[Frontiers in Bioscience 6, 104-119, January 1, 2014]

Polycystic ovary syndrome: current status and future perspective

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1. ABSTRACT

Polycystic ovary syndrome (PCOS) is a widespread reproductive disorder that encompasses many associated health conditions and has an impact on various metabolic processes. PCOS is depicted by hyperandrogenism, polycystic ovaries, and anovulation. It increases the risk of insulin resistance (IR), type 2 diabetes, obesity, and cardiovascular disease. The etiology of the disease remains unclear, and the subjective phenotype makes a united diagnosis difficult among physicians. It seems to be a familial genetic syndrome caused by a combination of environmental and genetic factors. It can be linked with metabolic disorders in first-degree family members. PCOS is the cause of up to 30% of infertility in couples seeking treatment. Currently, there is no cure for PCOS. Despite the growing incidence of this syndrome, limited research has been done that encompasses the entirety of PCOS spectrum. In this review, the current status and possible future perspective will be discussed.

2. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common reproductive and endocrinologic disorder found in 6-10% of the female population (1). The three main phenotype characteristics of this condition are hyperandrogenism, polycystic ovaries, and ovulatory dysfunction (2). This syndrome can also be associated with metabolic issues including obesity, insulin resistance (found in 60-80% of women with PCOS) (3), hyperinsulinemia, and type 2 diabetes mellitus (T2DM). PCOS is associated with cardiovascular problems, neurological and psychological effects on quality of life (including anxiety and depression), and breast and endometrial cancers. As many as 20% of women with infertility problems (including fecundability and early pregnancy loss) have been diagnosed with PCOS (4). It is often called the most common cause of anovulatory infertility in women (5). There is no known cause of PCOS, however there has been evidence that shows both environmental as well as genetic factors play a role in the etiology (6-8).

Recently, there has been an increase in interest in the field of PCOS research. In the past five years, there have been thousands of articles published concerning the different aspects and relationships regarding PCOS. Despite the high and increasing incidence of PCOS among the population, there are several aspects that remain ambiguous. Few studies have been conducted that grasp PCOS in its entire complexity.

Despite increased attention to PCOS, one of the most vital aspects of this disease is still highly disputed upon - the diagnosis. The etiology of this disease has not been well understood. There is a fundamental need for more research regarding the pathogenesis of PCOS in order to identify the underlying causes. An increasing number of publications infer that genetics is the primary factor of this disease, and take unique approaches to understand this genotypic-to-phenotypic association. Genetic abnormalities have been shown to play a significant role in the metabolic complications (including IR), and appear among both male and female first-degree relatives of women with PCOS. However, genetic research in PCOS is still new, and previously published findings need to be reevaluated. There are several inconsistencies among genetic studies regarding PCOS.

The genetic evaluation of PCOS is also the gateway to many other novel areas of research. Since researchers are perplexed by the rapid evolution of the disease, the identification of genomic loci would give considerable insight. The connection between PCOS and male relatives, a contentious topic, could be better understood with the advancement of genetic analysis. These two areas require a fundamental basis upon which to build theories in order to expand our knowledge on the etiology of the disease. These discoveries would also help create a novel treatment or cure.

The indefinite diagnostic criteria in addition to its immense intricacy make PCOS a challenging area of research. The aim of this article is to review the present status and formulate an interesting and clinically relevant research direction that is essential to move the field of PCOS forward.

3. METHODOLOGY

A Pubmed database search was done using the phrase “polycystic ovary syndrome”. This search (1990-present) yielded 8,267 articles and 237 of these were selected for further analysis. After examining abstracts, 81 were selected for investigation of the complete articles and their relevant references.

4. DISCUSSION

4.1. Causes, risk factors, and diagnosis

PCOS is a prevalent condition found in 6-10% of the female population in developed countries (9). It is a familial polygenic condition thought to be attributed to both genetic and environmental factors (6-8). There has been much debate about the origin and pathological cause of PCOS in the past decade. Recently, many studies indicate that a defect in insulin action may be the primary cause of PCOS (10-12).

Environmental factors have been shown to play a role in the pathogenesis of PCOS. There have been several studies observing the role of socio-economic status (SES) and unhealthy behavior, including smoking, poor diet, and lack of exercise (13, 14). One of the most common associations with low SES is obesity, which also has a high rate of co-morbidity in PCOS (15, 16). In a recent study, Merkin *et al.* found a correlation between low childhood SES and PCOS (17). This risk of PCOS was even higher among obese women. Further research regarding environmental influence could help pinpoint high-risk groups and develop a better understanding of developmental origins.

