

Polycystic Ovary Syndrome: Insulin Resistance, Infertility, and Treatment

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Capstone Project Description

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.

Introduction

Polycystic ovary syndrome (PCOS) was first identified in 1935 by Drs. Irving Stein and Michael Leventhal, two Chicago gynecologists. PCOS is a common endocrine disorder affecting women of reproductive age. This syndrome is characterized by multiple symptoms including hyperandrogenism, menstrual irregularities, infertility, increased pregnancy complications, insulin resistance, and higher risks of developing type II diabetes, endometrial cancer, and cardiovascular diseases (Kurgdoglu, Kurgdoglu, Demir, & Sahin, 2012). The purpose of this literary review is to focus on the specific symptoms of insulin resistance (IR) and infertility associated with PCOS and the treatments usually given to manage or overcome those symptoms, with a special focus on lifestyle management, specifically diet and exercise.

Symptoms and Risk Factors of PCOS

PCOS is a heterogeneous disorder that is difficult to define due to it not having a singular abnormality or diagnostic test which defines it (Farshchi, Rane, Love, & Kennedy, 2007). It is estimated that 6 - 21%, depending on diagnosing criteria, of women of reproductive age have PCOS (Moran et al, 2013). Symptoms often associated with PCOS are hyperandrogenism; specifically alopecia, hirsutism, and acne, infertility, obesity; especially fat accumulation in the abdomen, insulin resistance, menstrual irregularities, and polycystic ovaries (Wehr et al, 2011). Women with PCOS also experience increased pregnancy complications, increased risk factors for type 2 diabetes mellitus and cardiovascular diseases, and an increased risk of psychological problems such as depression and anxiety (Moran et al, 2013). PCOS also shares most symptoms

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

Diagnosing PCOS

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. Other diseases with similar characteristics, such as androgen-secreting tumors, Cushing's syndrome, and congenital adrenal hyperplasia must be ruled out.

Cause of PCOS

The cause of PCOS is uncertain, but has been linked to changing levels of hormones, potentially linked to abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis (Lucidi, 2013). Women with PCOS experience an imbalance of estrogen, progesterone, and androgens (male hormones) (Vorvick, 2012). High levels of androgen are found in women with PCOS which accounts for many of the symptoms (Wehr, Trummer, Giulianil, Gruber, Pieber, & Obermayer-Pietsch, 2011).

Insulin Resistance in PCOS

Insulin resistance (IR) is a common symptom in women with PCOS and has been shown to be a primary contributor to many of the other symptoms experienced. Paulil, Raja-Khan, Wu, & Legro, (2011) said, "Many studies suggest that the paradox of insulin activity is not only

present in the macro-environment but also in the microenvironment within the ovary. Insulin resistance as the primary defect in the polycystic ovary itself may confer this susceptibility” (p. 1446). This may be the reason PCOS involves multiple organ systems as well (Paulil, Rajakhan, Wu, & Legro, 2011). It is estimated women with PCOS have a 50% to 70% risk of developing insulin resistance (Farat, Mansour, & Attieh, 2011). IR is when an individual’s cells become resistant to the effects of insulin, which leads to an increased amount of insulin released by the pancreas to achieve the proper effects (Lebovitz, 2001). This results in hyperinsulinemia which is the body’s way of compensating for the resistance. In order for the resistant cells to utilize glucose, the pancreas increases production of insulin. Glucose levels may remain normal for many women with PCOS despite insulin resistance because of this compensation of the pancreatic b-cells. If insulin resistance continues untreated, it will eventually lead to the beta cells of the pancreas not able to produce enough insulin and lead to type 2 diabetes mellitus. These two factors (the insulin resistance and hyperinsulinemia) contribute to hyperandrogenism, obesity, as well as the increased risk for glucose intolerance and type 2 diabetes mellitus associated with PCOS (Ardabili, Gargari, & Farzadi, 2012). IR also causes a decrease in sex hormone-binding globulin (SHBG) which then increases free circulating androgen (Paulil, Rajakahn, Wu, & Legro, 2011). This free androgen then exacerbates IR as well as the other characteristics of the disease (Gower et al, 201). Women with PCOS are thought to have intrinsic insulin resistance which differs from obesity-related insulin resistance which is extrinsic (Moran et al, 2013). This may be due to impaired insulin signaling and mitochondrial dysfunction in the skeletal muscle which is the primary site of glucose uptake. These “defects within the skeletal muscle insulin signaling pathways are thought to contribute to PCOS intrinsic IR with post-receptor abnormalities contributing to overall reduced skeletal muscle responsiveness to glucose”

(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).

