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PCOS OVERVIEW — Polycystic ovary syndrome (PCOS) is a condition that causes irregular menstrual periods because monthly ovulation is not occurring and elevated levels of androgens (male hormones) in women. The elevated androgen levels can sometimes cause excessive facial hair growth, acne, and/or male-pattern hair thinning. The condition occurs in about 5 to 10 percent of women. Some, but not all, women with PCOS are overweight or obese, and they are at higher than average risk of developing diabetes. For women with PCOS who want to become pregnant, hormone pills or injections are often needed to help women ovulate.

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.

PCOS CAUSE — The cause of PCOS is not completely understood. It is believed that abnormal levels of the pituitary 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 luteinizing hormone (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) After ovulation, the ovary produces both estrogen and progesterone, which prepare the uterus for possible implantation and pregnancy.

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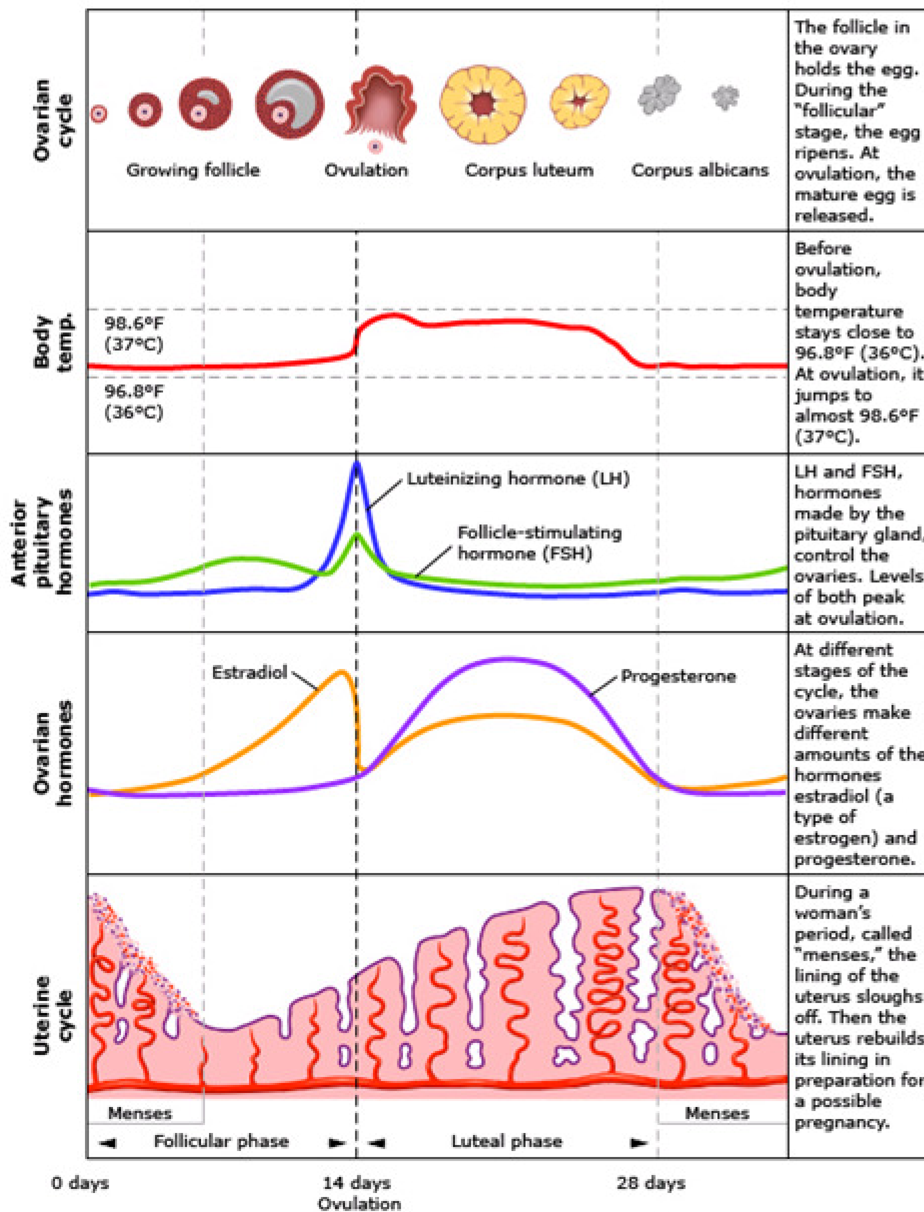
Normal menstrual cycle