Genetics also play a momentous role in the origin of this disease. PCOS is thought to be an ancient disorder, which is most likely passed down between fertile carrier males and subfertile females (18). This can be seen through high familial rates of hyperandrogenism and type 2 diabetes in first-degree relatives of women with PCOS (19, 20). In 2011, Zhao *et al.* found that single-nucleotide polymorphism (SNP) rs13429458 is significantly associated with familial-based risk of PCOS; association among three loci was delineated (21, 22).

Additionally, other studies suggest that ethnicity may be associated with PCOS. In one study among women in the US, there was an 8.0% prevalence among African Americans and a 4.8% prevalence among Caucasians (not significantly different) (23). There was a 6.8% prevalence in Greek women (24) and a 6.5% prevalence among women in Madrid, Spain (25). Mexican-Americans have one of the highest rates, with a 13% prevalence (26). It is possible this is due to the greater degree of insulin resistance and type 2 diabetes among this population (27). Prevalence rates were found among women of reproductive age group.

According to the Rotterdam Criteria, there are three key diagnostic features of PCOS: anovulation, hyperandrogenism, and polycystic ovaries (2). Patients must display two of the three phenotypes to be diagnosed as having PCOS. Anovulation is the most common phenotype among PCOS patients, with up to 95% of women with PCOS experiencing some type of anovulation (28, 29). This is often displayed as oligomenorrhea with less than eight periods in one year, or amenorrhea with no period for more than three months. Women with PCOS are usually not entirely sterile and do ovulate spontaneously. The frequency of ovulation has not been well studied, but some suggest that ovulation occurs in up to 32% of menstrual cycles (30).

Hyperandrogenism is another persistent diagnostic phenotype in PCOS and is seen in approximately 60% of patients (31). Clinical markers for hyperandrogensim are hirsutism, acne, and alopecia. Hyperandrogenism can also be assessed biochemically by measuring circulating androgen levels (32, 33).

The presence of polycystic ovaries (PCO) is an important diagnostic criterion for PCOS. However, the presence of polycystic ovaries alone does not guarantee PCOS. The definition of PCO in terms of ultrasound diagnosis is defined as: 'presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (>10ml)' (34). The prevalence of PCO in PCOS patients is estimated to be 17-33% (35). Determining the presence of the preceding phenotypes can be difficult.

It is important to rule out disorders that have manifestations similar to PCOS. Simple tests can be performed to exclude disorders such as hyperprolactinemia (causing anovulation), nonclassic congenital adrenal hyperplasia (causing excess androgen production), Cushing's syndrome (causing all three diagnostic criteria as well as insulin resistance), and the presence of any androgen-secreting tumors (2).

With age the PCOS phenotype, both clinically and endocrinologically, begins to transform. Many women with PCOS start to develop a more consistent menstrual cycle as they grow older (36, 37). In addition to this regularity, there is an overall improvement of most other phenotypes, including decreased androgen levels and decreased insulin resistance (38).

It can be seen that despite all of these various methods of assessing PCOS, there is a lack of any solid, objective test that that can provide an absolute affirmative diagnosis at this time.

4.2. Associated health conditions

There are a plethora of health implications that have been associated with the diagnosis of PCOS, many of these constituting lifelong complications. One of the most common risks includes the presence of metabolic anomalies and their associated manifestations.

4.2.1. Metabolic complications, obesity, and cardiovascular risk

Insulin resistance (IR) can be found in 60-80% of all women with PCOS and in 95% of obese women with PCOS (3, 39). In 2001, Dunaif *et al.* concluded that there is a defect in post-receptor insulin signal transduction that is independent of obesity and type 2 diabetes (40). In addition to metabolic disturbances, IR also contributes to hyperandrogenism, anovulation, and cardiovascular risks (41). IR is not the only metabolic disorder found in PCOS patients; there is also an increased prevalence of impaired glucose tolerance (IGT), gestational diabetes (GDM), as well as type 2 diabetes (42). In the future, more long-term studies need to be conducted to determine metabolic effects throughout the patient's lifespan, not just during reproductive age. It is also important to delineate the metabolic abnormalities that are specifically caused by PCOS versus those caused by obesity.

