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Polycystic Ovary Syndrome: Pathogenesis, health consequences, and treatment of PCOS in relation to insulin resistance

Danielle Bernier
University of New Hampshire - Main Campus

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The purpose of this paper is to present a review of the current research on polycystic ovary syndrome (PCOS). PCOS is one of the most common endocrine disorders in women of reproductive age, affecting 5-10% of the population. Despite its prevalence, PCOS remains largely under unknown. This review has been broken down into two separate chapters. The first is the pathogenesis and related health consequences of PCOS. This chapter focuses on the diagnosis of PCOS as well as the prevalence and incidence of the disease. It then delves into the pathogenesis with a focus on genetics, obesity, insulin resistance and birth weight. Lastly, the health consequences related to PCOS are discussed, with a focus on insulin resistance. The health outcomes reviewed include the metabolic syndrome, cardiovascular disease, and type II diabetes mellitus. The second chapter is a comparison of drug therapies and lifestyle modifications used to treat polycystic ovary syndrome. A short discussion on combination therapy is also included. By focusing on insulin resistance in treatment, it is possible to manage many of the symptoms of PCOS solely through lifestyle modifications. Although many questions remain surrounding polycystic ovary syndrome, this article provides a summary of the current research.

Pathogenesis and the Related Health Consequences of Polycystic Ovary Syndrome In Relation to Insulin Resistance

Introduction

Polycystic Ovary Syndrome (PCOS) is a heterogeneous disorder. As one of the leading causes of anovulatory infertility, it is believed that 5-10% of the reproductive-aged female population is living with polycystic ovary syndrome. (1) First recognized in 1935, PCOS is characterized by the presence of polycystic ovaries, menstrual irregularities, and clinical/biochemical hyperandrogenism. (43) The development of PCOS has been linked to hereditary and environmental factors including genetics, insulin resistance, obesity and birth weight. The presence of PCOS is associated with an increased prevalence of adverse health conditions such as the metabolic syndrome, cardiovascular disease and type II diabetes mellitus. Insulin resistance is believed to play a key role in the development of PCOS and in the development of related conditions. In the past few years, research has been done to better understand the mechanisms behind the development polycystic ovary syndrome and the impact it has on the female body, particularly in relationship to insulin resistance.

Diagnosis

Polycystic ovary syndrome is a largely under diagnosed disorder. PCOS was first identified in 1935; it was described as a clustering of symptoms including enlarged ovaries, obesity, hirsutism, and chronic anovulation. (43) However, it took another fifty-five years before formal criterion were proposed for the diagnosis of PCOS. (48) Polycystic ovary syndrome is

now diagnosed based on the presence of the following criteria: clinical and biochemical hyperandrogenism, menstrual irregularities, and the presence of polycystic ovaries. Common features of the disease which are not part of the diagnosis include insulin resistance, luteinizing hormone (LH)/follicle stimulating hormone (FSH) concentrations, and obesity. (33)

Clinical Hyperandrogenism

Clinical hyperandrogenism is one of the more noticeable features of PCOS. Women are often diagnosed with PCOS when they seek treatment options from their healthcare provider for some of the negative cosmetic outcomes associated with PCOS. Clinical androgen excess in women with PCOS manifests in the form of acne, hirsutism, and/or alopecia. Acne typically occurs on the face or the back. The presence of acne is correlated with an increase in DHEAS and it is often one of the first clinical signs of hyperandrogenism in women. (38) Hirsutism is male-pattern excess hair growth. Common areas for hair growth include the side-burns, chin, naval area, and chest. Hirsutism is ranked according to the Ferriman-gallwey scale. (33) A score of 6-8 is mild, 8-15 is serious, and greater than 15 is classified as overt hirsutism. A woman is considered hirsute with a score greater than eight. (15) Alopecia, or hair loss, occurs in the form of male-pattern baldness. Alopecia is less common in women with PCOS than hirsutism and acne but it does still occur. With each of these clinical symptoms, it is important to remember that there could be another cause responsible other than PCOS. It is important to rule out other possible etiologies.

Biochemical Hyperandrogenism

Biochemical hyperandrogenism is another key feature in women with PCOS. Androgens measured for diagnosis include total testosterone, dehydroepiandrosterone sulfate (DHEAS), and

free androgens. Some researchers believe serum androstenedione and free testosterone should also be used in the diagnosis of PCOS. However, these androgen levels can be difficult to measure. For this reason, specific cut-off points for hyperandrogenism have not been identified. Instead there are ranges for each androgen which may be indicative of PCOS. When measuring for biochemical hyperandrogenism, it important to exclude other etiologies. Examples include Cushing's syndrome or virilizing tumors. (33)

Menstrual Irregularities

Menstrual irregularities including oligio-/amenorrhea or chronic anovulation are common features of PCOS. Women are often diagnosed with PCOS when they seek treatment for menstrual irregularities or when they have difficulty becoming pregnant. A woman with oligio-/amenorrhea has infrequent or very light menstruation. During the first two years post menarche, irregular cycles are common. After this time, cycles should normalize. At this time, oligiomenorrhea can be identified as less than 9 menstrual cycles per year. Amenorrhea is defined as cycles lasting more than 90 days. (16) Some women with PCOS may have normal menstruation patterns but they may not ovulate. This means ovulation cannot be determined solely by the presence of menstruation. Chronic anovulation is diagnosed based on progesterone levels on days 20-24 in the menstrual cycle. (33) Menstrual irregularities are one of the main reasons women with PCOS have difficulty becoming pregnant. Often, it is not until a woman has difficulty becoming pregnant that she will seek guidance from a medical provider.

Polycystic Ovaries

As referenced by the name, PCOS can also be identified by the presence of polycystic ovaries. Polycystic ovaries are identified by the presence of at least one ovary greater than 10

cm^3 or the presence of 12 or more follicles between 2-9 mm in diameter. Follicles are fluid-filled sacs which can grow on one or both of a woman's ovaries. The presence of polycystic ovaries is typically identified with a transvaginal ultrasound. This produces better results than the transabdominal route. However, for virgin, adolescent girls, the transabdominal route is a suitable method for diagnosing the presence of polycystic ovaries. (33)

National Institute of Health Criteria

From the time it was identified in 1935, until 1990, there was no formal tool for diagnosing polycystic ovary syndrome. In 1990, a conference was held by the National Institute of Health (NIH) to finally establish minimal criteria. A questionnaire was sent out to 58 researchers who voted on the criteria. Researchers agreed that PCOS would be defined as menstrual irregularity- oligomennorhea or anovulation, clinical or biochemical signs of hyperandrogenism, and the exclusion of other causes of these two criteria such as androgen-secreting tumors or Cushing syndrome. (48) This remained the main the diagnostic tool for PCOS until the Rotterdam conference was held in 2003. (See Table I)