Menstrual cycle in PCOS — In women with PCOS, multiple small follicles (small cysts) may develop. The follicles are unable to grow to a size that would trigger ovulation. Therefore, small follicles (4 to 9 mm in diameter) accumulate in the ovary, hence the term polycystic ovaries. None of these small follicles are capable of triggering ovulation. As a result, the levels of estrogen, progesterone, LH, and FSH become imbalanced.

Androgens (male-type hormones) are normally produced by the ovaries and the adrenal glands. In addition, some tissues (such as fat cells and the liver) can convert other steroid hormones into androgens. Examples of androgens include testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S). Androgens may become increased in women with PCOS

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because of the high levels of LH, but also because of high levels of insulin that are usually seen with PCOS.

PCOS SYMPTOMS — The changes in hormone levels described above cause the classic symptoms of PCOS, including absent or irregular and infrequent menstrual periods, abnormal body hair growth or scalp hair loss, acne, weight gain, 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 and 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 about 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, and upper or lower abdomen. Acne is a skin condition that causes oily skin and blockages in hair follicles.

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 is said to have **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, up to 35 percent of those who are obese develop impaired glucose tolerance by age 40, while up to 10 percent of

obese women develop type 2 diabetes. The risk of these conditions is much higher in women with PCOS compared with women without PCOS. 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.

Infertility — Many women with PCOS do not ovulate regularly, and it may take these women longer to become pregnant. An infertility evaluation is often recommended after 6 to 12 months of trying to become pregnant.

Heart disease — Women who are obese and who also have insulin resistance or diabetes might have an increased risk of coronary artery disease, the narrowing of the arteries that supply blood to the heart. It is not known for sure 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, 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, cardiovascular problems, such as high blood pressure, heart attack, abnormal heart rhythms, or stroke. This risk may be changes in heart rate and blood pressure that occur during sleep.

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.

PCOS 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 anovulation 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, androgen-secreting tumors, or hyperprolactinemia).

Blood tests are usually recommended to determine whether another condition is the cause of your signs and/or symptoms. Blood tests for pregnancy, prolactin level, thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) may be recommended.

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 screening 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 DHEA-S may be recommended.

All women who are diagnosed with PCOS should be monitored by a healthcare provider over time. Symptoms of PCOS may seem minor and annoying, and treatment may seem unnecessary. However, untreated PCOS can increase a woman's risk of other health problems over time.

PCOS TREATMENTS

Birth control — 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) cancer or overgrowth by inducing a monthly menstrual period. OCs are also effective for treating hirsutism and acne. A skin patch and vaginal ring are also available.

Women with PCOS occasionally ovulate, and oral contraceptives 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.

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

Before prescribing an oral contraceptive, a clinician will perform an examination or a blood test to be certain that a woman is not pregnant. If a woman has not had a period for six weeks or longer, the clinician may first prescribe a hormone (eg, Provera) to induce a menstrual period.

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. 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 (eg, Provera®) for 10 to 14 days every one to three 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 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.

Weight loss — 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 is 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 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 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.

Metformin is not recommended for women with PCOS who have excessive hair growth (hirsutism). Birth control pills alone, or in combination with an anti-androgen 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 an oral medication that stimulates the ovaries to release one or more eggs. It triggers ovulation in about 80 percent of women with PCOS, and about 50 percent of these women will become pregnant.

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. In addition, it is not clear if metformin is safe during pregnancy (but metformin is FDA category B in pregnancy, which is generally interpreted as reasonably safe); women who take metformin before pregnancy are usually advised to stop it once they become pregnant.

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If a woman does not ovulate or is unable to conceive with clomiphene, gonadotropin therapy (FSH injections) may be recommended. Ovulation occurs in almost all women with PCOS who use gonadotropin therapy; approximately 60 percent of these women become pregnant.

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