Obesity is present in at least 30% of PCOS patients, with reports of up to 61-76% in the United States and Australia (43). The precise association of PCOS and obesity has yet to be delineated; however, obesity aggravates many features of the syndrome and halts successful treatment of phenotypes.

Metabolic abnormalities lead to an increased risk of cardiovascular problems in PCOS patients as they age and obesity exacerbates these risks. Studies have indicated that a higher risk of cardiovascular disease (CVD) is associated with increased severity of PCOS phenotypes in both obese and non-obese patients (44, 45). There is minimal research that has been conducted on the long-term outcomes of CVD and PCOS. Identifying clinical characteristics in post-menopausal women could be a novel way to determine risk factors for possible prevention of CVD and other cardiovascular problems (46).

4.2.2. Neurological and psychological functions

Other than the evident endocrinologic and reproductive manifestations of PCOS, there are also serious mental health consequences. There have been several studies that show a correlation between women with PCOS and a reduced health-related quality of life (47-49). In addition to impaired quality of life, the prevalence of anxiety, depression, and poor self-perception are also higher among women with PCOS (50). It is recommended that all women with PCOS should undergo psychological screening and take appropriate interventions where required (29). This comes with no astonishment, since the foremost phenotypes of this syndrome (obesity, infertility, hirsutism) are major issues that would undoubtedly cause psychological stress on any patient. It needs to be confirmed that it is indeed the manifestation of PCOS, and not the syndrome itself, that is causing these psychological problems.

4.2.3. Cancer

There has been a cohort of studies that have suggested an increased rate of endometrial and breast cancer among women with PCOS (51, 52). The anovulatory features (unopposed estrogen, insufficient progesterone) have been shown to cause proliferative tissue growth in the endometrium, leading to carcinoma. Endometrial carcinoma has additional risk factors, including obesity, insulin resistance, and type 2 diabetes, which can all be associated with PCOS. There is a 2-3 fold increase in risk for endometrial cancer in women with PCOS (54).

4.3. Infertility

Polycystic ovary syndrome is the most common cause of menstrual irregularity that leads to infertility. Out of all couples seeking treatment for infertility, 30% of cases are due to anovulation. It is estimated that 90% of anovulation cases are actually caused by PCOS (55).

The oogenesis process in PCOS patients is different than that of a normal cycling fertile woman. The individual activation from primordial to primary follicle during folliculogenesis is independent of gonadotropins (56, 57). The disruption of the PI3K and FOXO3 pathways in mice results in the activation of all primordial follicles in the pool, causing follicular depletion and premature ovarian failure (58-61). The theca cell layer produces androgens for

adjacent granulosa cells to convert to estradiol (62) in response to LH stimulation (63) as well as insulin levels (64). These two factors, LH and insulin, are especially significant to PCOS patients since 60-80% of patients display insulin resistance (IR), which can contribute to hyperinsulinemia. An excess of insulin in the ovaries can enhance the granulosa response of LH, producing a surplus of androgens at the site (65). In healthy women, the LH stimulation signals to continue follicle development from the primary to the secondary follicular stage. An increase of LH can also cause early maturation of granulosa cells (66).

PCOS patients often use methods of assisted reproductive technologies (ART) for conception. The first technique often used is ovulation induction to encourage the development of multiple follicles that will eventually be suitable for fertilization. The most common drug treatment used for ovulation induction is clomiphene citrate (CC) (67). CC has been shown to result in pregnancy 50% of the time after three cycles of treatment, and 75% of the time after nine cycles (68).

4.4. Treatment and management

There is currently no cure for PCOS. For women with PCOS not seeking pregnancy, combined oral contraceptive pills (OCPs) are the first line of treatment. Not only do these pills regulate the menstrual cycle, but they also decrease the production of adrenal androgens. A healthy lifestyle will not reverse characteristics of PCOS, but will help control associated health conditions such as obesity, cardiovascular disease, and infertility. Hirsutism, a common manifestation of PCOS, is often treated at the discretion of the patient, using OCPs alongside anti-androgen (29). Laser-hair removal is also a common means of controlling hirsutism among PCOS patients.

5. CURRENT RESEARCH AND FUTURE PERSPECTIVE

During the last five years, there have been over 3,172 articles published related to PCOS, with an increasing number of articles published each year. Of these articles, the topics of insulin resistance (IR) and metabolic abnormalities associated with PCOS were the most researched.