Rotterdam Criteria

In 2003, a conference was held by the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology in Rotterdam, Netherlands. The purpose of this conference was to revisit the criteria for diagnosing PCOS. Experts in Europe believed that polycystic ovarian morphology detected by ultrasound should be considered as a diagnostic criterion. The decision made in Rotterdam for the diagnosis of PCOS was that women must meet two of the following three criteria: chronic oligo-ovulation or anovulation, clinical or biochemical androgen excess with the exclusion of other etiologies, and the presence of

polycystic ovaries based on an ultrasound. The Rotterdam definition provided a broader set of criteria than the NIH definition, allowing for increased diagnosis. Under the Rotterdam criteria, women without androgen excess or without menstrual irregularities could still be diagnosed with PCOS. (46) These criteria remained the main diagnostic tool until 2006. (See Table I)

Androgen Excess Society Criteria

In 2006, the Androgen Excess Society proposed that the criteria for the diagnosis of PCOS be tightened. There was controversy surrounding androgen excess as a key feature of PCOS. Many believed that androgen excess is an integral component of the disease. After a review of the phenotype literature on PCOS, the panel of experts concluded that only those with clinical or biochemical hyperandrogenism are at increased metabolic risk. The diagnosis criteria were changed once again to include androgen excess as a necessary component with the exclusion of other etiologies. Additionally, a formal diagnosis required the presence of either oligo/anovulation or polycystic ovary morphology. (33) Currently, the National Institute of Health, Rotterdam, and Androgen Excess Society criteria remain the three main diagnostic tools for PCOS in the adult population. (See Table I)

Adolescents

Criteria for adolescents suspected of suffering from PCOS have not been specifically identified. It is suggested that the criteria used by adults also be used for adolescents. However, this proves to be difficult, especially during puberty and in the early years following menarche.

One problem with using the adult criteria for the diagnosis of PCOS is that it is difficult to identify menstrual irregularities in the first few years post menarche. It can take up to 3-5 years for menstrual cycles to become normal. (34) A Chilean study found the average menstrual

cycle length to be 45.4 in the first year following menarche. (5) Based on this information, most young girls would meet the adult criteria for menstrual irregularities. It has been suggested that for adolescents, menstrual dysfunction should be defined as cycles lasting longer than 90 days or persistent cycles lasting more than 45 days. (34)

Another problem with using the adult diagnostic tools is that it can be difficult to identify hyperandrogenism during puberty. Serum testosterone concentrations are higher during adolescence and do not peak until around twenty. This would make it appear that most girls are suffering from biochemical hyperandrogenism. Clinical signs of PCOS are also difficult to diagnose. In the first few years post-menarche, adolescents have had little exposure to the androgens in their body. Increased androgen levels have had little time to manifest as the clinical symptoms of PCOS such as acne, hirsutism, and alopecia.

In an article in *Fertility and Sterility*, it was suggested that adolescents should be diagnosed with PCOS based on the presence of four of the following five criteria: clinical and biological evidence of hyperandrogenism, hyperinsulinism, oligo-/amenorrhea, and polycystic ovaries. (44) This is an interesting set of criteria since it suggests hyperinsulinism which is not normally a diagnostic tool for PCOS. Further research would have to be done before using this set of criteria in practice.

Regardless of the diagnostic criteria used, it is important to screen for polycystic ovary syndrome at a young age. When PCOS is diagnosed early on, healthcare practitioners can work with young women to help manage the disease and possibly delay or prevent the development of some of the manifestations of PCOS. This could ultimately improve the reproductive health of

adolescent girls and deter the development of other diseases associated with PCOS which will be discussed later.

Prevalence and Incidence

Prevalence

Based on the current criteria, the prevalence of PCOS is between 5-10% in reproductive aged women. (1) It is difficult to determine the exact prevalence of PCOS for a variety of reasons. One issue is that healthcare providers do not always use the same criteria to identify PCOS. As mentioned above, there are the National Institute of Health, Rotterdam, and Androgen Excess Society criteria which are all in use.

A retrospective birth cohort study was done on 728 women born between the years of 1973-1975 to analyze the difference between these three criteria. The 728 women were interviewed when they were between the ages of 27-34. Based on the NIH criteria, 8.7 +/- 2% were diagnosed with PCOS. Based on the Rotterdam criteria, the prevalence was 11.9 +/- 2.4%. Lastly, under the AES recommendations, PCOS prevalence came in at10.2 +/- 2.4%. Although the same women were analyzed for all three criteria, results varied.

A similar study was done in 2009 of Iranian women living in Isfahan, Iran. Again, there was a large range in the prevalence of PCOS based on the different criterion used. The prevalence was estimated at 7% for the NIH criteria, 15.2% for the Rotterdam criteria, and 7.92% for the AES criteria. In this study, the results of the Rotterdam criteria were double that of the other two. (32)

A second problem with determining the prevalence of PCOS is that it remains a highly undiagnosed disease. In the study of the 728 women born in the US, 68-69% of the women suffering from PCOS had not been previously diagnosed. (31) Also, adolescents are rarely screened for the disease in studies since parental consent must be obtained. Based on an Iranian study, the current estimate for adolescents with PCOS is around 3%. This was a random cross-sectional study done in Iranian high schools. (21) One reason this value is much lower than among the adult population is that a specific set of criteria has not been identified for adolescents in diagnosing PCOS.

It has been determined that the prevalence of PCOS also varies based on ethnicity and geographic location. In a 1998 study done in the Unites States, 4.7% of Caucasian women were diagnosed with PCOS compared to 3.4% of African American women. (27) In a separate study on Mexican-American women, this number was much higher, estimated to be at around 12.8%. (35) In a study of 393 premenopausal women from Madrid, Spain and 199 women from Bologna, Italy, prevalence of PCOS was found to be 5.4% (95% CI: 3.6-7.2). This was based on the National Institute of Health Criteria. In contrast, in a study done in Darwin, Australia, a staggering 15.3% of women had PCOS. The reason behind ethnic and geographic differences is not completely understood. One reason again may be differences in criteria. Another reason may be genetics and differences in dietary habits. Both of these factors will be discussed later.

Incidence

Similar to the prevalence of PCOS, the incidence of this syndrome can be difficult to determine. Although PCOS was first recognized in 1935 by Stein and Leventhal, it was not until 1990 that the NIH criteria became a standardized diagnostic tool, making it difficult to study the

incidence of PCOS before 1990. Again, the variety of diagnostic tools makes it difficult to determine the incidence. Over the past few years, there appears to have been an increase in the prevalence of this disease. However, it is not known if more women are developing PCOS or if the disease is becoming more well known and medical practitioners are becoming better at diagnosing it.

Looking just at the results of the studies conducted by March and Mehrabian, little can be drawn about trends in the incidence of PCOS. The NIH percentages ranged from were 8.7 and 7, the Rotterdam percentages ranged from 11.9 and 15.9, and the AES percentages were 10.2 and 7.9 respectively. Depending on the criteria used, the incidence of PCOS both increased and decreased between these two studies. Of course, these two studies are not the best comparison since one took place in the United States and the other in Iran. As previously mentioned, there are differences in the prevalence of PCOS based on geographic region. To properly analyze the incidence of PCOS, similar populations would need to be analyzed using the same diagnostic criteria over a period of time.