Insulin Resistance and Obesity

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-inflammatory gene expressions which can lead to chronic inflammation. It is this link between obesity and chronic inflammation that is thought to contribute to insulin resistance in PCOS individuals. These inflammatory mediators appear in fat, liver, and skeletal muscle which results in decreased liver regulation of glucose in the blood and impaired insulin sensitivity in skeletal muscles. Marino et al (2012) went on to state, “In

both lean and obese PCOS patients, circulating markers of low-grade inflammation are elevated, suggesting that inflammation can promote insulin resistance, atherosclerosis, and other pathologies associated with PCOS” (p.2).

Oral Contraceptives and Insulin Resistance

A common approach to treating symptoms of PCOS like hirsutism and irregular or absent menstruation is the use of oral contraceptives (OCP). These can be beneficial for the aforementioned symptoms, but have been found to increase insulin resistance especially progestin-only contraceptives (Haydardedeoglu, Simsek, Kilicdag, & Bagis, 2009). This correlation has been found in women without PCOS who have had long-term use with progestin-only pills and lower insulin sensitivity is commonly found at the beginning of the menstrual cycle when progesterone is high (Haydardedeoglu, Simsek, Kilicdag, & Bagis, 2009). Insulin sensitivity may also deteriorate with regular, low-dose OCPs as well. With this side effect of OCPs, as well as the side effects of increased weight gain and higher risk for cardiovascular events, caution should be used when taking them with PCOS especially those who are obese.

Untreated Insulin Resistance Risk Factors

If left untreated, insulin resistance can cause many problems and complications. Almost one-third to one-half of women with PCOS will develop the metabolic syndrome which is diagnosed by: “hypertension, high triglycerides, decreased high density lipoprotein (HDL), high blood sugar, excess body fat particularly in the abdomen and leads to cardiovascular problems such as atherosclerosis, heart attacks, and strokes, breathing problems such as obstructive sleep apnea and certain forms of cancer” (Farhat, Mansour, & Attieh, 2011, p. 326). The association of PCOS with the anomalies of metabolic syndrome (central obesity, dyslipidemia, hypertension

and glucose intolerance) is responsible for the documented relationship with type 2 diabetes, cardiovascular disease and hormonally-responsive cancers in later life (Farshchi, Rane, Love, & Kennedy, 2007). Another risk of untreated insulin resistance is an increased risk to develop non-alcoholic fatty liver disease (NAFLD) (Paulil, Raja-Khan, Wu, & Legro, 2011). Farshchi, Rane, Love, & Kennedy (2007) stated,

Hyperinsulinaemia (which coincides with insulin resistance) contributes both to increased androgen production in response to LH (*luteinizing hormone that triggers ovulation and is produced in the anterior pituitary gland*) in the ovary and also to the increased levels of free androgen by decreasing SHBG (p. 763).

Another risk factor for untreated insulin resistance is the increased chance of cardiovascular diseases. Even when blood pressure is normal in women with PCOS, insulin resistance and hyperinsulinemia may cause alterations in the vasculature that could lead to hypertension or atherosclerosis later in life. Paulil, Raja-Khan, Wu, & Legro (2007) continued to explain this risk by saying,

Increased arterial stiffness and endothelial dysfunction have been demonstrated in obese women with PCOS compared with weight-matched control subjects. In the same study, insulin resistance and fasting insulin were independent predictors of arterial stiffness and endothelial dysfunction, respectively. In PCOS, hyperinsulinaemia may also lead to structural changes in the vasculature. Women with PCOS older than 45 years have increased carotid intima-media thickness compared with control subjects. In addition, compared with control subjects, coronary artery calcification is more prevalent in women with PCOS and the relationship between PCOS and coronary artery calcification appears to be mediated by insulin (p. 1451).

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.