5.1. Diagnosis

As described in section 4.1, there are several challenges in confirming the diagnosis of PCOS in women who present its characteristics symptoms. Although hyperandrogenism testing is the most promising diagnositic criteria, as it is seen in 60% of women with PCOS (69), its methods of assessment could result in diagnostic inconsistency.

The dilemma with the presence of hirsutism is that it is difficult to create a distinct profile of characteristics associated with PCOS. Clinically, hyperandrogenism is most often diagnosed through the presence of hirsutism. Other indicators such as acne and alopecia are occasionally taken into account. However, the biggest drawback of using hirsutism as a primary indicator of PCOS is its subjective assessment. It has been shown that women of different ethnicities display varying degrees of hirsutism, and symptoms are especially rare in Asian women (70) and not well understood in adolescent patients (71).

The second test to diagnose hyperandrogenism is to measure circulating androgen levels. Measurements of serum total testosterone (T) and sex hormone binding protein (SHBG) are often the markers for these tests. However, tests measuring androgens can be inaccurate/yield unreliable results (72). The accurate identification of hyperandrogenism in women is crucial to the overall diagnosis of PCOS. Since such a high percentage of PCOS patients display hyperandrogenism, a better method of evaluating and testing symptoms must be formulated.

5.2. Obesity

Much like PCOS, obesity has become a recent worldwide epidemic in the past decades, especially in developed countries. The highest rates of obesity in PCOS patients occur in the United States and Australia, where 61-76% of women with PCOS meet the criteria for obesity (29, 73, 74).

It has been established that the pathogenesis of PCOS likely has the influence of genetics, in addition to environmental factors such as diet and lifestyle. Studies unrelated to PCOS have shown that hyperandrogenism is associated with obesity during the onset of puberty (46, 75). If hyperandrogenism can be prevented by weight loss in prepubescents, it is possible that PCOS could be better maintained or even prevented in adult life.

Obesity not only intensifies the pre-existing PCOS phenotypes, but also projects poor treatment outcomes. Women seeking infertility treatment who have a high BMI are most likely to seek medical assistance for infertility (76). Lower rates of successful ART procedures are found among women with a high BMI, with an increased need for extended ovarian stimulation (77-79). In addition to this and the effects of the PCOS phenotypes, there is an amplified risk of miscarriage in patients with a BMI over 25kg/m^2 (80).

5.3. Genetics

There has been an increase in the hypothesis for a genetic predisposition to PCOS. Many recent studies have suggested that a genetic defect in a post-receptor insulin signal transduction can be linked to PCOS patients (10-12). This mutation can increase rates of insulin resistance and type 2 diabetes in first-degree relatives that are both male and female (19, 20) as well as twins (8). The vast complexity of phenotypic heterogeneity associated with PCOS complicates the focus of genetic studies. Currently, there have been many candidate gene association studies on PCOS phenotypes. These studies are easier to perform than case-control cohorts, but they do not yield consistent results and lack sufficient sample sizes (81). Many of these studies include the investigations on the insulin gene (*INS*), the

insulin receptor (*INSR*), and sex hormone-binding globulin (*SHBG*).

Genome-wide association studies (GWAS) have become a promising area of PCOS research. Since its introduction in 2005, GWAS have been used to scan entire genomes and pinpoint susceptible loci in many diseases, including Crohn's diseases, type 2 diabetes, and asthma. There have been only a few GWAS concerning PCOS to date (21, 82). The first GWAS included a group of 744 women with PCOS with 895 controls of Han Chinese women. The two replication cohorts included 2840 women with PCOS and 5012 controls, and 498 women with PCOS and 780 controls, respectively. The first locus was identified on chromosome 2p16.3, which contains two genes: *GTF2A1L,* expressed in testis, and *LHCGR*, which plays a role in LH receptors crucial for ovulation and pregnancy maintenance. There were also two separate SNPs located at the second locus on chromosome 2p21, in the *THADA* gene region (thyroid adenoma gene). The last locus was identified on 9q33.3 in *DENND1A*, which controls the production of endoplasmic reticulum amino-peptidase-1, used for membrane trafficking. This study is one of the leading studies on the genetics of PCOS.

Since the publication of the first GWAS PCOS study, there have been a small number of studies that have attempted to replicate these results. The first, performed by Goodarzi *et al.* in 2012, analyzed two cohorts of European women with PCOS as well as controls (83). They concluded only significant associations among *DENND1A* and *THADA* in their selected population compared to the original study including Chinese women. The second study was conducted by Welt *et al.* in 2012 on women from Iceland, Massachusetts, and Illinois (84). These women displayed a significant correlation only among the *DENND1A* gene.

