Thondan, M., Stepto, N., & Teede, H. J. (2013). Dietary Composition in the Treatment of Polycystic Ovary Syndrome: A Systematic Review to Inform Evidence-Based Guidelines. *Journal of The Academy Of Nutrition & Dietetics*, 113(4), 520-545.

National Institute of Health. (2011). Chromium. Retrieved from:  
<http://www.nlm.nih.gov/medlineplus/druginfo/natural/932.html>

National Institute of Health. (2011). Vitamin D: Fact sheet for health professionals. Retrieved from: <http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>

Paulil, J. M., Raja-Khan, N. N., Wu, X. X., & Legro, R. S. (2011). Current perspectives of insulin resistance and polycystic ovary syndrome. *Diabetic Medicine*, 28(12), 1445-1454.

Palomba, S., Falbo, A., Giallauria, F., Russo, T., Tolino, A., Zullo, F., Colao, A., & Orio, F.

, -./0/12\$0&-3)4/&1/#\*4-5 (