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# Polycystic Ovarian Syndrome: Causes, Complications, and Treatments

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# Polycystic Ovarian Syndrome: Causes, Complications, and Treatments

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**BMS 399 Independent Study**

**Abstract**

Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder prevalent in 6-10% of reproductive age women. The purpose of this review paper is to describe both genetic and environmental causes and symptoms of PCOS. Additionally, to summarize the complications women face with a PCOS diagnosis and present treatment and management options. The information forming this paper was compiled from various online heath journals. The results show that both clinical and biochemical examinations are used for the diagnosis of PCOS while the exact cause is unknown. Genetics and environmental factors, specifically the intrauterine environment, are discussed as causes. Management and treatment options for PCOS include prescriptions such as oral contraceptives, Clomid and Metformin and diet changes such as a low glycemic index diet.

Key words: polycystic ovarian syndrome, hyperandrogenism, hyperinsulinemia

**Introduction**

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder effecting 6-10% of reproductive aged women. The prevalence of PCOS within Caucasian women varies between 6.6% in America and 6.5% to 6.8% in European countries such as Spain and Greece, respectively. In the United Kingdom, PCOS and type 2 diabetes are more prevalent in Asian women (Dumesic, 2014). These differences in frequency may be due to exposure to different environmental factors such as diet and physical activity (De Leo, 2016). There are three classifications of PCOS that disturb the hypothalamic pituitary adrenal axis. These include women with a standard response to human corticotrophin-releasing hormone (hCRH), women with an overstated response of adrenocorticotropic hormone to hCRH, and women with

increased basal cortisol levels and reduced response to hCRH (Kondoh, 1999). The diagnosis includes both clinical and biochemical examinations. Clinical symptoms are hirsutism, acne, irregular menses and dark pigmentation of the skin, primary around the underarm and behind the knee. Biochemical examinations involve blood tests to analyze androgen levels and pelvic ultrasounds to determine the presence of ovarian cysts (Harwood, 2007).

Complications associated with PCOS include increased risk of insulin resistance resulting in metabolic syndrome and type 2 diabetes, infertility and pregnancy complications; such as, pre-eclampsia, gestational diabetes (GDM), and pre-term and low birth weight neonates (De Leo, 2016).

The present treatment of PCOS is mainly focused on diet therapy and weight maintenance as there is limited research on the outcomes of medication therapy. Oral contraceptives aiming to regulate androgens and follicular development are the most common drug treatment. Other medications used include Clomid to address fertility and Metformin to improve insulin resistance (Sinawat, 2012).

**Objectives**

The purpose of this independent project was to describe genetic and environmental causes and symptoms of PCOS. Additionally, to discuss underlying complications in women with PCOS and present significant regimens for treatment/management.

## Methods

The information found in this paper was gathered from a number of online journals, reports, and websites. All of the peer reviewed journal articles cited in this paper were found from online databases such as PubMed. The websites used for this paper are all nationally and internationally known organizations such as PubMed Central, Journal of Gynecology and Endocrinology, Cochrane Database.

## PCOS Etiology

### *Genetics*

Research over the years have led to the understanding that PCOS has a polygenic pathology rather than an autosomal dominant transmission that is linked to a single genetic defect (De Leo, 2016). There have been no genome-wide screens of PCOS, rather the reported genetic studies involving PCOS use a candidate gene approach. The candidate gene approach has focused on the associations between genetic variation within the gene of interest and phenotype of the disease. The candidate genes for PCOS include proteins used in steroid hormone biosynthesis, gonadotropin secretion, energy regulation, and insulin action. The candidate genes of interest have been compared to PCOS phenotypical changes, including androgen levels and insulin resistance to assess the correlations between the genotypes and phenotypes (Sam, 2003).

Although little is confirmed from candidate gene studies due to small sample sizes, some genome-wide association studies (GWAS) performed in Chinese populations have shown 11 genomic region variants. The GWAS gene variants include: DENND1A, LHCGR, FSHR, THADA, GSHR, C9orf3, YAP1, RAB5B/SUOX, HMGA2, TOX3, INSR, and SUMO1P1.