Pathogenesis

The cause of PCOS is currently unknown but the etiology appears to be heterogeneous. Links have been made between heritable and environmental factors. These factors include genetics, insulin resistance, obesity, and birth weight as related to the adipose tissue expandability hypothesis.

Genetics

Recent studies provide support for a genetic component of PCOS with evidence of the disorder occurring among women of the same family. A cross-sectional study was done evaluating 29 families with a history of polycystic ovary syndrome against 10 control families. There was found to be nearly a 50% prevalence of PCOS among siblings. (19) In a similar study, the first degree relatives of 14 women with PCOS were screened. Female relatives were screened for the presence of polycystic ovaries and male relatives were screened for male pattern baldness. Again, the first degree relatives of women with PCOS had a 51% chance of being affected. The results of these two studies indicate a single gene effect or autosomal dominant inheritance. (4)

It has also been found that siblings of women suffering from PCOS are at increased for hormonal abnormalities related to the disorder. Eighty-six siblings of women suffering from PCOS were compared to 100 controls. Mean testosterone, DHEA-S, androstenedione levels, and free androgen index were all higher among sisters of a woman with PCOS than among the control group. Similarly, men with a sister with PCOS experienced increased levels of DHEA-S. This provides additional support for a genetic component for the pathogenesis of this disease. (29)

Further research needs to be done to further evaluate the genetic component of PCOS. Although it appears to be of autosomal dominant inheritance, there is not enough evidence at this time to prove this theory. With continuing research on the human genome, it may be possible to someday identify the gene responsible for the development of polycystic ovary syndrome.

Insulin Resistance

Insulin resistance (IR) is a defining characteristic of polycystic ovary syndrome, occuring in 50-70% of the PCOS population. (9) Insulin resistance is an impaired metabolic response which occurs when cells cease to respond toordinary levels of insulin (37) IR occurs in both lean and obese women with PCOS. In contrast, in women without PCOS, insulin resistance occurs primarily in the obese. This suggests that IR is an intrinsic part of the disease. (38) Some believe that insulin resistance may be present in all women with PCOS. However, there is a lack of consistency in measuring for IR and so some women remain undiagnosed. (38).

Insulin resistance can be identified based on biochemical and clinical features. Biochemically, IR is defined as a fasting glucose/insuln ratio of less than 4.5 in obese women and less than 7 in adolescent women. One of the clinical feature of insulin resistance is the presence of acanthosis negricans. Acanthosis negricans are dark, thick skin patches located where the skin folds or bends. Common locations include the armpit, groin, neck, and joints of the fingers and toes. Visceral adiposity is another clinical feature of insulin resistance.

It is generally agreed that the euglycemic clamp technique is the most reliable tool for measuring insulin resistance. This technique works by administering a contant flow of exogenous insulin. The flow rateof exogenous insulin is held constant. At the same time this is occuring, plasma glucose concentrations are held at a normal fasting level. This allows insulin action to be compared between individuals under similar conditions. Although the euglycemic clamp technique is extremely reliable, it is also costly and time consuming. For this reason, simpler methods such as the insulin tolerance test are often employed. (37) Unfortunately, inconstistent methods of testing for IR means that it is often misdiagnosed.

A cross-sectional study was done on insulin resistance in 19 obese and 10 nonobese patients with PCOS. The PCOS patients were compared to 11 obese and 8 nonobese controls using the euglycemi clamp technique. Total body insulin-stimulated glucose usage was below the controls in 26% of obese PCOS patients and 60% of nonobese patients. (Dunaif) The results of this study suggest that inulins resitance is more prevalent among lean women with PCOS when compared to controls as opposed to obese women with PCOS when compared to controls.

Although less reliable than the euglycemic clamp technique, the triglyceride and glucose (TyG) index is a good replacement when the latter is impractal. A cross-sectional study was done to compare the effectiveness of these two techniques in measuring insulin sensitivity. There was no statistical significansce observed between groups, indicating that the TyG index is a suitable replacement for the euglycemic clamp technique. (20)

The mechanism explaining the pathogenic role of insulin resistance in polycystic ovary syndrome is not fully understood. However, there is evidence to suggest that insulin stimulates the production of androgens from the ovary. In a cross-sectional study, the effects of insulin were examined on ovarian stroma of four women with hyperandrogenism and three women without hyperandrogenism. In the hyperandrogenic patients, insulin was found to stimulate androstenedione and testosterone release from the stroma. In contrast, there was no significant release of androgens from ovarian stroma in the non-hyperandrogenic women. In the same study, a single dose of 50 ng/ml insulin was found to be equally effective as a single dose of 500 ng/ml insulin in stimulating the release of androgens from the ovarian stroma of a hyperandrogenic woman. These results suggest that hyperinsulinemia in androgenic women targets the ovarian stroma, stimulating the release of androstenedione and testosterone. (3) Based on the small

sample size of this study, additional research should be carried out to determine a relationship between insulin and the release of androgens from the ovaries.

In accordance with this, a cross-sectional study was done on a hyperandrogenic female with insulin resistance. Insulin was administered to her through an IV. Serum testosterone measurements were taken at baseline and throughout the study. After thirty-five days of this, serum total testosterone levels rose from 4.9 nmol/L to 22.8 nmol/L. Androstenedione measurements were also elevated and the volume of her ovary had doubled. When the insulin ceased to be administered, these levels all returned to normal. (8) Again, the small subject size in this study is a major weakness.

A prospective study was done to evaluate the effect that suppressing insulin has on serum testosterone levels. Insulin suppression was achieved with the administration of 100 mg, three times daily of diazoxide. Diazoxide is a drug which inhibits the secretion of insulin from the pancreas. When comparing baseline values with values upon completion, serum total testosterone levels fell from 2.5 nmol/L to 2.1 nmol/L. This again indicates a direct link between hyperinsulinemia and total testosterone levels in women with PCOS. (36)

Research suggests that levels of insulin resistance do not remain stagnant for women with PCOS. In a recent observational study, 1,212 women with PCOS were monitored for differences in hormonal, metabolic, and ultrasonographic features of PCOS between age groups. The age groups were broken down to less than 20 years old, 21-30 years old, and 31-39 years old. The degree of insulin resistance worsened as age increased. (Panidis) This is important to keep in mind given the relationship between insulin resistance and the development of other diseases. If the presence of polycystic ovary syndrome and insulin resistance can be identified early on,

perhaps the level of insulin resistance can be maintained at lower levels before it is able to worsen the symptoms of PCOS.

Obesity

Obesity is another component of PCOS which may contribute to the pathogenesis of the disorder. In patients suffering from PCOS, the incidence of obesity is somewhere between 50-75%, which is higher than in the general populaiton. (22) Not only is obesity more common among women with PCOS, research suggests that obesity may exacerbate many of the manifestations of PCOS including androgen levels and insulin resistance.

