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Polycystic Ovary Syndrome (PCOS): A risk factor for infertility

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a frequent hormonal disorder in women of reproductive age, which is characterized by irregular and rare menstrual cycles or even high levels of androgens. In women with PCOS, the possibility of various complications increases, including infertility. The main purpose of the review was to provide more information on the relationship between PCOS and infertility and highlight the most important evidence-based recommendations on diagnosis and efficient treatment for PCOS. This review includes the most recent literature sources such as clinical trials, systematic reviews, and meta-analyses (from 2019 to 2022) searched in Web of Science and PubMed databases using terms such as 'Polycystic Ovary Syndrome' and 'infertility'. Articles that did not primarily address PCOS and infertility or those that were just in the pilot trial stage were not included in the review. Based on the literature, infertility is one of the main complications of PCOS, which has been reported in 40% of these cases. According to several evidence-based studies the diagnosis of infertility in PCOS women can be achieved according to the Rotterdam criteria based on the level of anti-Mullerian Hormones, FSH, LH, prolactin, estradiol, and testosterone. Options for management or control of infertility disorders in women with PCOS include stimulation of ovulation, intrauterine insemination as well as cycles of assisted reproductive techniques. On the other hand, the most effective treatments for women with PCOS include the use of metformin, letrozole, and minimally invasive laparoscopic techniques. Nevertheless, because the etiology of PCOS is unknown in most patients, therapy is not always successful. Future studies that concentrate on lifestyle factors and any other external variables that may favorably impact the attainment of suitable therapy are required to provide PCOS patients with appropriate and effective treatment.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a condition closely related to the female reproductive and endocrine organs, which can cause infertility and various metabolic abnormalities (Heidarzadehpilehrood et al., 2022).

Infertility is known as the inability of a couple to conceive after a year of unprotected sexual contact. In women with PCOS, the possibility of various complications increases, including infertility (Zehravi et al., 2021; Collée et al., 2021).

Patients with PCOS show high ovarian response during the process of controlled ovarian stimulation which can be associated with decrease in the quality of oocytes and a low rate of fertilization, from these data high rates of cycle cancellation and abortion are reported for these women who are affected. Studies show that disorders of oocyte maturation and embryo development in women with PCOS are closely related to endocrine factors, metabolic dysfunction, and changes in the microscopic intercellular environment during folliculogenesis and follicular maturation (Moini et al., 2022).

PCOS is the usual endocrine dysfunction in fertile women which is characterized by heterogeneous presentation of hyperandrogenism, ovulation failure, and changes in the morphology of the polycystic ovary, these disorders can be morphological or mainly biochemical. Although PCOS has a high prevalence of disorders, the lack of well-defined diagnostic criteria or specific diagnostic tests for the disease makes it even more difficult. PCOS can also be complicated by other conditions including metabolic syndrome, obesity, depression, apnea, endometrial cancer, hepatitis, and most importantly disorders related to infertility (Jahan & Wing, 2020).

Gynecologists have made psychological comparisons of infertile women with PCOS and without PCOS for better management of PCOS in the eradication of infertility; higher levels of coping with anxiety are accompanied by high levels of coping with stress, where all this has complicated the disease even more (Basirat et al., 2020). Non-ovulatory infertility accounts for about 30% of infertility, while PCOS accounts for 90% of these cases. PCOS patients are prone to ovulation disorders leading to infertility, they are also more likely to have poor pregnancy outcomes (Li et al., 2022). Cunha and Póvoa (2021) found that PCOS was the main cause of infertility, accounting for approximately 70% of all cases. The main aim of the review study was to provide more information for women who have symptoms of PCOS to get the right and efficient treatment so that after a few years they do not end up with infertility because then the treatment is even more difficult. There are not many research articles in the literature regarding PCOS and its impact on women's fertility. The current paper aimed to review the relationship between infertility and PCOS, the diagnostic criteria of PCOS, symptoms of the condition, and current treatments. Furthermore, the review study will provide information on the relationship between PCOS and endometrial cancer which is a long-term complication of PCOS. PCOS treatment is not always effective because in most cases the etiology of the condition is not known. The current study will highlight the most important challenges and evidence-based recommendations for PCOS diagnosis and treatment.