However, the receptors that have known association with the functionality of PCOS are luteinizing hormone/choriogonadotropin receptor (LHCGR), follicle-stimulating hormone receptor (FSHR), and insulin receptor (INSR). LHCGR/FSH, INSR and TOX3, are linked to phenotypes associated with PCOS; such as, BMI and waist circumference. LCHGR is also thought to be overexpressed and can influence hyperandrogenism, which leads to an excess of LH secretion from adipocytes (Dumesic, 2014). A marker locus on chromosome 19p, which is located near the gene that encodes for the insulin receptor, has shown association with the hyperandrogenic phenotype that is common with PCOS. The PCOS gene of interest is found on chromosome 19p13 (Sam, 2003). The role of the other variant genes in PCOS are presently unknown.

Hyperinsulinemia amplifies the production of androgens through the type 1 IGF receptor in the mutant insulin receptor syndromes. This directly targets the insulin receptor in the brain. However, not all insulin resistant women struggle reproductively and that is where family studies become relevant. These genetic studies suggest that there is a susceptibility to hyperandrogenemia and insulin resistance in women with PCOS. There is evidence for linkage between the locus of the insulin receptor and hyperandrogenemia phenotype (Sam, 2003).

*Obesity and hormonal imbalances*

Women with PCOS have a greater prevalence of obesity, as 40-80% of women diagnosed are considered obese. The distribution of fat in these women is highly concentrated in visceral tissue, which is a source of hunger and inflammatory hormones. The excess hormones can contribute to both additional weight gain and insulin resistance. This then may aggravate the metabolic

complications involved with PCOS such as beta-cell dysfunction and type 2 diabetes as well as fertility, and pregnancy complications associated with PCOS (Sam, 2007).

Although many hormonal imbalances contribute to the diagnosis and etiology of PCOS, leptin specifically appears to play an important role and has been the focus of research. Leptin, a hormone released by gastric, fat and placental tissue, inhibits hunger and maintains energy homeostasis (Ahima, 2000). Leptin levels have been reported to be higher in obese women with PCOS as compared to obese women without PCOS. The reason for the elevated levels is not understood, but obese individuals may be leptin resistant; therefore, hunger is not inhibited, and weight gain may occur. Leptin resistance may also make it more difficult to lose weight. In summary, these higher leptin levels in obese women with PCOS may result in greater weight gain and make it more difficult to lose weight. The exact mechanism of elevated leptin and its role in PCOS patients requires further studies (Baldani, 2019).

Resistance to insulin is highly prevalent in women with PCOS. Fifty to eighty percent of women are reported experiencing this resistance (Bahri Khomani, 2018). Under normal conditions, insulin is released from pancreatic beta cells in response to glucose and facilitates the intracellular transport of glucose. In an insulin resistant (IR) condition, both serum glucose and insulin are not transported intracellular resulting in an elevation of both blood glucose and insulin. IR can directly increase androgen production, indirectly reducing the production of sex hormone-binding globulin. This leads to women having an increased risk of gestational diabetes (Bahri Khomami, 2018).

Adiponectin regulates glucose levels and fatty acid breakdown as well as causes insulin sensitivity. Produced by adipose tissue, decreased levels of adiponectin occur in obesity and have been linked to insulin resistance, metabolic syndrome, type 2 diabetes and cardiovascular disease. Adiponectin is higher in women with PCOS of healthy BMI and lower in overweight/obese women with PCOS. Adiponectin is the most specific hormone when diagnosing PCOS. As high leptin levels and low adiponectin levels are associated with increasing BMI, it is not surprising increased leptin is associated with decreased adiponectin levels (Baldani, 2019).