Treatments for Insulin Resistance

Metformin

Metformin is the first line drug of choice for treating IR in women with PCOS (Paulil, Raja-Khan, Wu, & Legro, 2011). Metformin is in the biguanides class of drugs and is routinely used for diabetes type 2 for its insulin sensitizing effect. It has been safely used for women with PCOS for a variety of conditions and in all ages (Paulil, Raja-Khan, Wu, & Legro, 2011). Severe complications are rare in women with good renal function and without vascular disease. The usual side effects are gastrointestinal upset. There is no known fetal toxicity or teratogenicity and the Food and Drug Administration (FDA) has classified it as a category B drug. Since metformin increases the body's response to insulin, it was a logical approach in treating IR in women with PCOS (Yasmin, Glanville, Barth, & Balen, 2011). Treatment with metformin increases insulin sensitivity and decreases circulating insulin and has beneficial effects on both glucose metabolism and reproductive function (Gower et al, 2013). Studies have shown drug therapy using metformin in PCOS helped by improving menstrual cycles; by increasing ovulation, regularity and time in between cycles, reduced hyperinsulinemia, and hyperandrogenism as well as reducing overall insulin resistance (Yasmin, Glanville, Barth, & Balen, 2011). Some participants in metformin studies experienced weight loss as well which is a crucial part in managing PCOS (Yasmin, Glanville, Barth, & Balen, 2011). Another benefit of metformin is it significantly reduces renin levels in women with PCOS. This is important since

hyperinsulinemia stimulates the renin–angiotensin-aldosterone system which increases renal sodium reabsorption and increases blood pressure. This increased renal sodium reabsorption correlates with increased insulin resistance (Paulil, Raja-Khan, Wu, & Legro, 2007). The typical dosage of metformin starts at 500 mg per day and then increases to 1000 mg after a week and then to 1500 mg by the third week. Increasing the dose gradually helps minimize the usual side effects such as gastrointestinal upset, giving the patient increased tolerance to metformin. Those patients who do not respond at the 1500 mg dose usually will respond at 2000 mg (www.lef.org). In some studies, it has been found that BMI can determine the effectiveness of metformin which could account for the effective dose variations (Yasmin, Glanville, Barth, & Balen, 2011). Metformin should be taken with meals to help avoid gastrointestinal upset. A possible drawback of metformin found in some studies, is it becomes ineffective in inducing insulin sensitivity after a 12 months of administration. Therefore, using metformin alone to manage insulin resistance and other symptoms of PCOS is debatable in long-term management (Haydardedeoglu, Simsek, Kilicdag, & Bagis, 2009).

Rimonabant and Metformin

Metformin in combination with rimonabant has had some initial success. Studies are limited, but the few studies done have shown the following benefits. Rimonabant, also known as Acomplia, Bethin, Monaslim, and Riomont is an anti-obesity drug and its main effect is reduction in appetite. A study mentioned in *Fertility Weekly* (Metformin Aids Weight Loss and Metabolic Parameters Following Rimonabant Therapy, 2009), indicated that rimonabant reduces weight and improves insulin sensitization and reduces free androgens better than metformin alone in obese PCOS patients when treated for a 12-week period. Metformin was not only found

to help maintain the weight loss, but also enhanced the metabolic feature achieved by treatment with rimonabant when compared to six months of metformin alone (Fertility Weekly, 2009).

Thiazolidinedione

Another drug therapy used occasionally to treat insulin resistance is thiazolidinedione, also known as glitazones. This drug is often prescribed for the treatment of type 2 diabetes and works by improving peripheral insulin sensitivity and makes improvements in beta-cell functioning in the pancreas (Paulil, Raja-Khan, Wu, & Legro, 2011). Paulil, Raja-Khan, Wu, & Legro (2011) also stated that an initial multi-center study of troglitazone (a type of thiazolidinedione) showed a decrease in serum testosterone, insulin and glucose levels, and an increase in sex hormone-binding globulin (SHBG) levels and ovulation. Unfortunately, this class of drugs' side effects, as well as their unknown risks on pregnancy, outweigh the benefits. These side effects range from mild such as weight gain, retention of water, muscle pain, and headaches to more severe such as hepatic toxicity with troglitazone, increased cardiovascular events with rosiglitazone, or bladder cancer with pioglitazone (Paulil, Raja-Khan, Wu, & Legro, 2011).

