

Advance Research on Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a condition that causes irregular menstrual periods because monthly ovulation is not occurring and levels of androgens (male hormones) are elevated. It is an important cause of female infertility and a precursor for other critical conditions such as obesity, cardiovascular diseases, type - 2 diabetes and endometrial cancer. It has both reproductive and metabolic effects. It is very difficult to diagnose PCOS during the first 2 years following menarche because normal pubertal changes can mimic symptoms of PCOS. These symptoms are anovulatory menstrual cycles, transient multi-follicular ovarian morphology, increased androgen effects and relative insulin resistance. Common clinical features of PCOS include irregular or heavy or no menstrual periods, excess facial and body hair, acne, pain in the pelvis, difficulty to get pregnant and patches of thick, darker, velvety skin. Diagnosis of PCOS is based on any two of the following three findings. They are no ovulation, high androgen levels and ovarian cysts. Cysts may be distinguishable by ultrasonography. PCOS treatment may involve lifestyle modifications such as weight reduction and regular exercise. Birth control pills help to improve the regularity of menstrual periods, excess hair growth and acne. Metformin and anti-androgens may also help. Other typical acne treatments and hair removal techniques may be used for the treatment of PCOS. Weight loss, clomiphene or metformin also helps to improve fertility. The month of September is considered as Polycystic Ovary Syndrome (PCOS) awareness month around the world. It helps to initiate a conversation about this under diagnosed medical condition. Women who have PCOS are at high risk for several serious complications, some of them can be life threatening complications. Early diagnosis and treatment helps to reduce the risk for many of the complications.

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Introduction

Polycystic ovary syndrome (PCOS) is a condition that causes irregular menstrual periods because monthly ovulation is not occurring and levels of androgens (male hormones) are elevated. The condition occurs in approximately 5 to 10 percent of women. The elevated androgen levels can sometimes cause excessive facial hair growth, acne, and/or male-pattern scalp hair thinning. Most, but not all, women with PCOS are overweight or obese, and they are at higher-than-average risk of developing diabetes and obstructive sleep apnea. For women with PCOS who want to become pregnant, fertility medications may be needed to trigger ovulation.

Although PCOS is not completely reversible, there are a number of treatments that can reduce or minimize bothersome symptoms. Most women with PCOS are able to lead a normal life without significant complications.

Cause of PCOS

Reproductive System Abnormalities: The cause of PCOS is not completely understood. With regards to the reproductive system, it is believed that abnormal levels of the pituitary hormone luteinizing hormone (LH) and high levels of male hormones (androgens) interfere with normal function of the ovaries. To explain how these hormones cause symptoms, it is helpful to

understand the normal menstrual cycle.

Normal Menstrual Cycle: The brain (including the pituitary gland), ovaries, and uterus normally follow a sequence of events once per month; this sequence helps to prepare the body for pregnancy. Two hormones, follicle-stimulating hormone (FSH) and LH, are made by the pituitary gland. Two other hormones, progesterone and estrogen, are made by the ovaries.

During the first half of the cycle, small increases in FSH stimulate the ovary to develop a follicle that contains an egg (oocyte). The follicle produces rising levels of estrogen, which cause the lining of the uterus to thicken and the pituitary to release a very large amount of LH. This midcycle "surge" of LH causes the egg to be released from the ovary (called ovulation) approximately 36 to 48 hours following the LH surge. If the egg is fertilized by a sperm, it develops into an embryo, which travels through the fallopian tube to the uterus. After ovulation, the ovary produces both estrogen and progesterone, which prepare the uterus for possible embryo implantation and pregnancy.

Menstrual Cycle in PCOS: In women with PCOS, multiple small follicles (small cysts 4 to 9 mm in diameter) accumulate in the ovary. None of these small follicles/cysts are capable of growing to a size that would trigger ovulation. As a result, the levels of estrogen, progesterone, LH, and FSH become imbalanced.

Androgens are normally produced by the ovaries and the adrenal glands. Examples of androgens include testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS). Androgens may become increased in women with PCOS because of the high levels of LH but also because of increased levels of insulin that are usually seen with PCOS.

Metabolic System Abnormalities: The metabolic system controls the processing of carbohydrates, fats, and proteins. Important hormones in the metabolic system include insulin, glucagon, glucagon-like peptides, and many others.

Insulin abnormalities: PCOS is associated with elevated levels of insulin in the blood. Insulin is a hormone that is produced by specialized cells within the pancreas; insulin regulates blood glucose levels. When blood glucose levels rise (after eating, for example), these cells produce insulin to help the body use glucose for energy.