*Intrauterine environment*

Maternal hormones in the intrauterine environment may play a role in the etiology of PCOS in female offspring due to the stimulation of fetal ovaries. Amniotic fluid plays a large role in the intrauterine environment as it holds nutrients, hormones, and antibodies for the growing fetus. Pre-natal androgen exposure has been suggested as a possible intrauterine cause for PCOS. Hyper-androgen exposure can contribute to adult PCOS phenotype. The origin of the excess androgens within the placenta are unknown because in normal women, maternal androgens are absorbed by the placenta; therefore, do not lead to fetal androgen excess. In diabetic mothers, increased amniotic fluid androgen levels have been discovered in female offspring which specifies that the fetal ovaries can produce androgens when there are no inherited defects in steroidogenesis (Sam, 2003).

Gene variants discovered in the genome wide association study showed potential influences on fetal development of PCOS because of the alterations in fetal and maternal androgen production.

Irregular androgen from the mother can impact placental steroid hormone production and lead to pregnancy complications. A hypothesis by Dumesic et al is that increased LHCGR from mother can lead to increased LH and INSR secretion, causing a surge in fetal ovary insulin response, which would in turn cause fetal hyperinsulinemia. Fetal hyperinsulinemia leads to maternal hyperglycemia. Maternal hyperglycemia can cause maternal beta-cell hyperplasia. This can lead to an increase in fetal metabolism, decrease in lung maturation, and decease in parathyroid maturation within the fetus (Dumesic, 2014).

Leptin levels may also play a role in the etiology of PCOS in the intrauterine environment as it is not only released from adipose tissue but also placenta tissue. The exact role of leptin is presently unknown, but higher leptin levels are associated with poor pregnancy outcomes (Baldani, 2019).

## Complications Related to PCOS

### *Infertility*

Ovarian folliculogenesis, an endocrine feature of PCOS, is regulated by a fragile equilibrium between extra and intra-ovarian factors. When the equilibrium between the two is disrupted, follicular development and formation of mature oocytes can be altered, leading to infertility (De Leo, 2016). Approximately 76% of women with PCOS seek treatment options for infertility (Bahri Khomami, 2018). Potential treatment for infertility might be weight loss through diet and exercise regulation. In a study of 24 obese PCOS women participating in a low-calorie and fat-free diet for 7 months, 13 women lost over 5% of their weight and experienced an 82% increase in ovarian function. In fact, 5 of the 13 women became pregnant. In a second study of 144

women with PCOS on diet therapy, it was concluded that weight loss showed improvements in reproductive function as 50% of these women were fertile pre-diet and increased to 75% fertile women post-diet. Reproductive function increased as well as menstruation cycles were regulated (Tolino, 2004).

*Pregnancy complications: Gestational diabetes mellitus, pre-eclampsia*

A study conducted by *Bjercke et al*, controlling for BMI, showed pre-eclampsia was higher in women with PCOS (13.5%) when compared to women without PCOS (7%) (Bjercke, 2002). Gestational diabetes mellitus (GDM) in women with PCOS (7.7%) was higher than women without (0.6%) (Foroonzanfard, 2020). Androgen levels may play a role as high or levels in women with PCOS were predictive of both pre-eclampsia and pre-term delivery. Insulin resistance with gestational diabetes may also play a role in pre-eclampsia due to metabolic and hormonal dysfunctions (Foroonzanfard, 2020).

*Endometrial cancer*

An association between PCOS and endometrial cancer was found almost 50 years ago by small case reports that were limited by small sample size and lack of control groups (Harris, 2016). However, body mass index (BMI) was not considered in any of the studies which is required to determine the role of PCOS as an independent risk factor for endometrial cancer as women with PCOS are more likely to be obese and BMI is a known risk factor for endometrial cancer (Harris, 2016). The mechanism for endometrial cancer in women with PCOS is possibly due to both hyperinsulinemia and low progesterone, both of which can be caused by obesity. Additionally, endometrial cell proliferation is increased by estrogen stimulation and women with PCOS have

an increased risk of developing endometrial cancer because their endometrium has been found to stay in a proliferative state because of their lack of balance by progesterone. Progesterone acts as an inhibitor against estrogen-driven grown and proliferation of the endometrium. Typically, contraceptives containing progesterone are prescribed to inhibit endometrial proliferation, but 30% of women with PCOS do not respond to the treatment. The lack of response results in an increased risk of endometrial cancer.