Infertility and PCOS

Another common symptom of PCOS is infertility attributed to irregular cycles and anovulation. PCOS is recognized as the leading cause of anovulatory infertility (Harrison, Lombard, Moran & Teede, 2011). Ovulation does occur in women with PCOS although infrequently. Aubuchon & Legro (2011) found “over the course of 12 weeks, ovulation occurred in 32% of PCOS menstrual cycles with a median time of 67 days to first ovulation...although ovulation frequency increases as PCOS women age, they are less likely to conceive and deliver a baby” (p. 677). Hyperinsulinemia, caused by insulin resistance, causes increased ovarian

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 Options for PCOS Related Infertility

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).

Metformin

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 not improve live-birth rates (Costello et al, 2012).

Clomiphene Citrate

Clomiphene citrate (CC) is a selective estrogen receptor modulator and has been used to induce ovulation since 1967 (Costello et al, 2012). The mechanism of action for clomiphene is it inhibits estrogen at the hypothalamus thus prompting an increase pituitary gonadotropin secretion promoting follicular growth in the ovaries (Aubuchon & Legro, 2011). Studies have shown clomiphene to have 60-85% ovulation success rate and a 30-50% pregnancy rate after six

ovulatory cycles. Common side effects of clomiphene are hot flashes, headaches, mood changes, headaches, visual disturbances (rare), and ovarian hyperstimulation syndrome (OHSS) which is also rare (Aubuchon & Legro, 2011). It is also associated with a 5% – 7% increased chance of multiples, with a 1% chance of being triplets or more (Costello et al, 2012). Other complications of clomiphene are potential thinning of the endometrium, decreased ability for embryo implantation, concern about the long half-life and the effects of accumulated clomiphene, and possible fetal teratogenic effects (Legro et al, 2012). Also, using clomiphene citrate for more than 6 months has been associated with an increased rate of ovarian cancer (Ayaz, Alwan, & Farooq, 2013). The usual dosing schedule of clomiphene citrate is as follows: after a spontaneous or progesterone-induced period, 50 mg daily starts on day 2 to 5 and continues for 5 days. The dose amount increases in 50 mg increments to a maximum daily dose of 150 mg per cycle. This continued for a maximum of six cycles. If ovulation is not achieved at 150 mg daily, the woman is determined to have clomiphene citrate resistance (CCR). If after six cycles ovulation is not achieved, then she is deemed a clomiphene citrate failure (CCF) (Costello et al, 2012).

Metformin and Clomiphene Citrate Combined

“Clomiphene citrate is superior to metformin in PCOS in terms of ovulation, pregnancy, and live-birth rates...” (Costello et al, 2012, p. 401), but when combined with metformin has been shown to improve ovulation rates for those with clomiphene resistance or failure. About 20% of women with PCOS are termed clomiphene resistant and the combination of metformin and clomiphene citrate aids 10% of those women to achieve ovulation. Those that remain clomiphene resistant or failure need to be assisted with more aggressive therapies such as ovarian drilling and in-vitro fertilization (Aubuchon & Legro, 2011).

Gonadotropins

Other pharmaceutical therapies used for ovulation induction are gonadotropins, aromatase inhibitors, and thiazolidinediones. Gonadotropins are injections containing follicle-stimulating hormone (FSH), luteinizing hormone (LH), or both. FSH and LH are needed for egg production and have been in use for ovulation induction since the 1960s (Costello et al, 2012). The usual dosing schedule is started early in the menstrual cycle, with daily injections of one or both hormones for 12 days. Common side effects of gonadotropins are ovarian hyperstimulation syndrome, multiple gestation, ectopic pregnancy, ovarian twisting, possible increased risk of ovarian cancer, and injection site skin irritation. Several studies have found gonadotropins to be successful for those PCOS women that were CCR or CCF (Costello et al, 2012).

