# Polycystic Ovarian Syndrome and Insulin Resistance: An Evaluation of Treatment Modalities and Complication Prevention

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A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2021

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
fulfillment of the requirements for graduation from the
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## Abstract

Polycystic ovarian syndrome (PCOS) is a reproductive and endocrine disorder in women of childbearing age. This disorder includes multiple clinical manifestations, namely insulin resistance (IR) and infertility related to hormonal imbalances and anovulation. Despite being a common condition, its etiology and treatment modalities remain poorly defined. Without proper understanding and management of the condition, women may suffer numerous complications besides infertility such as diabetes mellitus type II (DMII), endometrial cancer, and cardiovascular disease. Therefore, further research is critical. This integrative review will create a comprehensive understanding of PCOS' pathophysiology, potential complications, treatment methods, and nursing considerations to promote the health and well-being of women affected by this condition.

# Polycystic Ovarian Syndrome and Insulin Resistance:

# An Evaluation of Treatment Modalities and Complication Prevention

Polycystic ovarian syndrome (PCOS) is an endocrine and reproductive disorder that affects approximately one in ten women. Especially when combined with insulin resistance (IR), PCOS causes systemic manifestations for women that negatively impacts their daily lives. However, due to the multifaceted nature of its etiology and clinical presentation, treatment modalities are primarily centered around symptom management. However, this does not resolve the underlying hormonal imbalances that cause ovarian dysfunction and other sequelae. Additionally, some physicians may be quick to prescribe combined oral contraceptives (COCs) for PCOS management without taking other possible treatments into consideration (Altinok et al., 2018; Morgante et al., 2018). These factors may be combined with a lack of patient knowledge or improper prevention, which can result in poor management of potential long-term multiorgan complications (Palomba et al., 2015; Berni et al., 2018). As such, many patients receive inadequate care of their chronic health condition that drastically interferes with their well-being. Considering the high prevalence of PCOS-IR and the severity of its complications, conducting research and providing thorough patient education regarding the best treatment modalities and complication prevention methods should be a high priority in nursing practice.

## Pathophysiology

### Etiology

There are numerous hypotheses regarding the etiology of PCOS; however, it remains largely undefined at present due to its multifactorial nature. The key factors identified in PCOS etiology are exposure to excessive androgens in utero and throughout life, obesity, genetics, and

hyperinsulinemia with IR. Even so, this varies among patients, leaving individuals with unique etiologies and medical needs.

High levels of androgens in utero cause changes within the hypothalamus-pituitary-ovarian axis that manifest as the endocrine irregularities of PCOS during puberty (De Leo et al., 2016). This is especially true if other factors compound with genetic and environmental factors in utero and throughout life. Typically, the fetus would be protected from excessive androgens by aromatase produced by the placenta. However, inhibited aromatase production may occur in a small number of women. Additionally, pregnant women with preeclampsia or PCOS may have impaired estrogen synthesis, which would impair regulation of fetal testosterone. Maternal hyperandrogenism may also increase the risk of PCOS in a female fetus due to the combination of cross-generational genetics and environmental factors. As such, epigenetics may be involved in reprogramming fetal reproductive tissue to contain abnormalities (De Leo et al., 2016).

The evidence regarding the effect of elevated testosterone is paired with previous research done by Abbott et al. (2005) demonstrating PCOS in rhesus monkeys and sheep when exposed to injections of testosterone prenatally. In these animal studies, pathologic changes in ovarian function, fertility, luteinizing hormone (LH) secretion, and IR were evident. Not only was ovarian dysfunction evident, animals in the study exhibited masculinization, irregular behavior, and other pathophysiologic changes. The conclusions of the study relating elevated testosterone in mammals are comparative to human pathophysiology due to the similarities in fetal programming of the female reproductive system, especially regarding ovarian development and oogenesis (Abbot et al., 2005).

Additionally, Fillipou and Homburg (2017) discuss since some women have polycystic ovaries prior to puberty, the origin of their condition is likely affected by conditions in utero and

compounded by genetic vulnerability. In such instances, the ovaries are reprogrammed with abnormal functionality. This is further confirmed through evaluations of placentas from PCOS women, which demonstrate a hyperandrogenic environment that alters placental tissue. The placentas were found to have decreased P450 aromatase and other altered enzymes related to steroid synthesis. Maternal hyperandrogenemia may also impact the fetal development of ovaries, which occurs throughout gestation. Both gonadotrophins and paracrine hormones, such as insulin-like growth factor (IGF), interact with steroidogenic enzymes and signaling pathways to develop the ovaries. Once this process is completed in mid-gestation, the fetal ovaries can produce androgens in utero, such as in response to insulin levels. Consequently, a combination of environmental androgen exposure with genetic variability is indicated (Filippou & Homburg, 2017).

Filippou and Homburg (2017) elaborate upon the effects of prenatal exposure to androgens and alterations in related genes using research that demonstrated elevated anti-Mullerian hormone (AMH) levels in connection with PCOS. Elevated AMH production by granulosa cells within the ovaries strongly inhibits follicular growth instead of providing proper physiologic maintenance of the ovulation cycle. The higher the AMH concentration, the more severe the degree of anovulation and amenorrhea in women with PCOS. Although there is a correlation between hyperandrogenism and elevated AMH, this does not indicate direct causation. At present, the cause of elevated AMH is unknown, but in some individuals, it may be caused by hypomethylation of the AMH gene, which would lead to intrinsic over-expression and increased synthesis of AMH (Fillipou & Homburg, 2017). Similarly, a study conducted by Gorsic et al. (2019) identified multiple genetic variations along the AMH pathway that are linked to PCOS through targeted resequencing of coding and regulatory components of the affected

genes. These variants along AMH and AMHR2, a specific AMH receptor, impair proper AMH regulation and subsequently inhibit ovulation cycles (Gorsic et al., 2019).

As indicated by De Leo et al. (2016), genetics play a strong role in the development of PCOS for many women. While the precise mechanism for genetic inheritance has not been determined thus far, both autosomal dominant transmission and polygenic transmission mechanisms have been postulated. The particular genes being researched are those involving the synthesis and regulation of androgens and insulin. Additionally, individuals with pro-inflammatory genotypes or irregular folliculogenesis may be linked to PCOS based on recent studies. Each of these previous hypotheses require extensive further research. Currently, only two susceptibility genes have shown to be identified: allelic variants of fibrillin-3 (FBN3) and variants of luteinizing hormone receptors (LHR). The A8 variant of FBN3 has shown to cause insulin resistance while altered LHR may cause dysregulation of ovulation, androgen production, and adipogenesis. For fetuses with any of the mentioned genetic abnormalities, ovarian dysfunction in utero may be present, causing excessive androgens due to irregular responses to maternal human chorionic gonadotropin (hCG), demonstrating further links to hyperandrogenism in utero as described previously (De Leo et al., 2016).