The most recent replication, by Pau *et al.* in 2013, compared European women to the original GWAS as well as a meta-analysis of the previous candidate gene studies (85). This cohort of women was one of the biggest populations studied to date. They found none of the formerly examined variants to be associated with risk for PCOS. However, there were two variants in the *FBN3* gene identified to be associated with a smaller waist circumference in the control groups and the PCOS group. This gene has been shown to code for the protein fibrillin-3, commonly used for structure in connective tissue (86), in addition to another intron associated with metabolic complications in women with PCOS (87). These two variants had a lower frequency in comparison to the control women, suggesting a reduction in fibrillin-3 expression leading to smaller waist circumferences in the carriers. Another variant was also located on the *SHBG* gene, and associated with lower levels of *SHBG* in women with PCOS. These data suggest that PCOS identifies more with BMI and obesity as the primary causative factors, rather than the factors related to fertility and reproduction.

At present, GWAS are undeniably the most promising area of genetic research in PCOS. However, the consistency of results among these genetic studies continues to be the foremost obstacle. Collaboration among investigators will strengthen the credibility and authority of future genome-wide and candidate gene association studies. It is essential to develop a system to gather large cohorts of women of varying ethnicities in order to examine a greater array of possible variants. The discovery of new, reliable, and steady data is the precursor to developing criteria for a structured risk-factor evaluation and possibly novel treatment modalities.

5.4. Immunology

Obesity has recently been classified as a status of low-grade inflammation due to the excessive production of cytokines, adipokines, and other reactants (88). These markers include TNF-α, IL-6, IL-1, IP-10, CRP and IL-18 (88-91), and they act as inflammation mediators to maintain inflammation in adipose tissue (92). It is thought that the constant release of these mediators is what initiates insulin resistance, type 2 diabetes, and other metabolic complications (88). It is also thought that this inflammation in PCOS could be causative of the common metabolic and cardiovascular difficulties.

C-reactive protein (CRP), a common marker of inflammation, is produced by adipose tissue in response to pro-inflammatory cytokines (93). High levels of CRP are strongly correlated with the risk of cardiovascular complications (94). It has been well-established that women with PCOS have increased levels of CRP when compared to healthy subjects (up to 96% greater, and 102% when BMI was matched) (95, 96). There is also a relationship between PCOS and interleukin-18 (IL-18), another pro-inflammatory cytokine. IL-18 is associated with IR and metabolic complications, and has been found to correlate with testosterone levels in women with PCOS (97). Increased levels of MCP-1, MIP-1α, WBC, IL-6, TNF-α, and oxidative stress are additional markers of inflammation found in women with PCOS (96, 98-101). It is thought that this increase in specific cytokines (CRP, IL-6, and TNF-α) is mostly attributed to obesity, and not solely to PCOS (102). However, most of these studies contain small groups of subjects with inconsistent data, and their results are not definite (103).

Inflammation is found in PCOS patients who are obese as well as non-obese. Women with PCOS of normal weight have a higher buildup of fat in the visceral area compared to other parts of the body (104). This distribution of visceral adiposity in non-obese women has been shown to be correlated with increased insulin resistance and is probably a causative factor of low-grade inflammation in these patients (105). These data suggest that obesity does not need to be present in a PCOS patient to experience low-grade inflammation.

These findings bring up a vital question that should be further examined: is the inflammation caused by PCOS, or a result of obesity/other metabolic problems? To our knowledge, there has been no study examining the effect of anti-inflammatory treatment in women with

PCOS. The response of anti-inflammatory drugs in PCOS patients needs to be examined.

In addition to anti-inflammatory treatment modalities, other types of drugs may be beneficial to these patients. Women with PCOS often exhibit low levels of progesterone, causing anovulatory complications. During a normal cycle, estrogen promotes the increased production of IL-6 during the follicular phase, which is later inhibited by progesterone in the luteal phase (106). The absence of progesterone in PCOS patients may lead to over-stimulation of the immune system, inducing autoantibodies (107). Combined oral contraceptive pills contain progesterone; this daily dose could help reduce the expression of pro-inflammatory cytokines (108), while simultaneously causing a decrease in testosterone levels in women with PCOS (109). OCPs provide a double-edged sword when administered - an improvement in hormonal balance as well as a reduction of inflammation.