Aromatase Inhibitors

Aromatase inhibitors (AIs), letrozole and anastrozole, are used to treat breast and ovarian cancer and as off-label use as ovulation-inducing drugs which started in 2001. Their mechanism of action is to prevent the conversion of androgen to estrogen (Legro et al, 2012). Third generation aromatase inhibitors are given orally. Letrozole is more commonly prescribed to induce ovulation and have been shown to have fewer or less severe side effects than CC although there is some concern regarding possible teratogenic effect (Costello et al, 2012). Studies have been few and more are needed to determine if there is more benefit in prescribing letrozole over clomiphene, at the time there is insufficient evidence (Costello et al, 2012). Side effects noted so far in relation to ovulation induction are gastrointestinal disturbances, asthenia, hot flashes, and back pain. The half-life of AIs is significantly shorter than CC thus reducing the concern over CC metabolite build up (Legro et al, 2012). This specific study mentioned by Legro et al (2012) has shown that AIs improve the endometrial thickness compared to CC and multiple pregnancy seem to occur less frequently as well with AIs. The trial has not finished yet as the researchers

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

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).

Surgical Treatments

Laparoscopic ovarian drilling.

More aggressive methods for treating infertility are laparoscopic ovarian drilling and in vitro fertilization (IVF). These surgeries are reserved until all other therapies have been tried and failed although laparoscopic ovarian drilling will be done when gonadotropin therapy is being considered due to similar hormonal outcome (Aubuchon & Legro, 2011). Ovarian drilling may be more desirable than gonadotropin therapy due to lower incidence of multiple pregnancy and less overall cost since it is equally effective to three to six treatment cycles of gonadotropin therapy (Costello et al, 2012). Laparoscopic ovarian drilling, first described in 1984, is done by drilling small holes by cautery or laser into the ovarian stroma (Costello et al, 2012). This is

thought to aid ovulation by decreasing ovarian androgens and make a favorable pituitary gonadotropin response (Aubuchon & Legro, 2011). Live birth rates were similar to clomiphene-metformin rates therefore using combination therapy may be worthwhile before trying laparoscopic ovarian drilling. Risks for ovarian drilling are postsurgical ovarian adhesions and premature ovarian failure in addition to usual surgery risks (Aubuchon & Legro, 2011).

In Vitro fertilization.

In vitro fertilization (IVF) is after all other treatments have failed or there are other infertility conditions such as tubal damage, severe endometriosis, or male factor infertility (Costello et al, 2012). IVF involves removal of oocytes from the woman and fertilizing them in a laboratory which is then followed by transferring some of the embryos to the woman's uterus. It also requires gonadotropin injections to stimulate the ovaries and additional medications to prevent premature ovulation and to allow for oocyte maturation (Aubuchon & Legro, 2011). Similar side effects are experienced with the gonadotropin and IVF as increased risks of OHSS and multiple pregnancy. Metformin has been shown potentially to reduce the risk of OHSS when combined with IVF. Since the number of embryos transferred is decided by the physician and patient, multiple gestations can be somewhat controlled. PCOS patients have similar outcomes as non-PCOS patients in relation to miscarriages and pregnancy success rates (Aubuchon & Legro, 2011).

Pregnancy Complications for PCOS Women

It is interesting to note that women with PCOS are at a higher risk for gestational diabetes, pregnancy-induced hypertension, preeclampsia, and preterm birth. If the woman is

obese, this may further exacerbate pregnancy complication in addition to PCOS (Aubuchon & Legro, 2011).

Lifestyle Changes as Treatment of Infertility and Insulin Resistance

Lifestyle changes; increasing exercise, decreasing BMI, and improved diet, improve the metabolic, psychological, and reproductive aspects of PCOS (Moran et al, 2013). Lifestyle therapy is the first-line treatment for both insulin resistance and infertility. The typical lifestyle changes recommended are caloric restriction and/or altered diet, and increased physical activity (Harrison, Lombard, Moran, & Teede, 2011). An effective approach to nutrition and exercise, even without marked weight loss, has been shown to improve the endocrine, metabolic, cardio, and reproductive symptoms of the disease (Farshchi, Rane, Love, & Kennedy, 2007). Lifestyle changes are difficult to study due to high drop-out rates and non-compliance of participants. This is often a result of the difficulty morbidly obese women have in adapting significant lifestyle changes. It is also difficult to achieve consistent and accurate study results due to the lack of a clinical infrastructure to implement lifestyle therapy in many settings throughout the U.S.

Current Diet Recommendation for PCOS

There is not a specific diet currently recommended as more effective for women with PCOS although some studies have shown a low glycemic index (GI) diet to be best due to the prevalence of insulin resistance and increased risk for developing diabetes type 2 (Harrison, Lombard, Moran, and Teede, 2011). Regulating appetite is complex and causes fluctuations in blood glucose that may play a part in stimulating appetite and increasing energy intake. Both insulin and blood glucose fluctuate more widely in patients with insulin resistance.