With excess weight gain, women who were previously asymptomatic may begin to show symptoms of PCOS. There is an increased prevalence of symptoms among obese PCOS patients when compared to non-obese controls. Obese women suffering from PCOS generally have higher serum androgen concentrations and a reduced response to fertility treatments when compared to lean women with PCOS. Obese women with PCOS experience greater menstrual irregularity when compared to non-obese patients. (23) There is also an increased presence of hirsutism at 73% compared to 56% for non-obese women. (26) The same can be said for the presence of acanthosis nigricans. (6)

In 2005, a single cross-sectional study confirmed many of these findings. The purpose of this study was to evaluate the impact of obesity on the manifestation of PCOS . Hormonal profiles, metabolic abnormalities, and clinical presentations of the disease were all assessed. 192 women with PCOS and 65 controls were analyzed and broken into two groups based on a BMI score above or below twenty-five. Obese women with PCOS were found to have a higher incidence of acanthosis nigricans (35.71% compared to 6.56%), higher free androgen index

levels (3.4 compared to 1.75), lower SHBG levels (108.7 compared to 192.49) and a higher prevalence of insulin resistance (82.76% compared to 20.49%). These findings provide support for the studies mentioned above. (30)

In women with PCOS, excess weight is held primarily in the abdominal region. When abdominal adipose tissue (AAT) is broken down, free fatty acid levels in portal circulation rise. This leads to chronic hyperinsulinemia. Free fatty acids impair the hepatic extraction of insulin. (45) As mentioned above, insulin resistance is a key feature in the development of PCOS. This provides additional support to explain why obesity exacerbates the symptoms of PCOS.

The age of weight gain may impact the development of insulin resistance. Obesity before menarche is associated with significantly higher androgen concentrations. This suggests that obesity associated with elevated ovarian androgen production may predispose adolescents to PCOS. (23) Weight gain should be closely monitored in adolescents to help prevent the development of insulin resistance and increased androgen levels which can lead to a subsequent decline in the symptoms of PCOS.

Birth Weight and the Adipose Tissue Expandability Hypothesis

In the general population, there is a strong positive correlation between obesity and insulin resistance. In the PCOS population, this remains true. However, the degree of insulin resistance among normal-weight women is increased. These women are identified as metabolically obese, normal-weight (MONW). A study done comparing MONW and metabolically normal controls in body fat composition found an increase in total, visceral, and subcutaneous fat in the MONW group. (10)

The relationship between MONW and PCOS may be explained by birth weight and the adipose tissue expandability hypothesis. According to this theory, each individual can safely store a certain amount of excess adipose tissue (AT) before adverse metabolic effects are observed. When this level is reached, called the metabolic set point, lipotoxicity occurs. Lipotoxicity causes an increase in free fatty acids, hypertriglyceridemia and lipid deposits in non-subcutaneous AT and in non-adipose organs. This can lead to insulin resistance**.** It is believed that women with PCOS have a lower metabolic set point than the general population. This explains why normal weight women with PCOS are insulin resistant. (50)

Birth weight is a key factor in determining an individual's metabolic set point. The number of adipocytes of an adult is set early in life. When prenatal growth is stunted, the development of AT is reduced and fewer adipocytes develop. Most infants suffering from stunted pre-natal growth will experience spontaneous catch-up growth. However, this is observed as an increase in adipocyte size rather than an increase in the number of adipocytes. With fewer adipocytes, the body has a decreased ability to safely gain fat before adverse metabolic affects are observed. When AT is properly expanded in fetal and early infant life, there seems to be increased protection against obesity related insulin resistance. (49)

Prenatal exposure to androgen excess may be one cause of stunted pre-natal growth, resulting in low-birth weight. If a woman has PCOS, she would have increased androgen levels which could potentially affect her developing fetus. However, data is inconclusive on this subject. Most of the research has only been done on animals and no effect has been observed in human studies. In one study, when exposed to testosterone, neither maternal androgenamia nor fetal androgenamia was seen to be elevated in girls who developed PCOS. Also, the fetus is protected from exposure to maternal androgens by the placenta. (49) This means that increased

maternal androgen levels should not impact the fetus. Based on this research, it seems unlikely that maternal androgen levels have much impact on birth weight. Other factors are likely responsible.

Although the adipose tissue expandability hypothesis is just a theory at this time, it provides a reasonable explanation for the relationship between insulin resistance, obesity, and birth weight in women who develop polycystic ovary syndrome. It also explains why PCOS women of normal weight are insulin resistant. Additional prospective studies need to be done to further establish a link on this topic.

Health Consequences

Women with polycystic ovary syndrome are at increased risk for a variety of health conditions. These conditions include the metabolic syndrome, cardiovascular disease (CVD) and type II diabetes mellitus (T2DM). Insulin resistance is a key feature in the development of each of these diseases.

Metabolic Syndrome

Women with PCOS are at increased risk for developing the metabolic syndrome when compared to the general population. The metabolic syndrome is a clustering of symptoms associated with insulin resistance. Diagnosis is based on the presence of three of the following five criteria: elevated waist circumference (greater than 40 inches for men and 35 inches for women), elevated triglycerides (greater than or equal to 150 mg/dl), reduced HDL cholesterol (less than 40 mg/dL in men and 50 mg/dL in women), elevated blood pressure (greater than or equal to 130/85 mm Hg), or elevated fasting glucose (greater than or equal to 10 mg/dl). (38)

One-third to one-half of all women with PCOS has the metabolic syndrome. This is more than double the prevalence of the general population. (13) In an NHANES study, this difference was even greater with 37% of girls with PCOS having metabolic syndrome, compared to only 5% among girls without PCOS. (42) In a long-term follow up study, 84 women diagnosed with PCOS were compared to 87 randomly selected controls for the prevalence of metabolic syndrome. The prevalence among women with PCOS was 23.8% compared to only 8.0% in the control group. (24)

The prevalence of metabolic syndrome is also more common among obese women with PCOS. The rate among obese women is 33-40% compared with 10-13% for non-obese controls. (7) This indicates a need to control for weight in the management of PCOS.

A cross-sectional study was done on metabolic syndrome in Mediterranean women with PCOS to help determine when and how to predict its onset. 196 PCOS women and 22 controls underwent a physical exam and laboratory evaluation for metabolic syndrome. Waist circumference, HDL, and triglycerides were determined to be the best predictors for determining risk for metabolic syndrome. It was also found that women with PCOS who met two of the criteria for metabolic syndrome were similar in a variety of parameters when compared to non-PCOS women with metabolic syndrome. These parameters included waist circumference, body mass index, blood pressure, bioavailable testosterone, triglycerides, insulin, SHBG and HDL. This indicates that women with PCOS who meet two of the criteria for metabolic syndrome are at similar risk of developing it when compared women in the general population who meet three of the criteria. (14)

The implications of these studies are important in that there is a clear association between PCOS and the development of metabolic syndrome. For this reason, there is an increased need to manage PCOS in regards to insulin resistance and obesity.