Beyond the potential genetic mutations directly controlling LH and androgen secretion, genetic mutations in the hypothalamic-pituitary-ovarian (HPO) pathway beginning with altered gonadotropin releasing hormone (GnRH) must be considered. Shaaban et al. (2018) concluded genetic and metabolic pathophysiological mechanisms for PCOS regarding GnRH contribute to its etiology. These alterations would indicate dysfunctional hypothalamic regulation of GnRH secretion along with faults in the GnRH receptor (GnRHR) gene, leading to improper levels of androgens, LH, and follicle stimulating hormone (FSH). PCOS women typically have high LH

concentrations due to GnRH excess. This consequently prevents proper fluctuations in LH levels that would normally produce follicle development and ovulation. Likewise, altered GnRH may also stimulate excess androgens, which prevents proper ovulation and negatively impacts female reproductive health, as established throughout this paper and indicated by Figure 1 (Shaaban et al., 2018).

De Leo et al. (2016) and Filippou & Homburg (2017) further identify metabolic factors as pertinent to the development of PCOS. IR is not only a common clinical manifestation associated with PCOS, it is also related in its pathogenesis. It has been established hyperandrogenism is linked to increased IR and insulin activity in utero, which also inhibits aromatase levels. Beyond IR and hyperinsulinemia consequent to hyperandrogenism, these factors are potential synergistic agents in PCOS etiology. This is due to their relationship with ovarian development and function throughout life. Along with hyperandrogenism, hyperinsulinemia is a contributor to elevated AMH, which negatively impacts ovulation as described earlier. Similarly, any other metabolic conditions, especially those experienced prenatally like impaired intrauterine nutrition and preeclampsia, are potential, though less influential, contributors to PCOS development due to their connection with IR and altered steroidogenesis (De Leo et al., 2016; Filippou & Homburg, 2017).

Condorelli et al. (2017) describe that PCOS-IR individuals have an abnormal biologic response to insulin where “anomalies involving the secretion of pancreatic cells (abnormal insulin or incomplete conversion of proinsulin to insulin), high blood concentration of hormones counterregulatory to insulin, anti-insulin antibodies or antibodies anti-insulin receptor, and also target organs disorders (because of a reduced quantity of insulin receptors or post-receptor defects)” (pp. 665) are present. As such, there is a significant reduction in peripheral insulin

sensitivity that interferes with the body's ability to regulate blood glucose levels, uptake glucose for cell metabolism, and increases glucose storage within adipose tissue. Consequently, the body produces excess insulin to counteract IR, which further perpetuates the problems of glucose irregularities, causes pancreatic beta cell dysfunction long-term, and may lead to liver dysfunction in the form of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH) in some women. Decreased secretory-cell activity is further noted when evaluating the first phase insulin response (FPIR) that occurs when glucose initially enters the bloodstream. This impaired secretory-cell function in response to glucose demonstrates the multifaceted dysfunction of insulin regulation within the PCOS-IR population (Condorelli et al., 2017).

Mcewen and Hartmann (2018) also elaborate upon the connection between PCOS and IR by discussing the apparent dysfunction of PCOS individuals to properly respond to insulin in both the ovaries and metabolically. In PCOS, impaired insulin-mediated glucose utilization within tissues along with paradoxical ovarian insulin sensitivity has been noted. This creates a hyperglycemic state along with increased androgen production by theca cells in the ovaries and within adipose tissue (Mcewen & Hartmann, 2018).

**Clinical Manifestations**

The type and severity of clinical manifestations of PCOS vary widely among women. Similarly, symptoms may change throughout a patient's life depending on management of their condition and other health factors. The most common and substantive clinical manifestations discussed within this review will include: oligomenorrhea and oligoovulation; polycystic ovaries; hyperandrogenism; weight gain and obesity; and mood liability and headaches (Palomba et al., 2015). There are many additional symptoms and sequelae associated with PCOS. However, for

the purpose of this integrative review, the focus will be to discuss those symptoms most commonly seen with PCOS.

### *Oligomenorrhea, Oligoovulation, and Polycystic Ovaries*

Due to the imbalance of multiple reproductive hormones, eggs with the ovaries do not mature appropriately (Patel, 2018). When hormones are improperly regulated, instead of being released into the fallopian tube during ovulation, eggs remain in the antral follicles and become cysts. These cysts are filled with water and may become as large as 10cm within the ovaries. When ovulation cannot occur, this typically prevents menstruation. However, in some cases, menstrual bleeding may occur despite an anovulatory cycle and may be paired with the absence of cramps or premenstrual syndrome (PMS). More mild hormonal imbalances result in oligomenorrhea with varying lengths in between cycles, whereas others present with complete amenorrhea and anovulation. In both instances, medications to prevent endometrial hyperplasia and other complications may be indicated. Follicular development is partially impaired by hyperresponsive ovarian theca cells that are stimulated by excess insulin to produce excess androgens. This is compounded by disrupted GnRH secretion that leads to irregular LH and FSH release, among other hormones, and consequent menstrual irregularities. When any one or multiple hormones are disrupted, it can create a compounding effect as other hormones become disrupted as well, leading to complex endocrine dysfunction (Patel, 2018).

### *Hyperandrogenism*

Pfieffer (2019) details that elevated androgen levels in women disrupts more than just the menstrual cycle. Hyperandrogenism may stem from multiple factors, such as polycystic ovaries, obesity, and poorly regulated hormone pathways. Acne and hirsutism are two clinical manifestations among multiple visible symptoms of hyperandrogenism that pose difficult to

manage for women with PCOS. Increased acne occurs consequentially to seborrhea, which makes the skin prone to bacterial growth within clogged pores. For many women, acne is severe in nature and may be classified as cystic lesions that are resistant to common acne treatments. Hirsutism is defined as the appearance of excess body hair in women on the face, chest, back, or extremities. Obesity intensifies the severity in many women. The severity may be evaluated based on the Ferriman-Gallwey Scale, but it used only for subjective purposes. Interestingly, male pattern baldness has also been correlated to hyperandrogenism and occurs in approximately ten percent of PCOS women. Often, hormonal acne and hirsutism are difficult to reduce without the use of antiandrogen medications such as spironolactone. While acne and hirsutism typically do not interfere with general health and well-being, it may cause lowered self-esteem related to perceptions of beauty and social implications (Pfieffer, 2019).

### *Weight Gain and Obesity*

In a study conducted by Broskey et al. (2018), it was established that many women with PCOS-IR demonstrate metabolic inflexibility due to the body's inability to regulate insulin production and use during both fed and fasting states. In a healthy individual, metabolic flexibility is described as the capacity to oxidize lipids in a fasted state and then switch to using carbohydrates in a fed state. The improper stimulation and use of insulin leads to prolonged hyperglycemic states and increases stress on the pancreas' beta cells. This is similar to metabolic changes present in patients with DMII and also increases the likelihood of DMII development in PCOS patients. Additionally, the metabolic inflexibility increases the risk of weight gain and obesity due to inhibited non-oxidative glucose metabolism. Not only is glucose retained in the body as fat, the ability of patients to lose weight, even with appropriate diet and exercise, is inhibited because of their inhibited metabolic processes. The study also reiterated the propensity

of PCOS women to have high levels of free testosterone and elevated free androgen index. As such, the combination of PCOS with IR statistically increases the chances of weight gain and obesity (Broskey et al., 2015).