Hypoglycemia has been shown to cause increased feelings of hunger which increases total food

and fat intake. Many women with PCOS experience carbohydrate cravings and this often causes difficulty in losing weight (Farshchi, Rane, Love, & Kennedy, 2007).

Diets Most Likely to Benefit Women with PCOS

Few studies have been done on diet and its direct effects in women with PCOS and many seem to be conflicted on the best approach. Some suggest high protein/low carbohydrate to be the best for women with PCOS due to the high risk of insulin resistance and others believe a diet too high in protein could negatively affect hormone levels. All agree diet management to be very important in managing symptoms and risks of PCOS. It is important and useful to focus on the eating pattern and macronutrient content of the diet initially rather than to promote healthy eating and weight loss too rapidly. Also, it is important to individualize caloric intake per patient instead of an overall caloric need for PCOS women (Farshchi, Rane, Love, & Kennedy, 2007). Since women with PCOS tend to be overweight or obese, energy deficit can be achieved by decreasing caloric intake. Decreasing calories by 200 kcal/day can help prevent weight gain if they are already at a healthy weight and promote weight loss over term. For the average person a calorie deficit of 500 kcal/day is needed to lose 0.5 kg/week and 1,000 kcal/day is needed to lose 1 kg per week (Farshchi, Rane, Love, & Kennedy, 2007). In order to maintain weight loss, 60 minutes of daily, moderate-intensity exercise is needed (Turley & Thompson, 2013). These can be difficult changes and explains why many fail to achieve enough weight loss. It is often thought, although insufficient evidence exists to verify, that women with PCOS have a harder time losing weight than average, healthy women. Due to the insulin resistance and abdominal obesity often associated with PCOS, it is very important for women with PCOS to maintain healthy weights. There are many benefits of modest weight loss although the goal should be to get as close to normal body weight and composition as possible which is why many health

providers are turning more to diet management in recent years (Farshchi, Rane, Love, & Kennedy, 2007). Some diet therapies that are recognized as benefiting women with PCOS are: short-term meal substitution, high protein, low glycemic, moderate carbohydrate, and reducing overall fat intake specifically saturated fats.

Short-term Meal Substitution

Short-term meal substitution is the use of a twice daily meal replacement that is enriched with vitamins and nutrients. These are often effective to “jump start” weight loss, but difficult to continue for long term. Moran et al (2006) found improved reproductive improvements in their study.

High Protein Diet

High protein diets are controversial, but may have some benefits in regards to PCOS. Women with PCOS often complain of low satiety which leads to consuming more calories than actually needed and increased body weight. Recent evidence suggests consuming more protein than normal may increase satiety which may help decrease total caloric intake. High protein diets have been shown in studies to decrease abdominal adipose tissue, lower the risk for type 2 diabetes, improve insulin sensitivity, increase basal metabolism, increase postprandial thermogenesis, and decrease postprandial glucose (Toscani et al, 2011). Another proponent of high protein is to ensure adequate protein to protect lean muscle as well to increase muscle in response to exercise. The diet advocated by public health agencies recommends 15% protein, 55% carbohydrate, and 30% lipid. A low GI diet can be accomplished by consuming whole grains, legumes, vegetables, whole fruits, lean proteins and low-fat, calcium-protein rich foods while minimizing the intake of refined carbohydrates and added sugars. In a high protein diet,

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 Diet

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).

Low or Moderate Carbohydrate Diet

A low-carbohydrate diet is different from a low GI diet in that the diet is restricting all carbohydrates to less than recommended in a normal diet. The Acceptable Macronutrient Distribution Range (AMDR) for carbohydrates is 45-65% of the Calories consumed. On a low-carbohydrate diet, carbohydrate consumption is as low as 5% up to 40%. A popular 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).

Reduction in Overall Fat Intake Diet

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).

My Plate and Therapeutic Lifestyle Changes Diets

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). 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).