- If glucose levels do not respond to normal levels of insulin, the pancreas produces more insulin. Excess production of insulin is called hyperinsulinemia.
- When increased levels of insulin are required to maintain normal glucose levels, a person is said to be insulin resistant.
- When the blood glucose levels are not completely controlled, even with increased amounts of insulin, the person is said to have glucose intolerance (sometimes referred to as "prediabetes").
- If blood glucose levels continue to rise despite increased insulin levels, the person may have impaired glucose tolerance, often referred to as "prediabetes," which can ultimately lead to development of type 2 diabetes.

These conditions are diagnosed with blood tests. Insulin resistance and hyperinsulinemia can occur in both normal-weight and overweight women with PCOS. Among women with PCOS who are obese, there appears to be a three-fold increase in risk for prediabetes when compared with women without PCOS who are obese; up to 35 percent of those who are obese develop impaired glucose tolerance ("prediabetes") by age 40 years, while up to 10 percent of obese women develop type 2 diabetes. A family history of diabetes, overweight and obesity, as well as race and ethnicity (particularly African American and Hispanic), can increase the likelihood of developing diabetes among women with PCOS.

Symptoms of PCOS

The changes in hormone levels described above cause the classic symptoms of PCOS, including absent or irregular and infrequent menstrual periods, increased body hair growth or scalp hair loss, acne, and difficulty becoming pregnant.

Signs and symptoms of PCOS usually begin around the time of puberty, although some women do not develop symptoms until late adolescence or even into early adulthood. Because hormonal changes vary from one woman to another, patients with PCOS may have mild to severe acne, facial hair growth, or scalp hair loss.

Menstrual Irregularity: If ovulation does not occur, the lining of the uterus (called the endometrium) does not uniformly shed and regrow as in a normal menstrual cycle. Instead, the endometrium becomes thicker and may shed irregularly, which can result in heavy and/or prolonged bleeding. Irregular or absent menstrual periods can increase a woman's risk of endometrial overgrowth (called endometrial hyperplasia) or even endometrial cancer.

Women with PCOS usually have fewer than six to eight menstrual periods per year. Some women have normal cycles during puberty, which may become irregular if the woman becomes overweight.

Weight Gain and Obesity: PCOS is associated with gradual weight gain and obesity in approximately one-half of women. For some women with PCOS, obesity develops at the time of puberty.

Hair Growth and Acne: Male-pattern hair growth (hirsutism) may be seen on the upper lip, chin, neck, sideburn area, chest, upper or lower abdomen, upper arm, and inner thigh. Acne is a skin condition that causes oily skin and blockages in hair follicles.

Infertility: Many women with PCOS do not ovulate regularly, and it may take these women longer to become pregnant. If a woman with PCOS has irregular periods, their fertility evaluation should start immediately as the chance of becoming pregnant is low without treatment.

Heart Disease: Women who are obese and who also have insulin resistance or diabetes might have an increased risk of coronary artery disease, which increases the risk of having a heart attack. It is not known with certainty if women with PCOS are at increased risk for this condition. Both weight loss and treatment of insulin abnormalities can decrease this risk. Other treatments (eg, cholesterol-lowering medications [statins] and treatments for high blood pressure may also be recommended.

Sleep Apnea: Sleep apnea is a condition that causes brief spells where breathing stops (apnea) during sleep. Patients with this problem often experience fatigue and daytime sleepiness. In addition, there is evidence that people with untreated sleep apnea have an increased risk of insulin resistance, obesity, diabetes, and cardiovascular problems, such as high blood pressure, heart attack, abnormal heart rhythms, or stroke.

Sleep apnea may occur in up to 50 percent of women with PCOS. The condition can be diagnosed with a sleep study, and several treatments are available.

Other Problems: Women with PCOS are at increased risk of other problems that can impact quality of life. These include:

- Depression and anxiety- There are treatments that can help with these problems, including therapy as well as medications.
- Sexual dysfunction-Women with PCOS are more likely than other women to experience lower sexual satisfaction.
- Eating disorders -These include bulimia and binge eating. Women with PCOS do not appear to be at increased risk of developing anorexia.
- If you think you might be experiencing any of these problems, talk with your health care provider. There are often treatments that can help.