### *Mood Liability and Headaches*

Palomba et al. (2015) along with the NICHD Staff (2017a) discuss that women with PCOS may have mood liability due to hormone fluctuations. Though this can be commonly associated with premenstrual syndrome (PMS) in the general female population, the severity and variance in presentation in PCOS patients is substantial. Many PCOS patients report mood liability that is not strictly associated with their menstrual cycle. This may progress to anxiety and depression when combined with other factors, as discussed later. In any case, the feelings of sadness, irritability, anger, or other unpleasant emotions associated with mood liability have the potential to drastically interfere with a woman's well-being. For some women, hormone fluctuations also increase the risk of chronic headaches or migraines. This may be worsened by PMS or by medications such as birth control that further impact mental health. IR may also play a significant role in both mood-related disorders and headache frequency related to metabolic abnormalities that affect regulatory pathways within the brain and endocrine system (Palomba et al., 2015; NICHD Staff, 2017).

## Complications

### Infertility, Miscarriage, and Pregnancy Complications

Consequential to hormonal dysregulation and oligoovulation, women often have difficulty conceiving. PCOS patients experience reduced frequency of mature egg release from the ovaries along with hormonal conditions not conducive to pregnancy maintenance. This

results in a higher rate of infertility and miscarriage among the PCOS population (Palomba et al., 2015).

Palomba et al. (2015) describes metabolic abnormalities that predispose women to pregnancy complications are also present in PCOS women. This is namely seen in the significantly increased risk of gestational diabetes mellitus (GDM), which may be upwards of threefold. IR along with the commonality of obesity put women at increased risk. IR may be worsened during pregnancy due to increased stress on the body and elevated metabolic demand. When the body cannot compensate adequately, GDM develops. This poses risks for both mother and baby such as premature birth, maternal and fetal development of DMII later in life, and cesarean delivery (Palomba et al., 2015).

According to Palomba et al. (2015), pregnancy-induced hypertension and preeclampsia are significant risk factors for PCOS patients due to a variety of factors. PCOS patients may be at a threefold greater risk than the average woman for developing these conditions. This increases the risk of prolonged hospitalization, bed rest, premature delivery, and potentially serious maternal and fetal health outcomes (Palomba et al., 2015).

**Diabetes Mellitus Type II**

Palomba et al. (2015) reiterates women with PCOS are statistically more likely to develop DMII. This is consequent to IR, along with other factors such as obesity and poor lifestyle habits. As a woman with IR ages, her ability to regulate blood glucose and transport it into cells decreases. This occurs as the beta cells of the pancreas become overworked and produce insufficient or dysfunctional insulin. Additionally, insulin receptors throughout the body may not respond to insulin properly. These factors potentiate the consequences of IR and may progress to DMII. Once DMII is diagnosed, PCOS patients may have difficulty managing it due

to hormone fluctuations, elevated androgens that reinforce IR, and challenges losing weight (Palomba et al., 2015). DMII poses significant health risks on its own, which are heightened when combined with PCOS-IR and described throughout this integrative review.

Condorelli et al. (2017) elaborates on the intricate pathophysiological nature of PCOS and IR that is related to genetic and hormonal mechanisms in conjunction with dietary and exercise considerations. There are a variety factors that affect PCOS and the development of DMII, which should be considered as part of PCOS patients' health maintenance. Patel (2018) also investigates the multifactorial, interdependent aspects that are both causative factors and subsequent consequences of DMII. PCOS-IR's complex presentation of hormonal and metabolic irregularities, weight gain, cardiovascular disease, and other characteristics both prior to and after DMII development cause researchers to continue to investigate disease manifestation, prevention methods, and treatment options (Patel, 2018).

**Cardiovascular Disease**

Palomba et al. (2015) elaborates that PCOS-IR women have an impaired ability to process glucose, leading to persistent hyperglycemic states. This is especially true if women do not regulate their diets, have prediabetes or unregulated DMII, and/or struggle with obesity. Each of these factors, particularly when combined with the potential for altered lipid metabolism, raises a woman's risk of cardiovascular disease. The numerous sequelae of these comorbidities, such as hypertension and hypercholesterolemia, increase the likelihood of plaque development within blood vessels. As lipids accumulate, the risk of myocardial infarction is significant. Additionally, hyperglycemic states increase the likelihood of thrombi as glucose irritates and damages the cardiovascular endothelium. Once the vasculature is damaged, inflammation worsens the condition by propagating clotting and further raising cortisol levels, which only

propitiates the hyperglycemia. As such, those with DMII are at highest risk for developing cardiovascular disease and experiencing complications due to the compounding nature of PCOS and DMII on the body. Further research is necessary regarding the complex relationship between PCOS and cardiovascular disease both with and without the presence of factors such as IR and obesity (Palomba et al., 2015).

For PCOS women on hormonal birth control, the risk of cardiovascular disease is further elevated. Discussed in further detail later, these medications have known risk factors associated with elevated clotting risks and hypertension (Sanoski & Vallerand, 2019). Women over 35 years old or with cardiovascular conditions are warned against taking these medications for this very reason. As such, there is a conflict between prescribing birth control for menstruation regulation and protecting PCOS patients' cardiovascular health (Sanoski & Vallerand, 2019).

**Non-Alcoholic Fatty Liver Disease**

Petta et al. (2017) explains that when IR and hyperandrogenism are present, PCOS patients have a higher risk of developing non-alcoholic fatty liver disease (NAFLD). This stems from altered lipid metabolism that increases the likelihood of adipose tissue depositing within tissues, primarily the liver. Another consideration that increases risk is the presence of obesity due to the higher percentage of adipose tissue within the body and obesity's impact on metabolism and IR as described earlier. The study by Petta et al. (2015) observed that steatosis was present in 68.8% of the studied patient population. This and other statistical analysis concluded that PCOS can be classified as an independent risk factor for development of steatosis. Additionally, liver steatosis may cause impaired liver function. This may remain asymptomatic depending on severity, but can become problematic as it begins to impair liver function. As steatosis progresses, women may develop elevated levels of aspartate

aminotransferase (AST) and alanine aminotransferase (ALT). AST and ALT are two key liver enzymes involves in glycogen production. When elevated, they indicate tissue damage within the liver. In severe cases, this could further progress to nonalcoholic steatohepatitis (NASH). As such, evaluating PCOS patients for the presence of NAFLD and altered liver function is critical to diagnosis and management of potential liver damage (Petta et al., 2017).

**Depression and Anxiety**

Palomba et al. (2015) along with Berni et al. (2018) explain that women with PCOS are prone to depression, anxiety, and other mood-related disorders due to hormone fluctuations along with psychological stress regarding PCOS complications, poor body image, and other factors. Depression and anxiety are often disregarded as symptoms of PCOS; however, evidence displays that endocrine and metabolic abnormalities have psychological ramifications among the PCOS population. Similarly, poorly managed mental health has potentially severe consequences, such as inhibited health maintenance and suicidal ideation. Mood liability is often described as a key symptom among PCOS patients (Palomba, et al., 2015; Berni et al. 2018).

A woman's difficulty with body image and low self-esteem associated with PCOS often stems from hirsutism and obesity. These may make a woman feel unfeminine, especially if she is criticized by others. This is compounded by infertility, which is disrupts what many individuals would consider an integral aspect of womanhood. Women may experience both anticipatory grief over potential infertility and disenfranchised grief over current infertility and miscarriages. Infertility may also lead to anxiety over societal perceptions and stress within romantic relationships related to intimacy, family ideals, and health maintenance. Additionally, women may lack social support, struggle with isolation, or feel overwhelmed by the consequences of having a health condition largely out of their control. Any one or multiple of these contributes to

PCOS patients' risk of depression and anxiety, indicating the need for increased screening of mental health disorders by physicians (Berni et al., 2018).