Cardiovascular Disease

Women with PCOS are also at increased risk for many of the risk factors associated with cardiovascular disease. Risk factors include the metabolic syndrome, diabetes, high blood pressure, high cholesterol, obesity, hyperandrogenemia, and dyslipidemia. (10, 39, 28)

A cross-sectional study was done to help establish the link between PCOS and CVD. Sixty-two women with PCOS were analyzed in comparison to forty-eight healthy controls. BMI, waist circumference, and blood pressure were taken as well as plasma concentrations of glucose, triglycerides, total cholesterol, and HDL. Women with PCOS showed a significantly higher TG/HDL ratio when compared to the control group. This indicates that women with PCOS are at increased risk for cardiovascular disease. The variable which had the most influence on Tg/HDL ratio was waist circumference. This indicates that abdominal obesity remains an important feature in the development of CVD, in PCOS women and the general population alike. (41)

A cross-sectional study was done to determine if the risk factors in PCOS for CHD are independent of BMI and abdominal obesity. 488 patients with PCOS were compared to 351 healthy controls. As expected, after adjusting for BMI, the PCOS women still had higher LDL, triglyceride, blood pressure, insulin and glucose levels than the control group. Additionally, PCOS women with a normal BMI also had increased insulin and glucose levels when compared to the control group. These findings indicate that the increased risk for CHD in women with

PCOS is not caused solely by the increased BMI in PCOS women. However, BMI remains a contributing factor. (18)

Although PCOS causes an increase in the prevalence of cardiovascular risk factors, there is little evidence to suggest a link with an increase in cardiovascular events. A retrospective cohort study was done to compare cardiovascular events in 309 women with PCOS and 343 women without PCOS. Women with PCOS had an average BMI of 29.4 compared to 28.3 in the control group. Despite this, there was no observed increased in cardiovascular events including myocardial infarction, coronary artery bypass graft surgery, death due to CV disease, or stroke. The last follow-up on these women was conducted at a median age of 46.7 years. Different results might exist if follow-up had been at a later age. (25)

Although there is little evidence to support a link between cardiovascular events and the presence of PCOS, a link still remains between PCOS and risk factors for CVD. With additional studies, which follow women for longer periods of time, a link might be found between PCOS and CVD events. Until then, control of insulin resistance and obesity should be the primary goal of women with PCOS.

Type II Diabetes Mellitus

Another disease women suffering from PCOS are at increased risk for developing is type II diabetes mellitus (T2DM). Insulin resistance contributes to the development of T2DM by causing the exhaustion of beta-cells. This leads to hyposecretion of insulin and which can then lead to impaired glucose intolerance (IGT) and T2DM. (2)

Approximately 30-35 % of women with PCOS have impaired glucose tolerance and approximately 7.5-10% have T2DM. (Legr**o,** Ehrmann) This places the incidence of diabetes at five- to ten-fold higher in women with PCOS compared to the general population. (12)

Type II diabetes mellitus should be diagnosed in women with PCOS by an oral glucose tolerance tests rather than fasting glucose. This was demonstrated by a retrospective study of 247 women with PCOS. When administered an oral glucose tolerance test, 14 women were diagnosed with T2DM. In contrast, only three cases were identified based on fasting glucose levels. (40)

Similar to the metabolic syndrome and cardiovascular disease, there appears to be a link between obesity and IGT and T2DM in women with PCOS. In a cross-sectional evaluation, 225 women with PCOS underwent an oral glucose tolerance test. 6 of the 104 lean women and 15 of the 121 obese women had IGT. T2DM was present in 1 of the 104 lean women and 3 of the 121 obese women. Based on this study, it appears that IGT is significantly more common among obese women with PCOS when compared to lean women. There is also a difference in the prevalence of T2DM. (47)

A similar prospective, controlled study, of 254 women with PCOS found supporting results. The purpose of this study was to determine the prevalence of and risks of developing glucose intolerance in women with PCOS. In obese women, 31.3% had impaired glucose tolerance and 7.5% had diabetes. In contrast, in the non-obese PCOS women, 10.3% had impaired glucose tolerance and 1.5% had diabetes. Despite these differences in groups, it appears that PCOS puts women at increased risk of developing T2DM and glucose intolerance,

regardless of weight. This is supported since glucose intolerance was significantly more common among PCOS women than among controls. (28)

There are nine metabolic biomarkers identified which could help to identify women with PCOS who are at risk of developing IGT and/or T2DM. They include: leucine, isoleucine, citrate, glucose, creatinine, valine, glutamine, alanine, and HDL. When compared with controls, the following biomarkers were significantly reduced in women with IGT or T2DM: valine, HDL, and alanine. When compared to controls, glucose levels were elevated. These biomarkers were identified based on a series of published studies on the topic from the years 1993-2010. Although these results are preliminary, this information has the potential to help predict the development of IGT and T2DM in women with polycystic ovary syndrome. (17)

Similar to metabolic syndrome and cardiovascular disease, it is important to identify the risks associated with PCOS and the development of IGT and T2DM. If these risks can be identified and eliminated, the development of metabolic syndrome, CVD and T2DM can be dramatically reduced. At this time, insulin resistance and obesity are two of the main factors to control for.

Conclusion

Although PCOS is one of the most common endocrine disorders in women of reproductive age, there is currently no cure for polycystic ovary syndrome. For this reason, early diagnosis of the disease based on established criteria is important. With an early diagnosis, it is possible to manage the manifestations of PCOS. With proper management, obesity and insulin resistance can be controlled for as well as the associated diseases. The current forms of treatment for PCOS will be discussed in the next chapter. The main focus is on drug therapy and

lifestyle modifications. With the proper management of insulin resistance and obesity, it is possible to dramatically decrease the negative health outcomes associated with polycystic ovary syndrome.

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A Comparison of Drug Therapies and Lifestyle Modifications Used to Treat Polycystic Ovary Syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility in women of reproductive age. (7) Affecting as many as 1 in 10 women in the United States, (21) this common endocrine disorder remains largely undiagnosed. Typically, it is not until a woman has difficult becoming pregnant that her healthcare provider will begin to notice the clustering of symptoms associated with PCOS including clinical and biochemical signs of hyperandrogenism, menstrual irregularities, and the presence of polycystic ovaries.

The majority of women with PCOS suffer from insulin resistance. Insulin resistance and the resultant hyperinsulinaemia play a key role in the pathogenesis of PCOS. Although insulin resistance is exacerbated by weight gain, normal-weight women with PCOS are also insulin resistant.

The pathogenesis of PCOS is not completely understood; there is not yet a cure for the disease. However, with the proper management of PCOS, it is possible to restore fertility, improve menstrual regularity and reduce androgen excess. This is achieved primarily through an improvement in insulin sensitivity.

The most common methods of managing PCOS are drug therapy and lifestyle modifications. Drug therapy includes the use of oral contraceptives, anti-androgens, and insulin sensitizing agents. Lifestyle modifications include weight loss, diet, and exercise. Each of these treatments can be used alone or in combination. The following review will investigate the efficacy of the major forms of treatment of PCOS.