Symptoms after Menopause: Less is known about PCOS symptoms after menopause. Research suggests that women with PCOS may continue to have high androgen levels after menopause (when monthly periods normally stop), but that they decline to normal after approximately age 70. However, even women who have been through menopause and whose hormone levels are returning to normal can have symptoms like excess hair growth.

Diagnosis

There is no single test for diagnosing PCOS. You may be diagnosed with PCOS based upon your symptoms, blood tests, and a physical examination. Expert groups have determined that a woman must

have two out of three of the following to be diagnosed with PCOS:

- Irregular menstrual periods caused by an ovulation or irregular ovulation.
- Evidence of elevated androgen levels. The evidence can be based upon signs (excess hair growth, acne, or male-pattern balding) or blood tests (high androgen levels).
- Polycystic ovaries on pelvic ultrasound.

In addition, there must be no other cause of elevated androgen levels or irregular periods (eg, congenital adrenal hyperplasia [classic or nonclassic], androgen-secreting tumors, or hyperprolactinemia).

Blood tests are usually recommended to determine whether another condition is the cause of your signs and/or symptoms. If you have irregular periods, blood tests for pregnancy, prolactin level, thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) should be done. Insulin levels are not used to diagnose PCOS, partly because insulin levels are high in people who are above normal body weight and because there is no level of insulin that is "diagnostic" for PCOS.

If PCOS is confirmed, blood glucose and cholesterol testing are usually performed. An oral glucose tolerance test is the best way to diagnose prediabetes and/or diabetes. A fasting glucose level is often normal even when prediabetes or diabetes is present. Many clinicians who treat PCOS patients also recommend testing for sleep apnea with questionnaires or overnight sleep studies in a sleep laboratory. In women with moderate to severe hirsutism (excess hair growth), blood tests for testosterone and dehydroepiandrosterone sulfate (DHEAS) may be recommended.

All women who are diagnosed with PCOS should be seen on a routine basis by a health care provider for the metabolic and reproductive issues that may occur. In addition, depression and anxiety are common in women with PCOS.

Treatment

Oral Contraceptives: Oral contraceptives (OCs; with combined estrogen and progestin) are the most commonly used treatment for regulating menstrual periods in women with PCOS. OCs protect the woman from endometrial (uterine) hyperplasia or cancer by inducing a monthly menstrual period. OCs are also effective for treating hirsutism and acne by suppressing ovarian androgen production. A skin patch and vaginal ring are also available for contraception. Some women choose intrauterine devices (IUDs) containing a type of progesterone to minimize uterine bleeding and protect against uterine cancer. However, unlike OCs, patch, and ring, the IUD is not effective for treating acne or facial hair.

Women with PCOS occasionally ovulate, and OCs are useful in providing protection from pregnancy. Although an OC allows for bleeding once per month, this does not mean that the PCOS is "cured"; irregular cycles generally return when the OC is stopped.

OCs decrease the body's production of androgens, and antiandrogen drugs (such as spironolactone) decrease the effect of androgens. These treatments can be used in combination to reduce and slow hair growth. OCs and antiandrogens can also reduce acne. Other prescription skin treatments (eg, medicated lotions) or oral antibiotics may be recommended in some cases.

Professional societies do not require an examination or blood test to start an OC. Women without regular menses may need a test for pregnancy prior to starting OCs. This is no longer being done as frequently as in the past.

Side Effects: Some women who take birth control pills (not just those with PCOS) stop having monthly bleeding or develop irregular spotting and bleeding. Irregular bleeding usually resolves after a few menstrual cycles.

Many women worry that they will gain weight on the pill. In general, this is not a concern with the currently available low-dose pills. Some women develop nausea, breast tenderness, and bloating after beginning the pill, but these symptoms usually resolve after two or three months.

The pill is safe and effective, although it slightly increases the risk of blood clots in the legs or lungs; this is a rare complication in young, healthy women who do not smoke, but it is more of a concern in women who are obese and in older women.

Progestin: Another method to treat menstrual irregularity is to take a hormone called progestin (sample brand name: Provera) for 10 to 14 days every 1 to 3 months. This will induce a period in almost all women with PCOS, but it does not help with the cosmetic concerns (hirsutism and acne) and does not prevent pregnancy. It does reduce the risk of uterine cancer.

Hair Treatments: Excess hair growth on the face and/or other parts of the body can be removed by shaving or use of depilatories, electrolysis, or laser therapy. Many women worry that these treatments cause hair to grow faster, although this is not true.