The severity of PCOS-related mental and emotional symptoms may be worsened by hormonal birth control in some women. These medications can increase mood liability and may worsen depression due to estrogen and progesterone's interaction with brain chemistry (Sanoski & Vallerand, 2019). This is especially true for women who experienced symptoms of anxiety and depression prior to taking birth control or for women prescribed higher dose estrogen COCs. In such instances, the risk of severe depression and suicidal ideation is a clear contraindication of hormonal birth control. As such, other treatment options must be considered. However, due to limited gynecological knowledge and treatment options, women are often left with poorly managed PCOS and its related conditions.

**Endometrial Hyperplasia and Uterine Cancer**

Patel (2018) states that "PCOS can put a female at the risk for uterine cancer, as the prevailing high estradiol level and the lack of progesterone due to ovarian malfunction increases the risk of endometrial hyperplasia" (p. 28). When a woman does not have a regularly occurring menses, the endometrial lining built up during the menstrual cycle thickens and may develop into endometrial hyperplasia. This overgrowth of tissue within the uterus further interferes with fertility and increases a woman's risk for abnormal cell development, including the proliferation of cancerous tumors. The more severe the hyperplasia and the longer the excess endometrial tissue sits within the uterus, the more likely cellular mutations will occur. These risks remain relatively low for women who menstruate at least every 3 months. However, PCOS with severe oligomenorrhea or amenorrhea must be evaluated and treated for these potential complications (Patel, 2018; Palomba et al., 2016).

To combat the risk of hyperplasia in oligoovulation, women are typically prescribed hormonal birth control, such as COCs or progesterone only pills (POPs), to force the regular occurrence of menstruation (Kriedt et al., 2019; De Leo et al., 2016). Typical guidelines state menstruation should occur at least every 2-3 months to prevent overgrowth (De Leo et al., 2016). Current research has inconclusive or conflicting data as to whether metformin is effective in reducing endometrial hyperplasia risk (Palomba et al., 2015). Although hormonal birth control options may accomplish the goal of preventing hyperplasia, they have numerous side effects and often neglect to address the underlying health and reproductive concerns of PCOS, as discussed later.

## Treatment Modalities and Nursing Considerations

### Lifestyle Modification

The first line of treatment for PCOS, much like many diseases, is lifestyle modification. Avoiding unnecessary medications or medical procedures facilitates sustainable health, reduces health costs, and minimizes the risks of side effects (Schlesinger & Grob, 2017). The many systemic complications of PCOS reiterates the necessity of holistic care. PCOS patients should speak with their physicians regarding beneficial changes in diet, exercise, and other aspects of daily living that affect both mental and physical wellbeing. Nurses are especially important in promoting lifestyle modification as they build rapport and have considerable patient interaction with their patients. An overview of long-term complication management, including clinical assessment and therapeutic approaches, by Palomba et al. (2015) is included in Figure 3.

#### *Dietary Modification*

The importance of a healthy diet in disease prevention and management must be reiterated for patient well-being and is one of the key treatment considerations. This is especially

true for PCOS patients. Not only does incorporating a healthy balance of carbohydrates, proteins, and fats encourage proper weight management and prevention of countless diseases, it may reduce the risk PCOS sequelae, such as DMII (Merkin et al., 2016). Before simply prescribing medications, PCOS patients should initiate a healthy diet and evaluate its effectiveness in reducing symptoms. However, this requires considerable patient education on behalf of the healthcare provider on what is considered a healthy diet and why is has the potential to impact the courses of their chronic condition.

Current research is investigating the potential benefits of gluten free and dairy free diets. Though not widely discussed in practice currently, many patients may see improvements when instituting one or both dietary changes due to their potential to exacerbate insulin resistance and hormone disruption (Merkin et al., 2016). In any case, adhering to guidelines set forth within the Dietary Guidelines for Americans, as set forth by the United States Department of Agriculture and Department of Health and Human Services, can improve general health. Overall, research by Merkin et al. (2016) demonstrates the importance of dietary regimen adherence and weight management as keys to PCOS management.

**General Dietary Recommendations.** According to Dutkowska et al. (2019), eating carbohydrates with a low-glycemic index has shown to improve insulin sensitivity and reduce markers of inflammation. Whether for weight loss or weight maintenance, restricting the amount of lower quality carbohydrates is beneficial for menstrual cycle regulation and symptom reduction. Additionally, increasing the amount of protein to 20%-35% of daily dietary intake may help increase weight loss, promote normal metabolic parameters, and reduce depression. Increasing the number of omega-3 fatty acids may also promote regular menstruation in addition to their ability to improve insulin sensitivity. Consuming saturated fats and advanced glycations

end products (AGE) should be minimized dur to their role in stimulating proinflammatory proteins and interfering with metabolism. In general, many of these recommendations apply to multiple diseases, however, PCOS patients should become aware of how these specific dietary changes may have significant impacts on their long-term wellbeing (Dutkowska et al., 2019).

**Gluten Free.** Merkin et al. (2016) explains that gluten, simple carbohydrates, and added sugars are difficult for women with PCOS-IR to process due to their inability to regulate insulin and blood glucose levels. This leads to spikes in blood sugar, increased insulin production, and higher storage of carbohydrates as adipose tissue. In turn, weight gain becomes problematic along with exacerbated hormone irregularities. As previously explained, hyperinsulinemia stimulates excess androgens and worsens PCOS symptomatology. Research has indicated gluten sensitivities may be present in some PCOS patients, as gluten-free diets have shown to reduce symptoms in combination with the reasons listed previously. There is question as to the exact mechanism of hormone disruption associated with gluten. Current suggestions include the phytoestrogen production of gluten along with the influence of agricultural pesticides on the endocrine system (Merkin et al., 2016).

**Dairy Free.** As stated by Merkin et al. (2016), dairy has the potential to increase inflammation and raise testosterone levels, which can worsen symptoms in women with PCOS. The whey component of dairy is especially insulinotropic and may exacerbate hyperinsulinemia and hyperandrogenism seen in PCOS patients, especially those with IR. This suggests that PCOS patients should avoid foods and nutritional supplements that have whey as an ingredient and reduce overall dairy consumption. For some, eliminating dairy from their diets may be one beneficial component in managing PCOS (Merkin et al., 2016). However, more research is necessary to evaluate its effectiveness in comparison to other treatment modalities. There is not

enough current research to definitively conclude whether or dairy is a significant contributor to PCOS presentation. Becoming dairy free should be done with discretion and under supervision of a physician.

### *Regular Exercise*

Regular aerobic exercise has proven to improve health in a variety of ways for all individuals. Specifically in PCOS patients, aerobic exercise has the ability to promote a healthy metabolism and insulin usage, increase weight loss or promote weight management. However intense aerobic exercise regimens may stress the endocrine system and cause elevated cortisol release, which promotes inflammation and hormone imbalances in PCOS (Patel, 2018). As such, a more balanced routine that focuses on moderate intensity cardio workouts and weight training may be more effective in boosting metabolism and promoting sustained weight loss and management (Patel, 2018). Merkin et al. (2016) notes that resistance exercise is helpful in increasing base metabolic rate through gaining muscle mass. Yet, there are still potential gaps in research regarding what specific types of exercise programs may benefit PCOS patients the most. Currently, the most important consideration is engaging in regular physical activity for promotion of general wellbeing and prevention of DMII, obesity, and cardiovascular disease.