The administration of Vitamin D in these patients could also be a promising supplement during treatment. It is thought that communities who live near the equator synthesize a large amount of natural Vitamin D from the sun, reducing their risk for auto-immune diseases (110). In a recent study of women with PCOS, 72.8% of the patients had low levels of vitamin D and these women experienced worsened metabolic phenotypes (111). In addition, it has been established that obesity is also a risk factor for vitamin D deficiency (112). Therefore, the treatment with vitamin D supplement could help improve metabolic anomalies as well as autoimmune complications and potentially PCOS.

5.5. Evolutionary aspect

One puzzling question to address is: if PCOS is a hereditary syndrome that impedes fertility, why is its prevalence not diminishing? This paradox has created many evolutionary hypotheses among scientists in recent years. Some argue that PCOS may have worked in favor of women in centuries past in times when food was scarce. An increased insulin resistance in these women causes more fat storage and a decreased appetite (113), both beneficial characteristics to possess in times of famine. In this sense, women with PCOS would have a greater survival rate, thus having the advantage of reproducing and passing on their genes. Stored fat was also beneficial for a woman to be ready for pregnancy and to prolong her reproductive years. Even though women today with PCOS most often have a difficult time conceiving due to ovulatory dysfunction, it has been shown that these women actually develop a more regular cycle as they age (114). This suggests that women with PCOS have superior fertility at advanced ages compared to normal women. This also would have given women with PCOS in earlier times an advantage in terms of fitness and reproduction. Increased knowledge about the selections against the PCOS phenotype is crucial to comprehend the current evolution of PCOS (115).

5.6. PCOS phenotype in men

PCOS may not be just a reproductive disorder in women. We may infer that it is rather a *metabolic* disorder (with reproductive dysfunction) that can be seen in both men and women. The two reproductive characteristics of PCOS seen solely in women include anovulatory disorders and polycystic ovaries. These two characteristics are not found in all cases, nor are they specifically required for diagnosis. Other characteristics, such as hyperandrogenism, metabolic abnormalities, and cardiovascular problems, can all be found in both genders, especially in men who are relatives of women with PCOS. As discussed, the genetic basis of PCOS has been found in the close male relatives of women with PCOS. The insulin signal transduction defect found in PCOS patients is not specific to women or their reproductive system and therefore can be also seen in men.

There are a few published articles regarding PCOS phenotype in men. The findings suggest that male relatives of women with PCOS display premature male baldness as well as hirsutism (116, 117). One study by Dusková *et al.* concluded that in a population of men experiencing premature hair loss, close to 30% of men displayed hormonal resemblances to women with PCOS (low SHBG, gonadotropin abnormalities) in addition to an increased occurrence of insulin resistance (118). It is possible that this 30% represents the male equivalent of PCOS, which corresponds to the prevalence of PCOS in women.

Once the relationship between the male and female phenotype is better understood, it may be beneficial for male relatives of women with PCOS to be examined. Early detection of symptoms can help us further characterize risks and treatment options.

5.7. Treatment modalities

5.7.1. Assisted reproductive technology (ART)

There are several infertility treatments for PCOS patients, including (assisted reproductive technologies) ART. The first step of any ART treatment is ovarian hyperstimulation in hope of producing the growth of multiple follicles. However, women with PCOS may have an increased response to these gonadotropins, ensuing ovarian hyperstimulation syndrome (OHSS) (119).

Because of this, new methods of the *in vitro* maturation (IVM) are being utilized for women with PCOS (120). Overall, the current rates of implantation after IVM-IVF procedure are not as high as traditional IVF method (121). In an IVM-IVF procedure more embryos are often transferred. A study published by Shalom-Paz *et al.* in 2012 compared rates of IVM-IVF to traditional IVF (122). They found that the live birth rates were comparable between IVM-IVF (26.8%) and traditional IVF (25%) in women with PCOS. These promising results suggest that IVM could provide a better method than *in vivo* superovulation in PCOS patients. In another recent study, certain PCOS patient characteristics (antral follicle count, total testosterone, and circulating anti-Mullerian hormone) were measured and compared to outcomes of IVM cycles (123). These qualities were shown to be promising predictors in the outcome of IVM cycles in PCOS patients. Future studies in this type of research could yield a predictive model to help determine the probability of ART success for PCOS patients.