Drug Therapy

Drug therapy is an effective form of treatment for polycystic ovary syndrome. Drug therapy can improve insulin resistance and hormonal/metabolic profiles, restore menstrual regularity, and decrease the clinical symptoms associated with PCOS. Common forms of drug therapy include combined oral contraceptives, insulin-sensitizing agents, and anti-androgens. However, there are adverse side-effects associated with each of these drugs. It is important to understand the possible risks connected with each.

Combined Oral Contraceptives

Hormonal oral contraceptives are the most common form of drug therapy used in the treatment of PCOS. Oral contraceptives allow for a restoration in menstrual cycles, although ovulation does not occur. Regular menstrual cycles are associated with a decreased risk of developing endometrial cancer. (40) Oral contraceptives are also used to treat clinical symptoms of PCOS including hirsutism and acne. They work by increasing levels of sex-hormone binding globulin (SHBG). (14) Increased levels of SHBG decrease circulating androgen levels and decrease their bioavailability. (12) With an improvement in androgen levels, there is a subsequent improvement in the clinical symptoms associated with PCOS.

A variety of randomized, prospective clinical trials have been done on women with PCOS to evaluate the effectiveness of combined oral contraceptives (COC). In two separate trials, a reduction in free testosterone and androgen levels were observed among women with PCOS when prescribed an oral contraceptive for six months. (5) (39) An improvement in hirsutism and acne was also observed in one of these studies. (39) A similar study was done comparing the effectiveness of four different types of COCs. With each of these, there was found

to be a reduction in free and total testosterone and androsteredoine by 40-60%. DHEAS concentrations were also lowered 20-50%. (6)

The combined oral contraceptive pill typically contains 15 to 50 micrograms of ethenylestriadol (EE), a form of estrogen. (12) However, the type of progestogen in each pill differs. The previous study investigated the effectiveness of four different progestogens: drospirenone, chlormadinone, desogestrel, and gestodene. Those containing drospirenone and chlormadinone led to a greater reduction in androgen levels and a greater increase in SHBG compared to the other progestogens. (6)

Differences between progestogens are not always observed. In a study investigating desogestrel and cyproterone, there was no statistical significance observed between groups in improvements in hirsutism or testosterone and SHBG levels. (23) Information and studies on the different progestogens can be contradictory sometimes. Women who choose to use combined oral contraceptives to manage some of the manifestations of PCOS should consult with their doctor about which pill is right for them.

Based on recent studies, the use of combined oral contraceptives is an effective form of drug therapy for the treatment of PCOS. The end result is an improvement in many of the clinical and biochemical features of PCOS. Although their use is common among all women of child-bearing age, little research has been to evaluate the relationship between the use of oral contraceptives and the development of disease outcomes associated with PCOS. Some studies indicate that the use of oral contraceptives may decrease insulin sensitivity and glucose tolerance. This would increase the risk for T2DM which women with PCOS are already predisposed to develop. (7)

In the Mastorakos study, there was a decrease in insulin sensitivity and an increase in total, LDL, and HDL cholesterol observed among women prescribed the pill. (23) Some women may feel this cancels out the benefits of taking COCs. It is important to consider all the effects before starting on the combined oral contraceptive pill. (See Table II)

Insulin Sensitizing Agents

Insulin Sensitizing agents are another form of drug therapy used in the treatment of PCOS. Common forms of insulin sensitizing drugs include metformin and rosiglitazone. These drugs are intended to be used in combination with diet and exercise. They are commonly prescribed to people with type II diabetes mellitus. These drugs work primarily by inhibiting hepatic glucose production and increasing insulin sensitivity in the peripheral tissues. (3)

Treatment of PCOS with both rosiglitazone and metformin is effective in improving menstruation, androgen levels and the associated clinical symptoms. In a six month trial of each drug administered alone or in combination, both resulted in increased rates of ovulation when compared to a placebo. An improvement in serum free testosterone was also observed. However, fasting insulin levels only showed an improvement following the use of metformin. (4) In another 6 month trial, similar results were observed with both drugs including a decrease in fasting insulin, postprandial insulin, HOMA-IR, LH, triglyceride, LDL, and testosterone levels. A decrease in BMI was only observed with the metformin group. (20) Based on these and similar studies, metformin has emerged as the leading insulin-sensitizing agent prescribed in the treatment of PCOS.

To test its efficacy, a trial was done in India, investigating the impact of metformin when administered daily for three months. In this prospective study, there was an observed decrease in serum insulin and serum testosterone with a positive correlation between the two. This positive

correlation reveals an etiological connection between insulin resistance and some of the clinical features of PCOS related to increased testosterone levels. With metformin therapy, the study subjects also experienced a fall in fasting plasma glucose to insulin ratio; a marker of insulin resistance. (32)

The benefits of metformin treatment are obvious. However, similar to other forms of drug therapy, the risks of metformin should be carefully considered. Common side-effects include nausea and diarrhea. On rare occasion, lactic acidosis has occurred. This typically occurs in conjunction with renal or cardiovascular disease. It is unknown if metformin is safe to use during pregnancy. Despite this, medical practitioners continue to prescribe it to help prevent the development of gestational diabetes. (3) Before starting on metformin therapy, women with PCOS should carefully consider the associated risks, especially if they are pregnant or planning to become pregnant. (See Table III)

Anti-androgens

Anti-androgens are used to improve the biochemical profiles of PCOS women. This leads to an improvement in clinical symptoms such as hirsutism and acne. The improvements seen from anti-androgens are similar to those experienced with oral contraceptive use, but the improvements are greater. Anti-androgens work by attaching to androgen-binding receptors through competitive inhibition. Anti-androgens can also decrease androgen production. Examples of anti-androgens prescribed include spironolactone, flutamide, and finasteride. (3)

Of the anti-androgens mentioned, flutamide and sprinolactone are the most commonly used. In a prospective trial, when sprinolactone was taken over nine months in combination with Diane 35, a significant improvement in the ferriman-galleway score was observed. The effects with flutamide were similar. (25) However, in a 12 month clinical trial, flutamide was found to

be more effective than sprinolactone in the treatment of hirsutism. (24). In another six month trial, the use of sprinolactone was found to increase flow mediated dilatation. This leads to improved endothelial function and an improvement in cholesterol levels. (35) It is important to consider which aspects of PCOS you are trying to manage before beginning drug therapy. Although sprinolactone and flutamide are similar, the above studies indicate that they do not always have the same effects.

Once again, there are risks associated with taking anti-androgens which should be carefully considered. They can cause fatigue, dizziness, headaches, nausea, breast tenderness, weight gain, loss of libido, hypotension and hepatoxicity. Liver and renal function should be monitored while on these drugs. Anti-androgens can also cause menstrual irregularity and can feminize a male fetus if a woman becomes pregnant. For these two reasons, anti-androgens are often taken in conjunction with the oral contraceptive pill.