### *Weight Loss*

Maintaining a healthy weight is a high priority for PCOS patients. When at a healthy weight, there is less overall strain on the body and a higher potential for effective metabolic and hormone regulation. It is less strenuous on pancreas pertaining to insulin production, which promotes proper glucose usage and storage. Additionally, less adipose tissue also lessens the propensity for high testosterone due to the hormonal feedback loops involved. Merkin et al. (2016) discusses that “with a 5%–10% reduction in weight, hyperandrogenemia, ovarian volume,

and menstrual cycle irregularity are improved and SHBG [sex hormone-binding globulin] is increased" in addition to insulin sensitivity for most women (p. 19). Obesity is a prominent exacerbating factor of PCOS that can be largely controlled through lifestyle changes. Yet, maintaining a healthy weight does not necessarily eliminate all PCOS metabolic irregularities or symptomatology. As such, weight loss is only one of many considerations in managing PCOS.

### *Stress Reduction*

Lowering stress is a powerful way to help reduce illness and symptomatology for numerous diseases (Halter, 2018). This is true for PCOS-IR patients as well, particularly due the relationship between cortisol and insulin. Reducing stress lowers cortisol production and inflammation within the body, which subsequently reduces the body's demand for insulin. This promotes proper regulation of the body's metabolism and hormone levels. On the contrary, when in fight or flight mode, the body cannot regulate the reproductive system properly. Sympathetic nervous system (SNS) activation inhibits parasympathetic nervous system activity, therefore disrupting carbohydrate digestion, insulin regulation, and reproductive hormone release. As noted previously, elevated insulin promotes testosterone production, interfering with the menstrual cycle and worsening PCOS symptoms. Some stress reduction techniques that may be beneficial are journaling, cognitive reframing, meditation, relaxation exercises, or other calming and enjoyable activities. In essence, elevated stress impacts mental well-being and plays a significant role in pathological processes but can be managed through stress reduction methods (Halter, 2018).

### *Counseling*

Women with PCOS may benefit from receiving professional counseling, either in a group setting or one-on-one sessions. Counseling may help patients manage stress, reduce anxiety and

depression, address body image issues, and cope with infertility or other disease complications (Halter, 2018). With proper counseling, individuals may be better equipped to manage their condition and make healthier choices that affect both mental and physical health. Counseling within the general population has shown to be effective in reducing distressing emotions and promoting coping mechanisms (Halter, 2018). This can be expounded upon to PCOS populations as well, as indicated by a clinical trial for PCOS patients that implemented the use of cognitive behavioral therapy (CBT) for weight loss and improved quality of life (Cooney et al., 2018). Another study conducted by Abdollahi et al. (2019) in Iran also indicated that CBT reduced the prevalence of psychosocial fatigue and increased quality of life. CBT may be one of multiple counseling methods appropriate for PCOS patients, demonstrating the need for assessing a patient's mental health status and the potential benefits of counseling. Consequently, nurses should assess patients' mental health and refer patients who exhibit symptoms of depression or anxiety to therapeutic resources.

## Dietary Supplements

Dietary supplements such as inositol and vitamin D are newer areas of research regarding PCOS treatment. Other potential supplements not discussed within this review include, but are not limited to, chromium and folate. The hope is that using these natural supplements addresses the source of hormone imbalances and therefore reduces symptoms and PCOS complications.

### *Inositols*

Inositols are known insulin-sensitizing agents produced by the body, including the ovaries, in order to maintain physiologic activities (Roseff & Montenegro, 2020). Merkin et al. (2016) along with Wojciechowska et al. (2019) found that the stereoisomer myo-inositol (MI) is

beneficial in reduction of androgen excess and promotion of ovulation in PCOS patients. Physiologically,

> MI is converted to an inositolphosphoglycan (IPG) insulin second messenger (MI-IPG) involved in cellular glucose uptake, whereas DCI is converted to an IPG insulin second messenger (DCI-IPG) involved in glycogen synthesis. At the ovarian level, however, it has been shown that an MI-based second messenger is involved in both glucose uptake and FSH signaling, whereas a DCI-based second messenger is devoted to insulin-mediated androgen production (Roseff & Montenegro, 2020, p. 2).

The benefits of MI to d-chiro-inositol (DCI) are most effective when consumed in a 40:1 ratio, which mimics the body's natural production; 2-4 grams of MI per day is the typical recommended dosage for hormone regulation and promotion of ovulation (Merkin et al., 2016; Wojciechowska et al., 2019). However, Roseff and Montenegro (2020) discuss that DCI when given alone or in improper doses is an aromatase inhibitor and may elevate androgen levels. A study by Facchinetti et al. (2019) comparing the short-term effects of MI to metformin as insulin-sensitizing agents found both yielded similar metabolic improvements, however, metformin had significantly more side effects and potential complications.

Roseff and Montenegro (2020) reiterate that supplements should be chosen based upon scientific data, patient-specific needs, and therapeutic rationales. As such, women considering inositol supplements should discuss this with their physicians and do adequate research regarding supplement brands, safety, and efficacy. Further research should be conducted to evaluate current supplement options, long-term effectiveness for ovulation management and insulin sensitivity, and the potential for a Food and Drug Administration (FDA) approved medication containing inositols.

### *Vitamin D*

Vitamin D has been shown to have a positive effect on insulin production and usage, which is beneficial for glucose metabolism (Merkin et al., 2016). Many women may not meet the daily recommended dose of vitamin D through diet and sun exposure alone, which further demonstrates the benefits of vitamin D supplementation for PCOS women. This is further supported a systematic review and meta-analysis of trials involving PCOS and vitamin D supplementation conducted by Łagowska, Bajerska, and Jamka's (2018), which concluded that vitamin D supplementation alone or when paired with other medications and supplements can improve insulin sensitivity.

A randomized, placebo-controlled clinical trial by Kadoura et al. (2019) studied the effects of combining calcium and vitamin D supplements with metformin for PCOS patients. They found that both can support aims to regulate menstruation and promote insulin sensitivity. However, no statistically significant differences in gonadotrophins or IGF-1 systems were present. They noted that the underlying mechanisms of vitamin D usage, including when in combination with metformin, must be researched further (Kadoura et al., 2019).

PCOS patients should strongly consider having their vitamin D levels checked and implementing supplementation under the consultation of a physician. Having the proper levels of vitamin D is a relatively simple way to encourage proper metabolism and manage IR and its associated consequences.

## Pharmacologic Interventions

### *Metformin*

According to Balen et al. (2016), metformin monotherapy, while typically used for DMII, can be effectively utilized in women with PCOS-IR due to its ability to decrease serum insulin

levels and improve PCOS symptoms. The mechanism of action of metformin includes decreasing hepatic glucose production, stimulating hepatic and skeletal insulin-mediated glucose uptake, and reducing serum lipids through inhibited substrate availability involved in gluconeogenesis. According to Balen et al. (2016), metformin should be implemented prior to other insulin-sensitizing agents, such as thiazolidionediones and myo-inositol, due to a higher benefit-to-risk ratio and a current lack of evidence. Though weight loss is not classified as a side effect, metformin may enhance a woman's ability to lose weight related to its regulation of insulin utilization, thus reducing IR while also decreasing symptoms (Balen et al., 2016).