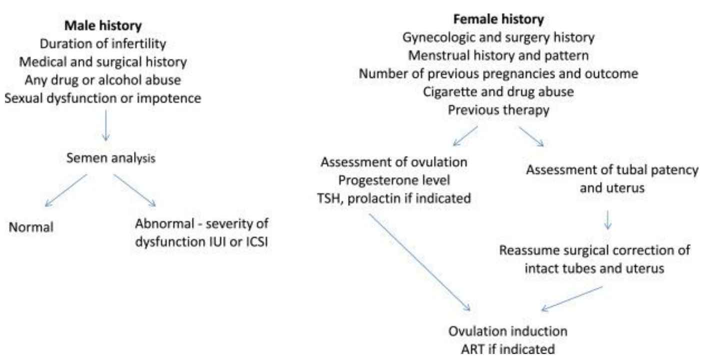
INFERTILITY

Infertility is the inability to conceive after ≥12 months of regular, unprotected sexual activity. In the absence of existing history during the examination or even physical findings, diagnosis, and treatment should be started at 12 months in women <35 years and 6 months in women ≥35 years. In women over 40 years of age, more immediate diagnosis and treatment are guaranteed, although diagnostic testing for infertility should be done without delay when a condition appears that is known to cause infertility. In these cases, we must consider the main elements that characterize it. which are: irregular periods of menstruation, cycle duration more than 25 days, intermenstrual bleeding, oligomenorrhea or amenorrhea, known or suspected uterine/tubal/peritoneal disease or endometriosis, known or suspected male subfertility, sexual dysfunction, conditions either acquired or inherited, that increase the risk of ovarian reserve decline, including chemotherapy or exposure to radiation. All women who need donor sperm to achieve their pregnancy also require an accurate assessment of the diagnosis given as infertile, this is achieved by undergoing a detailed history and physical examination as well as a laboratory evaluation. The determination of uterine cavity condition should be adapted based on the medical history and risk assessment which can be eliminated (Penzias et al., 2021).

Infertility affects both sexes equally, but women are the ones who are blamed more often, this threatens the self-esteem of infertile women and makes them feel guilty. Infertile women experience greater psychological stress compared to infertile men, they are often stigmatized as being infertile and childless. Many women experience infertility as a stigma, where this stigma of infertility is greater in developing countries, but infertility is stigmatized in the same way in both developed and developing countries. A person who is infertile may have interpersonal issues, despair, worry, stress, guilt, and lack of social support if they perceive their condition as a stigma (Taebi et al., 2021).

Knowing that many couples face this problem, it should be remembered that the diagnosis and treatment of infertility is expensive and there is still no single procedure that necessarily leads to pregnancy or the birth of a healthy child. The success rate for infertility treatment is quite constant, including about 25-35% of births, with this achievement we understand that the failure rate is 65-75%, which is quite disturbing for couples who undergo a treatment that also has high financial costs (Szamatowicz & Szamatowicz, 2020).

Figure 1:
Diagnosis and treatment of infertility

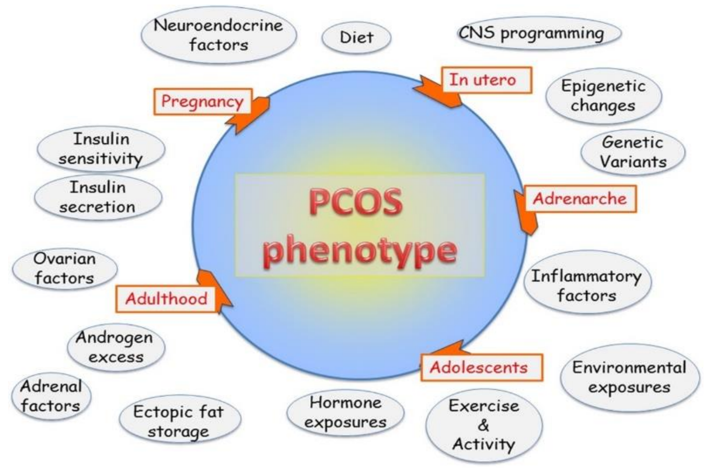


Source: Szamatowicz and Szamatowicz (2020)

PCOS PATHOPHYSIOLOGY

PCOS presents a phenotype that causes a vicious cycle that includes endocrine, metabolic, and ovarian dysfunction, on which many hypotheses have been studied regarding its pathophysiology. PCOS causes interactions between many proteins and genes that are affected by genetic and environmental factors **(Figure 2)**. Here are explained the factors that contribute to the development of PCOS in humans and preclinical models. Clinical and biochemical hyperandrogenism are the main features of a diagnosis like PCOS. PCOS begins to develop during the early years of puberty. Pre-clinical models made in animal and in vitro studies complement the clinical investigation, the latest clinical, experimental, and genetic data emphasize neuroendocrine involvement in the pathophysiology of PCOS manifestation (Witchel et al., 2019).

Figure 2:
Main factors influencing PCOS pathophysiology



Source: Witchel et al. (2019)

According to Abbott et al. (2019), animal models created from artificially induced hyperandrogenism during pregnancy or naturally existing PCOS-like traits more accurately depict the pathophysiology of the reproductive, neuroendocrine, and metabolic systems. Genetic studies have identified 17 genes at risk for PCOS, which account for approximately 10% of women with PCOS. Numerous PCOS risk genes regulate gonadotropin secretion, suggesting a reproductive neuroendocrine basis for the pathogenesis of PCOS. Additionally, several animal models using androgen excess fetal demonstrate epigenetic induction of features like those of PCOS, including neuroendocrine, reproductive, and metabolic dysfunction.