Nutrient Deficiencies Linked to PCOS

Vitamin D

Specific nutrient deficiencies have been linked to PCOS, specifically those that cause increasing insulin resistance and fertility issues. Vitamin D deficiency and its causal link in the pathophysiology of PCOS has been a focus of researchers in recent years (Wehr, Trummer, Giulianil, Gruber, Pieber, & Obermayer-Pietsch, 2011). Vitamin D receptors (VDR) are found on many tissues, including pancreatic islet cells, parathyroid glands, and the ovaries (Paulil, Raja-Khan, Wu, & Legro, 2011). The roles of vitamin D, which is a fat-soluble vitamin, are: promotes calcium absorption in the gastrointestinal tract, maintains adequate serum calcium and phosphate concentrations for normal mineralization of bone, is needed for bone growth and bone remodeling, neuromuscular and immune function, and in reducing inflammation. Vitamin D also modulates many gene encoding proteins that regulate cell proliferation, differentiation, and apoptosis (National Institute of Health, 2014). The effects of vitamin D are mediated through genetic and cellular pathways, specifically gene transcription and hormonal pathways (Thomson,

Spedding, & Buckley, 2012). Foods which contain vitamin D are some varieties of fish, cod liver oil, oysters, caviar, fortified juices, cereals, dairy products, and egg yolks. Another way to obtain vitamin D is through the skin by “sunlight-induced photochemical conversion of cholesterol to 7-dehydrocholesterol and subsequently hydroxylation in the liver and kidney” (Thomson, Spedding, & Buckley, 2012, p. 344). Normal serum concentrations of 25-hydroxyvitamin D (25OHD) are greater than or equal to 20 ng/mL. Thomson, Spedding, & Buckley (2012) stated,

Vitamin D deficiency disrupts the function of all the systems of the body and increases the risk of chronic disease, including physical diseases such as cancer, cardiovascular, autoimmune and infectious diseases; and psychological disorders such as depression and chronic pain (p. 343).

Deficiency in vitamin D is common in women affected by PCOS. It is estimated it affects 67-85% of patients with a serum concentration of 25OHD below 20 ng/mL (Thomson, Spedding, & Buckley, 2012). Studies have shown lower levels of 25OHD are associated with increased insulin resistance, ovulation and menstrual irregularities, hirsutism, obesity, cardiovascular disease, hyperandrogenism, and smaller chances of pregnancy success (Thomson, Spedding, & Buckley, 2012). There is increasing evidence supporting that vitamin D has an important role in fertility. Low levels of vitamin D have been found with anovulation and menstrual dysfunction. When vitamin D levels are high, they were associated with successful pregnancies and better menstrual function (Thomson, Spedding, & Buckley, 2012). Vitamin D deficiency has been shown to be associated with calcium deregulation. This deregulation can contribute to follicular arrest in women with PCOS which then causes reproductive problems (Thomson, Spedding, & Buckley, 2012). Paulil, Raja-Khan, Wu, & Legro (2011) stated, “There is some evidence that vitamin D deficiency is related to impaired glucose clearance and insulin secretion in animal and

human models....These findings show the complex effect of vitamin D on human metabolism” (Paulil, Raja-Khan, Wu, & Legro, 2011, p. 126).

Vitamin D and Possible Links to PCOS

The specific mechanism underlying vitamin D and insulin resistance is unknown. Some researchers estimate the biologically active form of vitamin D, 1, 25-dihydroxyvitamin D (1,25OHD), enhances insulin action which then increases insulin receptor expression or suppression of “pro-inflammatory cytokines that are believed to mediate insulin resistance” (Thomson, Spedding, & Buckley, 2012, p. 345). Vitamin D may also be linked to the level of adiposity, not to the level of insulin resistance in a woman with PCOS. Women with PCOS have a higher prevalence of obesity and adipose tissue accumulation around the abdomen and vitamin D is a fat soluble drug, thus much of this population’s deficiency may be attributed to the sequestering of bioavailable vitamin D in the fat tissues. Also, dietary preferences may contribute to vitamin D deficiency as well (Thomson, Spedding, & Buckley, 2012).