Kriedt et al. (2019) discusses that metformin may be used individually or in combination with CC or letrozole as an adjuvant treatment for ovulation induction. The typical dosage for this purpose is around 1500 mg per day. Especially when in combination with another medication for ovulation induction, metformin has shown to be clinically beneficial for conception and pregnancy. This is particularly encouraging for PCOS women with prediabetes or DMII who are likely already using metformin to manage this comorbidity (Kriedt et al., 2019). For those who utilize metformin alone for ovulation and conception purposes, they have poorer outcomes than when used in conjunction with clomiphene citrate (CC) or another ovulation-stimulating medication (Balen et al., 2016). It is also critical to note that metformin does not affect rates of miscarriage for women, especially for those who experience progesterone deficiencies (Balen et al., 2016).

As explained by Balen et al. (2016), metformin is primarily processed through the liver, which may be impaired if women have NAFLD with altered liver enzymes. Women should have their liver enzymes tested prior to prescribing metformin and periodically while taking the medication to ensure the healthy liver function and prevent complications. Additionally, the

commonality of gastrointestinal upset as a side effect of metformin decreases the likelihood of medication compliance. Gastrointestinal upset may also alter dietary intake and nutritional status, which may further negatively affect patient health and well-being. As such, these and other potentially serious side effects of metformin must be evaluated, especially considering many patients may be prescribed these medications long-term (Balen et al., 2016).

There are multiple potential questions that arise from this research. Since metformin is typically prescribed long-term, can metformin impair the function of pancreatic alpha cells over time? If so, does the short-term benefit of metformin in promoting insulin-sensitivity lead to long-term complications and the promotion of DMII development? Subsequently, research as to the duration of metformin's effectiveness should be evaluated. When prescribing medications for treatment, both short- and long-term considerations must be made. Currently, metformin is one of the first-line medications for PCOS-IR, yet there are no clear guidelines as to when or how metformin therapy should be initiated beyond the fact that lifestyle modification should be attempted first. As such, more clear delineation of metformin therapy for PCOS-IR should be researched to have the safest, most beneficial outcomes for women.

### *Hormonal Birth Control*

The various hormonal birth control medications utilized for PCOS have multiple applications. Common examples of birth control options include COCs and intrauterine devices (IUDs). There are numerous types within each of these categories that have various chemical compositions and mechanisms of action. Consequently, birth control as a treatment option will be discussed as a category and not include specific COC or IUD options.

Birth control is primarily meant for hormonal regulation and protection against endometrial hyperplasia in PCOS (Sanoski & Vallerand, 2019). This is a protective measure to

help preserve fertility in the future and reduce the risk of endometrial cancer. Birth control may also reduce symptoms such as acne and hirsutism (Sanoski & Vallerand, 2019). Yet, birth control does not address the underlying causes of PCOS' hormonal abnormalities that affect reproductive health and there is question as to whether these options have substantive impacts on patients' quality of life (Altinok et al., 2018).

> The ideal contraceptive for women with PCOS should be [*sic*]: limit antral follicle development and reduce androgen levels; counter the action of androgens on the pilosebaceous unit at peripheral level; restore the balance between estrogens and progesterone in the endometrium, ensuring good control of the menstrual cycle. For these women, an OC [oral contraceptive] containing 30 mg ethinylestradiol (EE) is the most indicated, because it ensures good control of the cycle and reduces ovarian androgen production in all phases of the cycle. This formulation also effectively stimulates liver production of SHBG, more than OCs with lower doses of EE [14,15]. SHBG binds and transports testosterone (T) into circulation. Thus, higher production of SHBG leads to a greater percentage of bound (inactive) T and less fT [free testosterone], giving the OC a greater antiandrogen effect (Morgante et al., 2018).

As mentioned previously, birth control may have major side effects such as hypercholesterolemia, blood clots, mood liability or depression, particularly for those with other risks factors such as cardiovascular disease or being above 35 years old (Sanoski & Vallerand, 2019). These are serious risks to consider for PCOS patients, especially because of PCOS' many potential sequelae. Unfortunately, many patients suffer side effects of medication in conjunction with PCOS symptoms because they lack knowledge or feel as if there are no other disease management options. For patients with NAFLD or other liver conditions that elevate liver

enzymes, patients are unable to take birth control medications because they are metabolized through the liver and may worsen liver damage (Sanoski & Vallerand, 2019). These patients require other types of PCOS treatment that is often not considered. Additionally, healthcare providers may neglect to check liver enzymes and other important lab values prior to prescribing birth control, leaving patients vulnerable to various medication complications. For patients who do not wish to take hormonal birth control for personal reasons, such religious beliefs, or due to medical contraindications, other PCOS management options should be offered by their physicians.

***Progesterone Only Medication***

POPs, such as medroxyprogesterone, are often regarded as a second choice for prevention of endometrial hyperplasia if patients cannot take hormonal birth control (Sanoski & Vallerand, 2019). POPs are often prescribed for 5-10 days. The cessation of the medication causes a drop in progesterone levels, stimulating menstruation to occur. Patients are instructed to take the POPs once every 1-3 months depending on the specific medication and whether the patient has menstruated on their own within the designated timeframe. While these medications are similar to birth control concerning their ability to stimulate menstruation upon cessation, they are not effective as contraception and do not have the same protective nature. (Sanoski & Vallerand, 2019;).

POPs may interfere with glucose regulation and cause hyperglycemia, especially for those with prediabetes or DMII (Sanoski & Vallerand, 2019). This is a serious effect considering the likelihood of IR in PCOS patients. Additionally, could POPs further interfere with PCOS patients' hormone regulation, leading to reduced ovulation and higher long-term sequelae? Though general side effects are minimal for most women, further research should be considered

regarding the long-term consequences of abnormal patterns of hormone ingestion on the reproductive system.

### *Antiandrogens*

Morgante et al. (2018) states that antiandrogen medications, such as spironolactone, are utilized to decrease hirsutism and acne among PCOS patients. Treatment usually must last longer than 6 months to receive the full effect in reducing hirsutism due to their impacts on terminal hair growth. These medications are typically second-choice if COCs are not effective. Current research indicates that they do not have the same impacts on estrogen and progesterone regulation as COCs. As such, they are not considered effective in addressing the other consequence of PCOS-related hormone imbalances (Morgante et al., 2018). However, considering the relationship between hyperandrogenism and PCOS-IR, further research is indicated to evaluate whether types of antiandrogen treatments could reduce the negative effects of hyperandrogenism on ovulation. Depending on the side effects of the specific antiandrogen medications, treatment may be contraindicated and should only be initiated after a comprehensive evaluation by a physician.