5.7.2. Laparoscopic ovarian drilling (LOD)

In cases where ovulation is not induced with clomiphene citrate therapy, other methods of ovulation induction may be used as an infertility treatment. Laparoscopic ovarian drilling (LOD) was developed in 1984 to replace the invasive ovarian wedge resection surgery (124). Today, this procedure is successful in creating a pregnancy in 84% of patients with PCOS-related infertility (125). LOD helps improve insulin resistance (126) and ovarian androgen production, as well as increase the SHBG levels (127). These improvements have been seen to last in long-term follow-ups in 54% of women 8-12 years after the procedure (128, 129). Due to the normalizing effect on the phenotypes, it is thought that LOD may result in lower rates of miscarriage in women with PCOS (130), although more research needs to be done to confirm this hypothesis. In addition, it also does not have the dangerous risk of multiple pregnancies or ovarian hyperstimulation seen after CC treatment. When compared to the possibility of multiple CC treatment, LOD was found to be less expensive (131, 132) and resulted in an increased chance for a second child (129).

LOD is most often performed as a second-line treatment once CC has failed. Few studies have been conducted on its success as a first-line treatment option. Some recent reports have used anti-Mullerian hormone (AMH) levels as a tool for predicting ovulation outcomes in women with PCOS treated with LOD (133, 134). Lower AMH levels (cutoff at 7.7 ng/ml) were found to predict a higher chance of ovulation in PCOS patients after LOD (133). The expansion of this study could lead to more advanced criteria for women with PCOS that would have optimal ovulation rates using LOD. The benefits of the LOD procedure could possibly outweigh any surgical risk if the women displayed favorable AMH levels. More research with large cohorts needs to be performed to confirm these findings.

5.7.3. Metformin

Metformin is a commonly used drug in the biguanide class used in the maintenance of type 2 diabetes. Along with diet and exercise, it works to control the blood sugar level in patients by controlling gluconeogenesis in the liver. It has been used in the treatment of metabolic derangements in PCOS for many decades, and there is no shortage of data confirming its effective use for hyperinsulinemia and insulin resistance. Metformin has been shown to help regulate hyperinsulinemia, reduce the level of androgens, and control the menstrual cycle of women with PCOS (135).

Metformin ameliorates the metabolic manifestations of PCOS, such as IR and type 2 diabetes. These phenotypes play a huge role in the increased risk factors of other associated health conditions, such as obesity and cancer. Recently, the use of insulin sensitizing drugs like metformin has been shown not only to improve metabolic symptoms, but also cause a decline in the frequency of cancer. Anovulation, a common phenotype of PCOS, has also been shown to have an increased risk of endometrial cancer (136). In 2009, Libby *et al.* concluded that metformin use among patients with type 2 diabetes was associated with a generally lower occurrence of cancer (137). Other studies have conferred that by activating the cellular AMPK pathway, the proliferation of epithelial cells downstream will decrease and thus inhibit the growth of breast cancer cells in women (138). Another recent study by Sarfstein *et al.* reported that Metformin promotes apoptosis and inhibits the growth of uterine serous carcinoma (USC) in endometrial cancer (139). All of these reviews are related to many of the associated health conditions of PCOS.

Even though all of these studies relate to associations with PCOS, little to none have thoroughly examined the relationship between the use of Metformin in women with PCOS and their long-term outcome with cancer, most specifically endometrial cancer. This could be a remarkable breakthrough in the treatment metabolic abnormalities in women with PCOS. Metformin would not only be effective in its traditional metabolic role, but would also act as a double-edged sword and reduce the risk of certain cancers.

5.7.4. Oral contraceptive pills (OCPs)

Combined oral contraceptive pills (OCPs) have been the first line of treatment for women with PCOS not seeking pregnancy for decades (19). Not only do they assist in the regulation of the cycle, but they also reduce androgen production and its corresponding physical manifestations, such as hirsutism and acne. OCPs have also been shown to reduce the risk of endometrial cancer (140-142). The OCPs contain a combination of estrogen (ethinyl estradiol) along with a progestogen. The primary function of estrogen in the OCPs is the anticipated rise in SHBG as well as the reduction in luteinizing hormone (LH) and follicle stimuatling hormone (FSH), which in turn suppresses the levels of free T (143) and ovarian androgen production (144). In negation of the estrogen, the progesterone actually works to decrease SHBG levels; therefore, it is recommended that a progestogen with low androgenic activity be used in the OCPs (145). Three commonly used progestogens are drospiernone, cyproterone acetate, and desogesterol. However, there are disadvantages of the use of OCPs. As previously stated, women with PCOS are at an increased risk of developing various metabolic disorders, including insulin resistance (IR), hyperglycemia, type 2 diabetes, and impaired glucose tolerance (IGT). Increased rates of LDL and decreased rates of HDL cholesterol have been linked to PCOS patients (146). Studies have shown that the use of OCPs can cause cardiometabolic effects among the general population, including thrombosis, blood pressure anomalies, and IR (147, 148). If there is an increased risk among a population of normal women, it is thought that women with PCOS would have an even greater risk of metabolic anomalies when using OCPs (149, 150). There has been no study to our knowledge which examined the long-term metabolic effects of OCPs on patients with PCOS. This is an extremely relevant area of research since OCPs are currently the primary treatment used in women with PCOS.