In women with PCOS, hormonal treatment of excess hair growth is typically approached in a two-step process. The first step is to prescribe an estrogen-progestin contraceptive (ie, a birth control pill). If, after six months of hormone treatment, sufficient improvement in excess hair growth has not been achieved, a second medication called spironolactone, an antiandrogen, is added. If hormone treatment with an estrogen-progestin results in a satisfactory reduction in excess hair growth, this therapy is continued.

Scalp hair loss can be treated with medications in some situations. Other options include hair replacement and wigs.

Weight Loss: For women with PCOS who are overweight or obese, weight loss is one of the most effective approaches for managing insulin abnormalities, irregular menstrual periods, and other symptoms of PCOS. For example, many overweight women with PCOS who lose 5 to 10 percent of their body weight notice that their periods become more regular. Weight loss can often be achieved with a program of diet and exercise.

There are a number of options available to treat obesity. These options are identical to those recommended for women without PCOS and include diet and exercise, weight loss medications (although their use is limited), and weight loss surgery.

Weight loss surgery may be an option for severely obese women with PCOS. Women can lose significant amounts of weight after surgery, which can restore normal menstrual cycles, reduce high androgen levels and hirsutism, and reduce the risk of type 2 diabetes.

Metformin: Metformin (sample brand name: Glucophage) is a medication that improves the effectiveness of insulin produced by the body. It was developed as a treatment for type 2 diabetes but may be recommended for women with PCOS in selected situations.

- If a woman does not have regular menstrual cycles, the first-line treatment is a hormonal method of birth control, such as birth control pills. If the woman cannot take birth control pills, one alternative is to take metformin; a progestin is usually recommended, in addition to metformin, for six months or until menstrual cycles are regular.
- Metformin may help a bit with weight loss. Although metformin is not a weight-loss drug, some studies have shown that women with PCOS who are on a low-calorie diet lose slightly more weight when metformin is added. If metformin is used, it is essential that diet and exercise are also part of the recommended regimen because the weight that is lost in the early phase of metformin treatment may be regained over time.

Metformin is not usually recommended for women with PCOS who have difficulty becoming pregnant, because it is not as effective as other treatments for ovulation induction, letrozole, and clomiphene.

An expert group does not recommend metformin for women with PCOS in whom excessive hair growth (hirsutism) is of primary concern. Birth control pills alone, or in combination with an antiandrogen medication, are a better option.

Treatment of Infertility: If tests determine that lack of ovulation is the cause of infertility, several treatment options are available. These treatments work best in women who are not obese.

The primary treatment for women who are unable to become pregnant and who have PCOS is weight loss. Even a modest amount of weight loss may allow the woman to begin ovulating normally. In addition, weight loss can improve the effectiveness of other infertility treatments.

Clomiphene is a US Food and Drug Administration (FDA)-approved oral medication that stimulates the ovaries to release one or more eggs. It triggers ovulation in approximately 80 percent of women with PCOS, and approximately 50 percent of these women will become pregnant.

Letrozole is a medication that is FDA approved for the treatment of breast cancer, but it is not approved for induction of ovulation. However, studies have shown that live birth rates are higher in obese women with PCOS when they are treated with letrozole rather than clomiphene. Many experts now recommend letrozole as the first choice of treatment for women with PCOS who want to conceive.

A few studies have shown that taking metformin in addition to clomiphene increases the rate of ovulation; other studies have shown no additional benefit of adding metformin to clomiphene treatment. Women who take metformin before pregnancy are usually advised to stop it once they become pregnant.

If a woman does not ovulate or is unable to conceive with letrozole, clomiphene, gonadotropin therapy (follicle-stimulating hormone [FSH] injections) is sometimes recommended. However, this treatment can cause multiple pregnancies, including triplets and quadruplets, particularly in patients with PCOS. In modern practice, IVF will often be suggested rather than FSH injections if clomiphene and letrozole do not result in a pregnancy. The risk of multiple gestations is lower with IVF and single embryo transfer when compared to FSH injections [1].

Vitamin D

There is increasing evidence suggesting that PCOS affects the whole life of a woman, can begin in utero in genetically predisposed subjects, manifests clinically at puberty, and continues during the reproductive years [2]. Vitamin D insufficiency or inadequacy affects 45-90% of reproductive-age women. According to research, vitamin D insufficiency was associated with a substantial reduction in ovulation rate, pregnancy rate, and the chance of a live delivery in PCOS women receiving ovarian stimulation for infertility [3-6]. Patients with polycystic ovarian syndrome, ovulation dysfunction, and metabolic disorders may benefit from vitamin D medication. To make firm conclusions on the effect of vitamin D supplementation on female reproductive health, randomized, prospective, and controlled studies are required [7].