PCOS AND OXIDATIVE STRESS

The level of oxidative stress is significantly increased in patients with PCOS, obesity, cardiovascular disorders, and cancer. The pathogenesis of PCOS in the context of oxidative stress includes disorders of cellular organelles and molecular and biochemical processes. The effect of oxidative stress can be evaluated by measuring the level of specific oxidants and antioxidants among different oxidants and antioxidants, where these markers provide knowledge for the development and treatment of disorders related to oxidative stress. These markers can be detected in serum or follicular fluid, the results of which provide insights into the development and treatment of oxidative stress disorders (Rudincka et al., 2022).

SYMPTOMS OF PCOS

Many PCOS patients start having symptoms around their first periods. Some others discover it only after they are overweight or unable to get pregnant. The symptoms that appear in women with PCOS are irregular menstruation where some have less than eight periods in a year, heavy bleeding, hair growth including their face, body, back, abdomen, and chest, acne which appears on the face, chest, and upper back, darkening of the face with dark skin spots appearing on the neck and under the chest, headaches (Mukerjee, 2020). In addition, PCOS also presents other symptomatic disorders related to psychological issues such as anxiety, depression, and low self-esteem. Also, with age, PCOS is a reproductive disease in metabolic disorders such as insulin resistance, impaired glucose tolerance, diabetes mellitus type 2, dyslipidemia, and cardiovascular risk factors (Louwers & Laven, 2020).

AMH AND LH LEVEL IN PCOS

To examine the role of AMH (Anti-Mullerian Hormone) and LH (Luteinizing Hormone) in determining the pregnancy rate in women who have a problem with PCOS, the measurement of AMH levels and how they help in reaching the diagnosis and prognosis of PCOS should be observed in detail. In the study of Mohammed and Qasim (2021), patient women went through ovarian stimulation that is controlled by prolonged agonist protocol followed by in vitro fertilization, where then the results for pregnant and non-pregnant women were compared. From the obtained results of this study, it was concluded that low levels of AMH represent low ovarian reserve. It is more common for AMH levels to decline gradually as a woman ages, but this is not a good sign for younger women, as low ovarian reserve can predict early infertility. The diagnosis of infertility is then restored with the recommendation of AMH fertility therapy, which involves IVF (In Vitro Fertilization) in response to FSH levels of 25 mL U/mL or above, which is regarded as positive. If FSH levels are at or above this value, then more than one FSH measurement should be done (Mohammed & Qasim, 2021).

In a study of 751 women with PCOS as well as ovulatory controls, a suitable sample of women with infertility complications was analyzed. Samples were analyzed for AMH by Access AMH where PCOS resulted in dominant ($p<0.05$) (Li et al., 2020). In another study of about 120 couples, the main cause of infertility in women was PCOS (46.6%), although the causes of infertility varied according to the age of couples and the age of marriage, PCOS remained the main etiology (Deshpande & Gupta, 2019). Khmil et al. (2020) conducted a study with 100 women aged 25-39 years with infertility due to PCOS, where they were diagnosed with infertility according to the Rotterdam criteria based on the level of anti-Mullerian hormones, FSH, LH, prolactin, estradiol, and testosterone in blood serum which were determined by ELISA. In women with PCOS, there was an increase in the results of AMH and LH values, estradiol and testosterone, and a decrease in the FSH level.

Increased secretion of anti-Müllerian hormone (AMH) is a defining feature of PCOS, the diagnostic value of AMH in PCOS is higher compared to the coefficient of free androgen index (FAI) and luteinizing hormone (LH)/follicle-stimulating hormone (FSH). Tandem mass spectrometry (LC-MS/MS) was used to measure BMI and AMH hormones in 4712 patients of reproductive age to compute age-specific reference ranges and diagnostic performance. In patients with normal ovarian function, the data showed a negative correlation between age and AMH values. In contrast, there was no correlation found between PCOS patients' age and AMH levels. Conversely, AMH revealed a slender relationship between FAI and the ratio of LH to FSH. The sensitivity for AMH, FAI, and LH/FSH ratio was 89/96%, 71/69%, and 75/72% respectively. When compared to FAI and the LH/FSH ratio, AMH is considered the most reliable diagnostic indicator for PCOS patients (Evliyaoglu et al., 2020).