In a prospective study, the consumption of licorice was found to reduce the diuretic effect of sprinolactone. Licorice works by impacting plasma rennin activity. (2) Unfortunately, the other side-effects of anti-androgens cannot be controlled through the consumption of licorice. It is very important to consider all options before beginning anti-androgen therapy. This is one of the last forms of treatment which should be used in the treatment of PCOS because of the associated side-effects. (See Table IV)

Lifestyle Modifications

Unlike drug therapy, there are no adverse side-effects associated with lifestyle modifications in the management of PCOS. (14) Lifestyle modifications should be the first line

of treatment prescribed to women with PCOS since is no evidence to suggest that drug therapy is any more effective. Lifestyle modifications include weight loss, dietary treatments, and exercise.

Caloric Restriction to Achieve Weight Loss

Mild to moderate weight loss dramatically reduces the symptoms of PCOS. Weight loss of only 2-7% of initial body weight leads to improved ovulation and a reduction in androgen levels (26). An important feature of weight loss is that it leads to an improvement in insulin sensitivity. This leads to a restoration in menstrual cycles, ovulation, and fertility and an improvement in androgen levels. (36)

Although the optimum diet for women with PCOS is unknown, hypocaloric diets can help facilitate weight loss. A hypocaloric diet is not designed to be restrictive in any particular nutrient. The goal is simply to reduce caloric intake. PCOS women on this type of diet experience improvements in both reproductive and metabolic abnormalities including insulin resistance. (34)

In a prospective study of 144 obese women with PCOS, participants were placed on caloric restriction for four weeks. Participants experienced an increase in SHBG and a decrease in free testosterone. When weight loss was greater than 5%, there was a statistically significant improvement in fasting insulin levels. More than 80% of those suffering from menstrual dysfunction saw an improvement in menstrual regularity. An improvement in hirsutism was also observed among women who lost more than 5 % of their body weight. (38)

Similarly, a study was done in which subjects were assigned to one of two energy restricted diets; either a high protein or high CHO diet, with a similar fat content in each group. Each diet led to weight loss and an improvement in menstrual and metabolic abnormalities. This includes an improved fasting insulin level following a 3-hour OGTT. Regardless of the content

of the diet, the energy restriction facilitated weight loss which led to an improvement in insulin sensitivity and an improvement in other symptoms.

The main goal of weight loss should be to reduce visceral adiposity which is associated with insulin resistance and the metabolic syndrome. In one study, 13 obese-women with PCOS were placed on a hypocaloric diet plan. Their mean weight loss was 12.4 kg with a reduction in truncal-abdominal skin-folds of 28% indicating that much of their weight loss was around the abdomen. This resulted in an improvement in insulin sensitivity of 132% and an increase in SHBG of 35%. (15)

One argument against lifestyle modification is that weight loss can be difficult for women with PCOS. However, a retrospective study of 117 women found that weight loss is attainable simply by providing women with general advice on weight loss and exercise. Of the subjects interviewed, 40% lost more than 5% of their initial body-weight 6 months after receiving advice from her medical provider. After one year, more than 20% had lost at least 10% of her body weight. With very little intervention, it was possible for obese women with PCOS to lose a significant amount of weight and to maintain this for more than three years. (28)

Based on this information, it is very feasible for women with PCOS to manage their symptoms through weight loss. Losing only a few pounds can have a profound effect and will also result in better overall health. (See Table V)

Diet- Macronutrient Modifications

In addition to caloric restriction, macronutrient modifications are another form of dietary treatment for PCOS. With the knowledge that insulin sensitivity and hyperinsulinaemia play important roles in the pathogenesis of PCOS, it is important to try to control blood glucose and

insulin levels through diet. The effects of dietary composition have been observed both in conjunction with weight loss and independent of weight loss. (22)

One proposed diet is the consumption of carbohydrates low on the glycemic index. Most women with PCOS experience compensatory hyperinsulinemia following carbohydrate ingestion. Consuming foods low on the glycemic index (GI) would help reduce this. In a randomized, prospective study, ninety-six women with PCOS were assigned to follow a reduced-energy, low-fat, low-saturated fat diet which was moderate-to-high in fiber. These women were then randomly assigned to consume foods which were either low or moderate-to-high on the glycemic index. They followed this diet until they had achieved 7% of weight loss or for 12 months. When prescribed the low-glycemic index diet, women with PCOS showed greater improvements in insulin sensitivity following an OGTT and greater improvements in menstrual regularity. Although similar results were observed with the conventional healthy diet, there was a statistical significance between groups. (20)

Restricting carbohydrate intake, independent of glycemic load, has similar effects. In a randomized, prospective study, subjects consumed a standard diet, low carbohydrate diet, and a high MUFA diet for 16 days each with a three week wash out period in between Subjects were instructed to maintain their weight, and the diets were developed to be eucaloric. Without weight loss, subjects on the low-CHO diet still experienced improved fasting insulin and AIRg levels compared to the standard diet. This indicates that although weight-loss is an important feature in the management of PCOS, carbohydrate content is another key feature. (8)

To investigate which is more important, weight loss or carbohydrate intake, a randomized, 12-week study was done to evaluate the difference between a hypocaloric diet and a low CHO diet. Improvements were observed for both groups in BMI, waist circumference, and

menstrual function. However, there was no statistical significance between groups. This indicates that weight loss and carbohydrate intake are two separate but important components in the treatment of PCOS. (27)

Another macronutrient studied in the treatment of PCOS is protein. In a cross-sectional study, subjects consumed either a high protein or high carbohydrate meal. The high carbohydrate meal caused more hyperinsulinemia and a greater change in blood glucose. Intake of the high-protein meal suppressed ghrelin levels longer which may have a satietogenic effect. This in turn would decrease appetite and potentially lead to weight loss. (17)

The effect of a high-protein diet can also be observed independent or carbohydrate consumption. In a 6-month prospective trial, subjects consumed either a high protein or standard protein diet. Women on the high protein diet experienced greater weight loss (4.4 kg), body fat loss (4.3 kg), and a greater reduction in waist circumference. When adjusted for weight loss, women on the high protein diet had greater improvements in glucose metabolism. (33).

Lastly, the third macronutrient to consider is fat. The consumption of long-chain polyunsaturated fatty acids (LC-PUFAs) are known to improve metabolic health. This suggests that an increased consumption in PUFAs could be beneficial to women suffering from PCOS. In a randomized, cross-sectional investigation, subjects were assigned to consume a PUFA supplement or placebo daily. Women with increased n-6 concentrations have higher levels of circulating testosterone and DHEA-S. A higher n-6: n-3 ratio is also associated with higher levels of circulating androgens. LC-N3 PUFA supplements should then lead to an improvement in androgen levels. As expected, the subjects who received the n-3 supplement experienced a decrease in plasma testosterone concentration. A similar reduction in testosterone levels was also seen in women who experienced a reduction in the ration of n-6 to n-3 PUFAs. (29)

Additional research needs to be done to further evaluate the effectiveness of various dietary programs on the treatment of PCOS. While hypocaloric, low-carbohydrate, high-protein, and high n-3 PUFA diets appear to reduce the symptoms of PCOS, there remains plenty of room for continued research. Little has been to evaluate the effectiveness of combined forms of dietary treatments which focus on more than one macronutrient. Perhaps the optimal diet for women with PCOS is a combination of the diets discussed above. (See Table VI)