However, there are recent studies that support a new treatment option: the addition of Metformin along with an OCP. Although this Metformin combination therapy has not been thoroughly examined, studies have observed positive effects when implemented, such as decreased androgens and increased SHBG when compared to OCPs alone (151-153). A recent study by Kaya *et al.* found that this treatment helps to ameliorate insulin resistance and aortic stiffness in PCOS patients (154).

The complexity and mechanisms of OCPs leave many questions unanswered. The future investigations of PCOS and OCP research must focus on balancing the pros and cons for different risk groups. OCP use can reduce risk of endometrial cancer by 50-70% in the PCOS population, where there is a 2-3 fold increase in this cancer (155). On the other hand, OCPs also have a risk of cardiometabolic effects, which are already heightened in women with PCOS, especially if they are obese.

5.7.5. Dietary therapy

Obesity is found in approximately 30% of PCOS patients with rates of up to 76% found in the US and Australia (43). Dietary therapies for weight loss have been shown to improve many symptoms of PCOS, including androgen levels, insulin resistance, anovulation, and irregularity of cycles (156-158). Unfortunately, the optimal outcomes of diet and exercise are not always long-term (159). Bariatric surgery has become a popular method to obtain and sustain weight loss in obese men and women worldwide with long-term survival rates (160). Recently, there has been an interest in the use of bariatric surgery as a therapy for morbidly obese women with PCOS. Escobar et al. studied the response of PCOS phenotypes to weight loss after bariatric surgery (161). Their findings suggested that the surgery resulted in an almost complete transformation of PCOS phenotypes. After weight loss, all patients gained regularity of their menstrual cycles, insulin resistance improved, and overall hirsutism and androgen concentrations decreased to a normal range (in all patients but one). It was concluded that none of the patients fit the criteria for PCOS after the surgery.

In addition to the amelioration of PCOS phenotypes, the weight loss also can improve the reproductive outcomes for the patient (162-169). Higher rates of spontaneous ovulation and pregnancy, as well as decreased rates of miscarriage, are associated with weight loss (162-164). These satisfying results suggest that bariatric surgery could become a first-line treatment option for some women with PCOS. More data is needed to identify which group will benefit the most with this treatment (i.e. morbidly obese vs. obese; young vs. old).

5.8. Long-term effects

As previously discussed, there are many chronic health conditions associated with PCOS. Little research has been done on the long-term health of post-menopausal PCOS patients. As discussed, age has been shown to help improve many phenotypes of PCOS; however, there is no recognized standard of phenotypes in post-menopausal women. It is assumed that these women will have increased rates of obesity, diabetes, and cardiovascular problems (29), but there has been no direct comparison between the mortality rates of normal vs. women with PCOS. The need for long-term studies is crucial to understand which phenotypes will present additional health risks at increased age and if there is a difference in morbidity rates among PCOS patients. GWAS can also be used to recognize and track genetic anomalies throughout the aging process in order to identify risk factors.

6. CONCLUSION

In conclusion, PCOS is becoming a more prevalent disorder among women of reproductive age with lifelong complications. One of the most challenging aspects of this syndrome is its ambiguous diagnostic criteria and vast complexity of characteristics. In the future, more research in the genetics and pathophysiology of PCOS is needed to determine preventative risk factors as well as successful treatment modalities for this syndrome.

7. ACKNOWLEDGEMENTS

The project described was supported by the NIH/National Institute of General Medical Science, U54GM104942. The content is the responsibility of the authors and does not necessarily represent the official views of the NIH. A special thanks to all members of the lab, especially Morgan Lough.

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Key Words: Polycystic ovary syndrome, PCOS, Obesity, Insulin Resistance, Diabetes, Metformin, Review

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