Benefits of Vitamin D Supplementation

Some possible benefits that have been found in various studies on increasing vitamin D and its correlation with PCOS are with each unit increase of vitamin D reduced the likelihood of a PCOS diagnosis by 96%, women undergoing IVF treatment who achieved pregnancy had higher follicular fluid levels of 25OHD, and normalization of menstrual cycles (Thomson, Spedding, & Buckley, 2012). Some preliminary studies have also shown to improve symptoms associated with hirsutism, acne, cardiovascular disease, and psychological well-being (Thomson, Spedding, & Buckley, 2012). Many studies are conflicting, some stating that women are too high in vitamin D, while the majority state that specific population it is too low. Also, there have been

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.

Folate and Vitamin B₁₂

Two other nutrients linked to insulin resistance are folate and vitamin B₁₂. 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 B₁₂ is an important vitamin specifically for keeping nerve and blood cells healthy, aids in making DNA, and helps prevent anemia. Food sources for vitamin B₁₂ 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 B₁₂ 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 B₁₂ in PCOS. Although the studies by Cemil, Cengiz, & Satiroglu (2009), found a possible correlation between folate, vitamin B₁₂, insulin resistance, and PCOS, further studies need to be done.

Essential Trace Minerals and PCOS

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.

Physical Activity Benefits and PCOS

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 of moderate physical activity, 20 to 30 minutes long, improves glucose disposal and increases skeletal muscle insulin sensitivity. If continued at least three to five times a week, exercise has been shown in high-risk groups to reduce the risk of type 2 diabetes and “improve cardiovascular risk factors (i.e. weigh, lipid profiles, and blood pressure)”. In addition to aerobic exercise, adding weight training or resistance exercise has been shown to improve health in high-risk

groups as well (Harrison, Lombard, Moran, & Teede, 2011). Therefore, it would follow that women with PCOS would also experience these benefits as well with increased physical activity. In a study conducted by Harrison, Stepto, Hutchinson, & Teede (2012), they found insulin resistance was improved by 16% after exercise. They also found BMI and lowered fitness levels affected those in the PCOS group more than the control group. This led to their conclusion “that modifiable factors are even more important targets for improvement in IR in this highly insulin-resistant group compared to in controls. This further emphasizes the importance of regular physical activity prescription, preferably with a vigorous exercise component for women with PCOS” (p.356). As mentioned before, not all PCOS women are over-weight, but can still be insulin resistant. Studies have shown that even for this group of women some small weight loss, particularly if they increase lean muscle and decrease abdominal obesity, improves their IR and other PCOS symptoms (Farshchi, Rane, Love, & Kennedy, 2007). Although it is often perceived as difficult for those with PCOS to lose weight, regular exercise of at least 40 minutes daily and a healthy diet, may help to change the overall body composition, such as reduced abdominal obesity, and increased insulin sensitivity. Regular exercise may change with an increase in lean body mass and decreased fat mass, but no change in weight. This increase in lean muscle mass raises the resting energy expenditure rate which may help improve hormone and metabolic factors in PCOS women (Farshchi, Rane, Love, & Kennedy, 2007). Overall, achieving moderate success in losing weight, especially abdominal circumference, has been shown to help in dropping testosterone amounts, increasing ovulation, increasing insulin sensitivity, and improving hirsutism.

Healthy People 2020 and Impact of PCOS

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 (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).

Some of the topics of concern listed on the site are: diabetes, heart disease, stroke, nutrition, and weight status. These topics are high risk factors those with PCOS face which can place a significant burden on the public health system. PCOS is under-recognized as a public-health problem due in part to limited research on various aspects of PCOS such as specific nutrition guidelines, no clear cause on what causes PCOS, lack of a pharmaceutical treatment for all of symptoms/causes of PCOS, and lack of public health knowledge. It is important to increase research and awareness among the public: health providers and patients alike, in order to promote health and wellness for women with PCOS and reduce the burden that PCOS-related conditions have on public health.

Conclusion

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, \$4.36 billion was spent on PCOS and related complications in 2004 and over 40% of the money spent was on infertility with another 40% to PCOS-related diabetes (Harrison, Lombard, Moran, & Teede, 2011). Most pharmaceutical interventions are focused on insulin-resistance and reproductive functions and no ideal pharmacological treatment is available other than to treat the symptoms as they occur. Lifestyle modifications, exercise and diet management, are first-line approaches and seem to offer large improving health outcomes for women with PCOS. It is important when considering management approaches to PCOS, to not focus only symptoms, but also on mitigating the long-term cardiovascular and metabolic risks.

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