ENDOMETRIAL CANCER

It is recommended women with PCOS should have regular check-ups to determine the risk in the early stages of endometrial cancer. According to Ignatov and Ortmann (2020), women with PCOS have a 2.7 times higher risk of developing endometrial cancer compared to non-PCOS women, which is confirmed by data from numerous studies. In a previous study, it was found that 36.3 % of 64,345 total patients were diagnosed with both PCOS and endometrial cancer. Meanwhile, from another four studies, it was found that women with PCOS exposed to clomiphene citrate had an increased risk of endometrial cancer (Murugappan et al., 2019). Barry et al. (2014) also reported an increased risk of endometrial cancer in 919 women with PCOS compared with women without PCOS. PCOS is a common reproductive disorder in women, while the risk of developing endometrial cancer is 2 to 6 times higher in these women. From a study with 285 PCOS patients, 103 of them were diagnosed with both PCOS and endometrial cancer (Wang, et al., 2021). Park et al. (2011) reported that PCOS is a disorder that affects 8-17% of women of reproductive age showing endometrial changes such as a thick endometrium with a diameter of 8.5 mm which can lead to endometrial hyperplasia or even endometrial cancer in women with PCOS. To reduce the risk of endometrial cancer young women with PCOS must start to diagnose and treat it as early as possible to prevent it.

In addition, the relationship between the use of oral contraceptives and endometrial cancer has been analyzed in several studies. It was reported that a significant decrease in the incidence of endometrial cancer in women who use oral contraceptives compared to women who did not use them. An examination of 36 epidemiological studies comparing 115,743 women without endometrial cancer to 27,276 women with the disease revealed that 39% of controls and 35% of endometrial cancer patients had ever used an oral contraceptive. For women who had endometrial cancer, the median length of time they had been using contraceptives was 4 years, whereas for healthy women it was 3 years. Moreover, endometrial cancer risk was significantly lower in first users than in never users.

DIAGNOSIS OF PCOS AND ENDOMETRIAL CANCER

The establishment of the diagnosis for PCOS is based on the presence of three specific elements regarding oligoanovulation, the increase of androgen, and the ultrasound evaluation of the morphology of the ovaries. From the presence of two of the three criteria, then we must deal with the diagnosis of PCOS in adult women (Hoeger et al., 2021).

Endometrial cancer is also a frequent and long-term complication of PCOS. The diagnosis of endometrial cancer is accompanied by clinical changes in 5-10% of cases, such as vaginal bleeding after menopause, while the most common is endometrial atrophy, which leads to suspicion of the respective disease. Through the physical examination in women with endometrial cancer, the uterus and adnexa are seen, which are palpated with unusual masses. endometrial, with ultrasound or hysteroscopy. In ultrasonography, the thickness of the endometrium is observed, if it is accompanied by changes of 5 mm-17 mm. Besides this, imaging tests with magnetic resonance can be used to verify the thickness of the endometrium. Hysteroscopy is used to evaluate bleeding and stop it along with curettage. Taking the sample through the Pipelle Method has always shown a correct diagnosis for the disease (Braun et al., 2016).

TREATMENT OF PCOS

For patients with PCOS, after establishing the diagnosis, the only goal is proper and adequate treatment for the disease. Treatment with metformin alone gives mild to moderate changes in the regulation of the cycle and hyperandrogens. According to the new guidelines, the combination of metformin with COC (combined oral contraceptive) is encouraged, especially in obese women with PCOS as well as in teenagers. A recent meta-analysis concluded that letrozole significantly improves the rate of delivery and clinical pregnancy, which is recommended as a first-line treatment for women with PCOS. Bariatric surgery is the most effective treatment for PCOS symptoms, while laparoscopic ovarian drilling is a procedure in which ovarian tissue is destroyed with laser beams or surgical needles using minimally invasive laparoscopic techniques, with the sole aim of rebalancing and improving ovarian function in PCOS (Hoeger et al., 2021).

CONCLUSIONS

PCOS in women is accompanied by various complications such as infertility which has been reported to affect 40% of the cases. In a study of about 120 couples, the main cause of infertility in women was PCOS (46.6%), although the causes of infertility varied according to the age of couples and the age of marriage, PCOS remained the main etiology. However, stimulation of ovulation, intrauterine insemination, as well as cycles of assisted reproductive techniques, are successful in the management or control of infertility disorders in women with PCOS. Anti-Mullerian Hormone (AMH) can be considered a better diagnostic factor in PCOS patients compared to free androgen index (FAI) and the ratio between luteinizing Hormone (LH) and follicle-stimulating hormone (FSH). Several studies have reported that women with PCOS have a higher risk of developing endometrial cancer. It has been reported that clinical determining factors of endometrial cancer in women with PCOS are a thick endometrium with a diameter higher than 8.5 mm and an age of higher than 25.5 years old. Metformin, letrozole, and minimally invasive laparoscopic techniques are effective in the treatment of PCOS. However, future research is necessary to achieve appropriate, efficient, and complication-free treatment methods in PCOS patients. In this context, special attention should be given to lifestyle factors and all other external factors that could positively affect the achievement of adequate treatment of women with PCOS that result in fewer complications and other pathological changes.

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