### *Assisted Reproductive Medication and Technology*

While there are many women with PCOS who conceive naturally, Kriedt et al. (2019) and Balen et al. (2016) discuss that it is the most common cause of anovulatory infertility. As such, PCOS patients desiring to conceive may need medical intervention to do so. The first steps to address infertility are understanding the underlying causes specific to each woman. These may include imbalances of reproductive hormones, being overweight or obese, and ovarian qualities. For women who are overweight or obese, weight reduction through dietary changes and exercise may be enough to improve the regularity of the menstrual cycle and frequency of ovulation

enough to promote conception. In other instances, weight reduction does not significantly improve hormonal regulation or ovulation frequency. Besides proper disease management noted earlier, the primary treatments to pregnancy are medications that promote ovulation. Other options include gonadotrophins, laparoscopic ovarian drilling (LOD), and assisted reproductive technology (ART). Invitro fertilization (IVF) is often not considered for PCOS due to the risk of ovarian hyperstimulation syndrome. Pharmacological interventions detailed within the realm of this paper for PCOS include CC, aromatase inhibitors, metformin, and gonadotrophins (Kriedt et al., 2019; Balen et al., 2016).

**Clomiphene Citrate**. Sanoski and Vallerand (2019) along with Kriedt et al. (2019) explain that CC blocks estrogen receptors to increase GnRH pulsatility and gonadotrophin secretion to promote ovarian follicular development and ovulation. Research demonstrates that CC is often successful in inducing ovulation in many women. Onset of ovulation should occur within 5-14 days after completing a course of the medication. For the medication to work properly, anterior pituitary, thyroid, and adrenal function must be present. Additionally, the medication is metabolized by the liver and should not be given to women who have liver disease or dysfunction. Other potential contraindications or cautions when using CC include pituitary tumors, undiagnosed uterine bleeding, endometriosis, and fibroids. There is always a risk of multiple pregnancy when using CC, so this must be monitored. Some women may experience side effects such as headaches, vision abnormalities, hot flashes, abdominal discomfort and irregularities, elevated liver enzymes, ovarian cyst formation or ovarian enlargement, weight gain, or ovarian hyperstimulation syndrome (OHSS). These side effects are potentially serious and should be evaluated on a patient-by-patient basis. OHSS states that the symptoms of OHSS may include ascites, pleural or pericardial effusions, and gastrointestinal upset. If left untreated,

OHSS may be fatal (Sanoski & Vallerand, 2019; Kriedt et al., 2019). Though there is the potential for successful conception, PCOS patients must consider the significant risks of complications, such as OHSS, prior to taking CC. Mental and physical well-being should be a high priority.

Sanoski and Vallerand (2019) along with Kriedt et al. (2019) state that typical dosage for ovulatory failure is 50 mg per day for 5 days beginning on the 5$^{th}$ day of the menstrual cycle. If this does not induce ovulation, a second course of 100 mg per day for 5 days may be 30 days later. If the ovaries are hyperresponsive, a lowered dose of 25 mg per day may be indicated. More than 3 courses of medication should not be administered back to back; if patients do not successfully conceive after more than 6-12 months of medication intervention with CC, a different treatment regimen should be considered. Patients should be instructed to take the medication at the same time every day. Beginning 48 hours prior to anticipated ovulation, the patient should engage in sexual intercourse every other day throughout the ovulatory period to increase the chance of conception. Prior to and during medication usage, the patient should be evaluated for ovarian characteristics, liver function, hormone levels, and other relevant health characteristics. Ultrasound monitoring should be done to evaluate endometrial development and optimal intercourse timing (Sanoski & Vallerand, 2019; Kriedt et al., 2019).

As indicated, CC may be a beneficial option for women who desire to conceive. Yet, it may not be effective or safe for all women as each patient has unique factors to consider. Further research could be initiated regarding the potential for creating medication similar to CC for general regulation of ovulation without the high risk of increased cysts and ovarian hyperstimulation. Additionally, potential long-term health risks should be evaluated for those who receive numerous doses of CC.

**Aromatase Inhibitors.** Aromatase Inhibitors, specifically letrozole, are given to reduce levels of estrogen and are typically used to treat certain types of breast cancers or for stimulation of ovulation for with infertility. Kriedt et al. (2019) discusses that aromatase inhibitors inhibit the conversion of androgens into estrogens to promote ovulation as estrogen levels drop and FSH and LH are stimulated. A meta-analysis conducted by Franik et al. (2018) concluded that there is substantive evidence for the use of letrozole for PCOS patients due to its effectiveness in stimulating ovulation and facilitating pregnancy. Additionally, Franik et al. (2018) concluded that letrozole may be more effective than CC while having similar risks for OHSS, miscarriage, or multiple pregnancy. A systematic review by Gadalla et al. (2020) reported the same findings; letrozole improves ovulation, pregnancy, and live birth rates in a statistically significant manner compared to CC with or without metformin. As such, Gadalla et al. (2020) states that letrozole should be considered an alternative first line treatment for ovulation induction to CC. Kriedt et al. (2019) also states that letrozole does not cause anti-estrogenic effects within the uterus or cervix, which is beneficial for pregnancy related to follicle development and preservation of feedback mechanisms between the ovaries and pituitary gland.

Side effects of aromatase inhibitors identified by Balen et al. (2016) include headaches, back pain, gastrointestinal problems, hot flashes, and asthenia. There is some concern regarding fetal safety and teratogenic effects as well; however, research supporting this is limited (Balen et al., 2016). Overall, further research regarding side effects, effects on androgen levels, and long-term consequences of letrozole with repeated doses should be conducted. Patients considering letrozole versus other methods of fertility treatments must heavily weigh the pros and cons of each with their physician due to the individualized, multifactorial nature of infertility and fertility treatment options.

**Gonadotrophins.** Kriedt, et al. (2019) and NICHD Staff (2017b) explain that gonadotrophins are considered second-line therapy and are reserved for circumstances where other medications were proven ineffective or caused significant side effects that prohibited further use. Additionally, they may be used as part of ART to facilitate follicle growth. Gonadotrophins, typically FSH, are given by subcutaneous injection. These medications require daily monitoring and patient-specific low dose regimens to reduce potential complications such as multiple pregnancy and OHSS. Monitoring should include transvaginal ultrasound to evaluate ovum development and bloodwork to monitor hormone levels, specifically estrogen production. Multiples occur at a higher rate with gonadotrophins than with CC or letrozole. Although this is typically not a dangerous result, it is something that must be taken into consideration prior to initiating the medication (Kreidt et al., 2019; NICHD Staff, 2017b).

Balen et al. (2016) elaborates that low dose step-up regimens or step-down regimens should be implemented to reduce the risks of ovarian overstimulation. However, the low dose step-up regimen may necessitate a treatment cycle of 28-35 days. The benefits of this form of gonadotrophin therapy must be weighed against the length of treatment and patient compliance. On the other hand, a shorter, higher dose regimen typically has higher risks of multiples and overstimulation that may negatively impact both maternal and fetal health. In either case, determining the best dosage is a difficult due to its patient specific nature and the variability of hormones. It can be concluded that the safest, most effective regimen of gonadotrophins should be used, which typically involves the lower dose step-up regimen (Balen et al., 2016).

Balen et al. (2016) further explains that three or more follicles are above 14 mm in size, the patient is at significant risk of OHSS and other complications. Therefore, gonadotrophin therapy will be discontinued, and sexual intercourse is not advised until levels resolve. The

benefits of gonadotrophin therapy are dependent upon individual patient factors, but primarily involve the successful induction of ovulation and conception of a singleton pregnancy for patients who are resistant to CC therapy (Balen et al., 2016).