Management of PCOS

Lifestyle Modifications

A right diet with adequate exercise has shown great results in PCOS recovery. Diet should be dominated with lots of fruits and vegetables on a daily basis. Minimum of 2 - 3 liters of water/day is essential. Regular exercise for 30 - 40 minutes daily (Brisk walking, yoga, and meditation) is recommended [8]. Obese women with PCOS can benefit from a low-calorie diet for their weight reduction [9].

Medical Management

There are various number of medical therapies used to reduce the different symptoms of PCOS. It includes for periods, fertility, excess hair, acne and weight gain. The medical therapies are oral contraceptive pills, insulin sensitizing drugs such as Metformin, hormones (gonadotrophins), testosterone lowering drugs, weight losing drugs, antidepressants and anti-anxiety drugs [9].

Surgical Management

Surgical management of PCOS is aimed mainly at restoration of ovulation. Ovarian wedge resection has been advocated because of postoperative adhesion formation and the successful administration of ovulation-inducing medications. Various laparoscopic methods, including electrocautery, laser drilling and multiple biopsies have been used with the aim of creating certain focal areas of damage in the ovarian cortex and its stroma [10].

Complications

The complications of PCOS include: diabetes (insulin resistance by the receptors for insulin leads to high levels of insulin being produced by the pancreas), obesity (hyperandrogenemia affects the distribution of body fat) infertility, (due to the development of numerous fluid-filled sacs in the ovaries and failure of ovaries to regularly release eggs for reproduction, hormonal imbalances and any abnormality in the menstrual cycle may also interfere with ovulation) atherosclerosis (clogged arteries), high blood pressure (hypertension), heart attack (increased levels of androgens and the low level of adiponectin cause cardiac diseases), breast cancer, endometrial cancer (prolonged ovarian function disorder in women with polycystic ovarian syndrome can alter endometrial cell growth, which in turn can cause cancer), metabolic syndrome [11-17]. (Central obesity, hypertension, atherogenic dyslipidemia, and insulin resistance in PCOS cause metabolic syndrome) and sleep apnea (insulin resistance makes difficult for the body to absorb energy which can cause weight gain and that can lead to trouble sleeping soundly) [17-19].

Result

Polycystic ovary syndrome is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. Many body systems are affected in polycystic ovary syndrome, resulting in several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. The cause of polycystic ovary syndrome is unknown, but studies suggest a strong genetic component that is affected by gestational environment, lifestyle factors, or both. They are no ovulation, high androgen levels and ovarian cysts.

Differential diagnoses of PCOS include adrenal hyperplasia, Cushing's syndrome, pregnancy, hypothyroidism and high blood levels of prolactin. PCOS treatment may involve lifestyle modifications such as weight reduction and regular exercise.

Discussion and Conclusion

Polycystic ovary syndrome is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. The major endocrine disruption is excessive androgen secretion or activity, and a large proportion of women also have abnormal insulin activity. Many body systems are affected in polycystic ovary syndrome, resulting in several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. Women with this disorder have an established increased risk of developing type 2 diabetes and a still debated increased risk of cardiovascular disease. The diagnostic traits of polycystic ovary syndrome are hyperandrogenism, chronic anovulation, and polycystic ovaries, after exclusion of other conditions that cause these same features. A conclusive definition of the disorder and the importance of the three diagnostic criteria relative to each other remain controversial. The cause of polycystic ovary syndrome is unknown, but studies suggest a strong genetic component that is affected by gestational environment, lifestyle factors, or both.

Due to a combination of genetic and environmental factors, PCOS occurs. Risk factors of PCOS are obesity, a lack of physical exercise and a family history of PCOS. Diagnosis of PCOS is based on any two of the following three findings. They are no ovulation, high androgen levels and ovarian cysts. Cysts may be distinguishable by ultrasonography. Differential diagnoses of PCOS include adrenal hyperplasia, Cushing's syndrome, pregnancy, hypothyroidism and high blood levels of prolactin. PCOS treatment may involve lifestyle modifications such as weight reduction and regular exercise. The medical therapies are oral contraceptive pill, insulin sensitizing drugs such as Metformin, hormones (gonadotrophins), testosterone lowering drugs, weight loss drugs, antidepressants and anti-anxiety drugs. Early diagnosis and treatment can help reduce the risk for many of the complications.

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