Both insulin resistance and hyperinsulinemia have been linked to an endometrial diagnosis a in women (Li, 2014). Insulin resistance causes the estrogen biosynthesis to activate estrogen receptor signaling in the endometrium. This causes the endometrium to transform from normal to hyperplasic and eventually malignant. Estrogen and insulin increase the expression of insulin growth factor while progesterone inhibits it. The activation of insulin growth factor in epithelial cells increases the development of endometrial cancer. Hyperinsulinemia induces hyper-androgen production within the ovaries and increases the aromatization of androgens to estrogen. Therefore, normal endometrial cells can transform into malignant with insulin resistance (Li, 2014).

**Treatment**

*Lifestyle changes*

As previously discussed in treatment for infertility, weight loss has been shown to be beneficial to improve infertility. Weight loss is recommended through both exercise and nutritional regulation. In women with PCOS, there is little research done on what diet should exactly be followed to achieve the best results. However, there is evidence that shows diets with reduced

glycemic load might be the most beneficial in patients with insulin resistance that is common with PCOS. Along with low glycemic index foods, overall caloric restriction is recommended as well for a 5% weight loss, appropriate for increased reproductive outcomes (Thessaloniki, 2008).

*Medication Treatments*

Clomiphene Citrate (CC), also known as Clomid, is the first oral therapy treatment recommended to increase ovulation in women with PCOS as a pre-pregnancy treatment. The benefits of CC include; low cost, oral route to administer and an abundance of evidence and data showing little side effects (Thessaloniki, 2008). However, side effects can include headaches, episodes of hot flashes and some vision difficulties. The drug is overall well-tolerated by the patients receiving treatment. The general dosage ranges between 50-150 mg/day and is only recommended to be used for six ovulatory cycles. The success rate of ovulation with CC is 75-80% in PCOS patients (Thessaloniki, 2008).

Metformin is an insulin sensitizing agent. The primary side effect with metformin is lactic acidosis which is typically only seen in patients with risk of renal, liver, or heart failure Thessaloniki, 2008). In patients with PCOS, metformin has shown to lower fasting insulin level, but does not contribute to significant changes of BMI. Improvement of ovulation is similar to weight loss through diet regulation and exercise. Two studies (Moll et al, 2006; Legro et al, 2007) suggest that metformin does not increase live birth rates when paralleled to treatment using clomid. *Legro et al* showed a large disadvantage in ovulation rate when metformin is compared to clomid (Legro, 2009). It is best that metformin is only prescribed to patients with glucose intolerance (Thessaloniki, 2008). Metformin, although non-toxic, can cross the placenta.

It is frequently administered to women with GDM but there is little information on its use for PCOS patients with GDM specifically. There have been a few nonrandomized studies that reported decreases in GDM and pre-eclampsia in women with PCOS that used metformin during their pregnancy, although it is considered insufficient research because the data was pooled from two randomized studies. Data on both short- and long-term health of offspring born with maternal use of metformin is limited. One observational study using 72 pregnant women with PCOS prescribed Metformin found no complications and improved pregnancy outcomes (Glueck, 2002). In summary, the role of metformin during pregnancy in PCOS patients without diabetes is unclear (Bahri, 2018).

**Conclusion**

Although the prevalence of PCOS within reproductive aged women is high, there is limited research on the exact genetic components and environmental factors making it difficult to administer the most effective treatment. It is suggested that women with PCOS be followed by an endocrinologist from diagnosis throughout their lifespan. This would facilitate future research on treatments that contribute the least amount of risk factors; such as, cancer and obesity-related diseases, common in women with PCOS. Future research also needs to be completed to determine the most efficacious drug therapy during pregnancy resulting in little to no short- or long-term health effects on the offspring as well as lessen pregnancy complications like GDM and pre-eclampsia. Finally, this continuity of care by an endocrinologist through a woman's lifespan could increase the research on the effects of PCOS in menopausal women and their increased risk of endometrial cancer.

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