**Laparoscopic Ovarian Drilling.** Mitra et al. (2015) explain that LOD is a surgical procedure conducted with general anesthesia that involves electrocauterization or laser removal of parts of the ovaries that overproduce androgens in aims of restoring regular ovulatory menstrual cycles. Typically, both ovaries are done at once, with 4 locations drilled per ovary for 4 seconds at 40 joules. Patients usually return home the same day of the procedure and may return to normal activity levels within a few days, or up to 2 weeks depending on individual recovery time (Mitra et al., 2015).

Kreidt et al. (2019) along with Balen et al. (2016) discuss that LOD has similar efficacy to gonadotrophins without the risks of multiples of OHSS. PCOS patients are more likely to benefit from LOD if they have high levels of LH; however, hyperandrogenism, obesity, and other factors may reduce the likelihood of effectiveness of LOD for ovulation induction. Risks associated with LOD may include postoperative adhesions, damaging the ovarian reserve, and other risks associated with surgical procedures like infection, bleeding, and accidental injury. LOD serves as a way to temporarily increase the likelihood of ovulation and conception, but does not solve the underlying condition and will not address any other clinical manifestations a patient may experience. Patients should be carefully selected for LOD due to its potentially damaging effects to long-term ovarian function, decreased ovarian reserve, and future fertility (Kriedt et al., 2019; Balen et al., 2016).

Mitra et al. (2015) elaborate that the exact mechanism of action is not yet determined. However, the currently supported theory involves the consequential rise in FSH after the

destruction of some ovarian follicles and decreased androgen levels. This may be combined with increased insulin-like growth factor-1 and gonadotrophin delivery related to the inflammation and bodily response to surgery. Success of LOD varies per person depending on other pertinent factors, such as the patient's androgen levels, weight, and severity of IR. Rates of miscarriage are low, as are the risks of multiples. The marked improvement in reproductive hormone release and regularity demonstrates the effectiveness of LOD. However, as mentioned previously, these results will likely only last for a year or so due to the chronic endocrine dysfunction present with PCOS. LOD is seen as more cost-effective than gonadotrophin therapy and has less need for monitoring. After a LOD procedure, anovulation for 6-8 weeks or failure to conceive for 12 months with regular ovulation is considered a failure. However, other ovulation induction agents may be considered due to the increased responsiveness to the ovaries after LOD. Repeating LOD, even after multiple years between procedures, is typically not conducted due to the increased risk of adhesions and premature ovarian failure (Mitra et al., 2015).

## Nursing Considerations and Patient Education

PCOS patients must consider a myriad of information upon diagnosis and throughout their lives as they manage their condition. Many patients, especially those who have low health literacy levels, may not understand the nuances of PCOS management without sufficient teaching. Nurses and other healthcare professionals must consider the extensive systemic ramifications of PCOS, including cardiovascular, endocrine, metabolic, and psychological, and the immense need for high-quality patient education. While this is most critical in women's health and endocrinology, medical professionals in all specialties need a comprehensive understanding of PCOS considering its numerous complications and prevalence among females. Holistic, comprehensive healthcare across a multitude of specialties provides the best care for

PCOS patients and may significantly improve outcomes. As such, registered nurses and advanced practice nurses have both the responsibility to and unique capabilities for educating PCOS patients and advocating on their behalf to achieve the level of care required to follow evidence-based practice.

The hands-on care and rapport developed between nurses or advanced practice nurses and patients have the potential to greatly affect patient outcomes. Foundationally, nurses can improve patient health and wellbeing by simply listening to symptoms and patient concerns. A thorough assessment may reveal symptoms, such as abnormal menstruation, hirsutism, and weight gain, that all are all connected to PCOS. This is the first step in diagnosing PCOS and its complications, followed by reporting the findings and taking proper action. Any symptom or concern warrants investigation and discussion to thoroughly promote health. Nurses are called to be patient advocates, which entails caring about their situation and initiating necessary actions. Additionally, nurses are key contributors to patient education, providing key information on disease prevention and treatment options during their conversations with patients. This requires nurses to be educated on treatment options and effectively communicate when patients have questions or lack sufficient knowledge to make informed decisions regarding their healthcare. This often begins with education about healthy diet and exercise and encouraging patients to engage in other regular health maintenance activities. Preventative education may help patients pursue comprehensive management of their well-being, both physical and mental. In essence, nurses and nurse practitioners have the power to change outcomes by equipping and empowering PCOS patients with practical knowledge.

## Conclusion

The extensive research compiled for this integrative review revealed promising research developments along with multiple gaps in the literature for PCOS patients. Although treatments are improving, there remains a need for gynecologic and obstetric research. PCOS patients often lack resources for disease management, particularly because they do not receive sufficient education or have adequate long-term medical counseling (Cooney & Dokras, 2018). This inhibits disease management, worsens health outcomes, and drastically elevates healthcare costs for this patient population throughout the lifespan (Cooney & Dokras, 2018). Hormonal birth control and assistive reproductive medications or procedures may help patients to some extent, but they do not address the source of the hormone and metabolic abnormalities associated with PCOS, especially PCOS-IR.

The complicated, multifactorial nature of PCOS, while puzzling and difficult to treat, also presents opportunities for research in numerous areas. Further research should continue to evaluate the etiology of PCOS, particularly any genetic links. Additionally, maternal influences, particularly androgen levels and PCOS diagnosis, should be researched. Currently, research indicates a correlation between maternal hyperandrogenism or PCOS and the prevalence of PCOS in female offspring, however, more evidence is necessary to determine the connection. For example, should women's testosterone levels be tested during pregnancy? Subsequently, if hyperandrogenism is present, are there medications or other ways to regulate testosterone and reduce the potential for PCOS in offspring? Similar questions can be asked of AMH levels. For women who have excessive AMH, can this be inhibited in some way to allow for proper ovulation? PCOS has been correlated with multiple conditions, including endometriosis and autism spectrum disorder (ASD). Thus far, maternal hyperandrogenism in utero along with fetal

genetic changes in the CYP17A1, CYP19A1, and CYP11B1 pathways have been linked to both ASD and PCOS, especially when mothers have PCOS and its resulting endocrine abnormalities (Fillipou & Homburg, 2017). These connections and others must be further investigated for genetic and etiologic similarities to progress potential treatment and management options.

As indicated throughout the research, efforts to maintain a healthy weight and other lifestyle factors that reduce IR are a foundational component of PCOS care. Yet, countless women with PCOS are ill-equipped to implement these changes due to a lack of education and empowerment. The current pharmacological treatment modalities primarily involve hormonal birth control options, with metformin for IR if necessary. However, birth control does not resolve the underlying problems associated with PCOS and may be ineffective or contraindicated in some patients. This brings into question whether physicians are quick to prescribe medications without educating patients on other PCOS management strategies.

Overall, research suggests that comprehensive care, including diet, exercise, and supplements must be an integral part of PCOS management. However, further research is necessary to evaluate specific dietary recommendations, exercise types, and potential supplements, particularly inositols, for PCOS management. Additionally, evaluating the potential benefits of providing PCOS patients with a nursing case manager for long-term disease management should be considered. The prevalence of PCOS and its potential ramifications indicate the need for both more extensive research and higher quality patient education to help improve their quality of life.

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