Diet- Micronutrient Modification

The focus of most dietary treatments for PCOS focus on macronutrient content. However, micronutrient content may also play an important role. Vitamin D is one of the micronutrients believed to impact PCOS. Through previous animal and human studies, it is known that vitamin D deficiency is associated with impaired insulin secretion and glucose clearance. (19)

To evaluate the impact of low 25(OH)D levels in women with PCOS, 100 infertile women were randomized to receive either a calcium and vitamin D supplement or a placebo. Following this six month prospective study, BMI decreased significantly for those taking the supplement. There were also greater improvements in menstrual cycle regularity, follicular maturation, infertility, and androgen levels. (9)

Vitamin D supplementation may also help improve insulin resistance. A cross-sectional study was done to evaluate vitamin D levels in over 500 women with PCOS. Anthropometric, metabolic, and endocrine measures were taken for each of these women as well as an oral glucose tolerance test. A negative correlation was found between the degree of insulin resistance and 25(OH)D levels. A positive correlation was found between 25(OH)D levels and insulin sensitivity. (41)) In contrast, in a randomized, placebo-controlled, double-blind trial of 50

women with PCOS, there was no statistical significance between groups in fasting serum insulin and insulin resistance when prescribed either a vitamin D supplement or a placebo. (1) Further studies need to be done before a conclusion can be made about the relationship between vitamin D deficiency and insulin resistance in women with PCOS.

Calcium and vitamin D are not the only micronutrients under investigation for their relationship with PCOS. In previous studies, Vitamin B12 and folate supplementation have improved insulin resistance in women with metabolic syndrome. A cross-sectional study was done to look for a similar relationship with PCOS women. Vitamin B12 levels were found to be significantly lower in obese women with PCOS compared to controls. Women with PCOS who were insulin resistant also had lower B12 levels when compared to PCOS controls who were not insulin resistant. (18) A prospective study with vitamin B12 supplementation should be done to further investigate the relationship between insulin resistance and vitamin B12. Similar to Vitamin D, no conclusions can currently be drawn about the relationship between vitamin B12 and insulin resistance. However, after speaking with a healthcare provider, it may be acceptable to take a Vitamin D and B12 supplement as a precautionary measure. (See Table VII)

Exercise

A final component of lifestyle modifications in the treatment of PCOS is the inclusion of exercise. Although weight loss can be achieved through diet alone, this will result primarily in muscle loss rather than fat loss as desired. Also, weight loss through exercise is better sustained better than weight loss through diet alone. (3) With exercise, the goal should be to lose abdominal fat since visceral fat is closely related to insulin resistance and the development of metabolic syndrome.

A prospective study was done comparing androgen levels between obese and normal-weight children placed on a high-carbohydrate, low-fat diet for one year in conjunction with an exercise regimen. At the start of the study, the obese girls were found to have higher testosterone and DHEA-S levels compared to their normal-weight counter-parts. Following weight-loss, the obese children experienced greater reductions in testosterone concentrations. However, the results from this study cannot be tied to exercise alone. (31)

A similar randomized, prospective trial was done with overweight/obese women with PCOS. These women were assigned to a dietary plan, a workout plan, or both. Menstrual regularity improved in 69% of the women with a return in ovulation for 34%. There was no statistical difference between groups. A resumption in ovulation most often occurred among women who experienced higher serum levels of insulin-like growth factor-binding protein 1 following intervention. This supports a link between insulin sensitivity and reproductive function. (26) In a similar trial, participants were assigned to diet alone, diet and aerobic exercise, or diet and aerobic-resistance exercise. Again, little variation was observed between groups with the exception of fat-free mass which decreased the most with aerobic exercise and the least with aerobic-resistance exercise. (37) This indicates that the type of exercise may also be an important factor.

Independent of weight loss, exercise remains an effective form of treatment for PCOS. In a prospective study of eight women assigned to 16 weeks of aerobic exercise training, there was a statistical increase in insulin sensitivity compared to baseline. (30) This suggests that the benefits of exercise for treating PCOS may go beyond facilitating weight loss. In a separate study, participants were instructed to follow an exercise regimen that did not result in weight loss. Similar results were found. In those subjects who experienced a return in ovulation, they

also had a reduction in central fat, fasting insulin and LH levels and an increase in insulin sensitivity. (16)

This information stresses the importance of treating PCOS not only through diet but in combination with exercise. It is also important to mix up the type of exercise being done. Even if weight loss is not achieved, it is still possible to reap the benefits of working out. (See Table VIII)

Combination Therapy

Although lifestyle modifications and drug therapy are effective alone, combination therapies can also be effective in the treatment of PCOS. Metformin is one form of treatment which is often used in combination with other therapies. In a 6-month trial, girls were prescribed to a high-CHO and low-PRO diet alone and in combination with metformin. While on metformin, 10 of the 11 girls resumed menstruation, 9 girls lost weight, and total plasma cholesterol and testosterone levels fell for all. (13)

Metformin can also be used in conjunction with other drug therapies such as anti-androgen drugs. In a prospective, placebo-controlled trial, PCOS women were prescribed to a hypocaloric diet and either metformin, flutamide, both metformin and flutamide, or a placebo for 12 months. The effects of flutamide and metformin were observed independently of each other suggesting that it is possible to benefit from each without an adverse reactions between the two drugs. Flutamide intake led to a decrease in visceral subcutaneous fat and a lower hirsutism score. Metformin led to an increase in menstruation, insulin sensitivity, and LDL levels. When taken together, subjects experienced all of these benefits. (10)

Research has also been done to evaluate the effectiveness of metformin in conjunction with oral contraceptives. In a randomized, placebo-controlled clinical trial, the combination of lifestyle modification/oral contraceptives and metformin/oral contraceptives was found to have a reduction in total testosterone and an increase in HDL. However, lifestyle modification and the oral contraceptive combination had the added benefit of a reduction in androgens and an increase in SHBG. (14)

Further research needs to be done to further evaluate the effectiveness of various combinations of therapy in treating PCOS. The major challenge with combination therapy is that as more components are measured, it becomes difficult to control for confounding variables. However, with continued research, it is possible to analyze the effectiveness of different forms of combination therapy. (See Table IX)

Conclusion

Although there are a large number of studies investigating different treatments for polycystic ovary syndrome, there remains plenty of room for continued research. This is especially true in the area of combined therapies. At this time, studies suggests that through lifestyle modifications alone, women with PCOS can improve menstrual regularity, androgen and lipid profiles, and the clinical signs of PCOS associated with androgen excess. If lifestyle modifications can improve upon all of these areas, there is no need to include drug therapy in the treatment of PCOS. Until there is evidence to suggest that drug therapy or combination therapy are significantly more effective than lifestyle modifications alone, it is safer to avoid them. At this time, therapy should focus on improving upon insulin sensitivity through weight loss, diet,

and exercise. By focusing on one of the main causes of PCOS, insulin resistance, improvements in the manifestations of polycystic ovary syndrome will follow.

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