

# Polycystic Ovary Syndrome (PCOS)

## Introduction

Polycystic ovarian syndrome is a term used to describe women who have a tendency, because of **abnormal ovulation** to develop multiple small cysts on their ovaries. This occurs in up to one in five women of reproductive age. It is not a good diagnostic term as there is not a single cause of PCOS and women who are given this diagnosis will have very different characteristic, different long-term outcomes and respond very differently to treatments. However, it is a term that has got stuck in the medical jargon and many women have been told they have this prior to arriving at S.O.F.T.



**Southern Ontario  
Fertility Technologies**

## Diagnosis of PCOS

The diagnosis of PCOS is based on criteria put in place by the Modified Consensus of the National Institute of Child Health and Human Development in 1990 and recently modified (2004) at an international consensus. Up until this conference, many different ways of diagnosing PCOS existed. To diagnose PCOS, **two major criteria or one major and two minor criteria should be present**. Major Criteria include chronic anovulation (not releasing an egg each month), hyperandrogenemia (increased male hormone), clinical signs of hyperandrogenemia, ultrasound evidence PCOS, and exclusion of other causes. Minor Criteria include insulin resistance, perimenarcheal (at the time of puberty) onset of hirsutism (increased hair growth in the male distribution) and obesity, or elevated LH/FSH ratio (see below). These criteria have been summarized in the table below.

### Do You Qualify For this Diagnosis?

<b>Major Criteria</b>		<b>Minor Criteria</b>	
<b>Chronic anovulation</b>		<b>Insulin resistance</b>	
<b>Hyperandrogenemia</b>		<b>Perimenarcheal onset of hirsutism and obesity</b>	
<b>Clinical signs of hyperandrogenemia</b>		<b>Elevated LH/FSH ratio</b>	
<b>Exclusion of other causes</b>			
<b>Ultrasound evidence PCOS</b>			

## The Normal Menstrual Cycle

Each month the lining of the uterus (endometrium) builds up, and then sheds resulting in a period (menses). The average cycle is about 28 days but can be shorter or longer (usually 25-35 days). The menstrual flow lasts 3 to 7 days. This type of normal menstrual cycle is possible because of a complex interaction of hormones secreted from the pituitary and the ovary. If all goes well, the interaction of these hormones results in ovulation (release of an egg) about mid-cycle. If this occurs, estrogen is the dominant hormone in the first half of the menstrual cycle and after ovulation, progesterone becomes

dominant. If ovulation does not occur, the high levels of progesterone do not develop. Instead, the ovary has a tendency to divert hormonal production into androgens (male-type hormones) with several undesirable consequences.

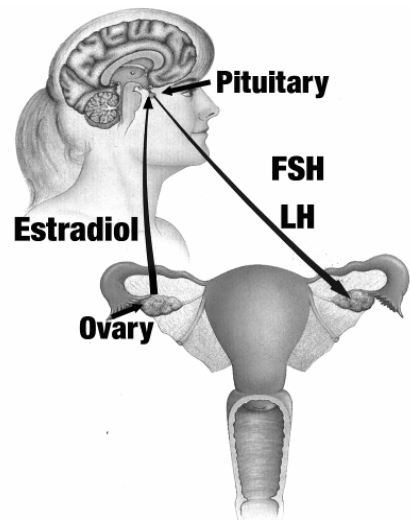
## The Symptoms of PCOS

### Menstrual Irregularities

Regular menstrual cycles occur when an egg is released each month. If menstrual cycles are anovulatory, they become irregular. This irregularity can range from amenorrhea (no periods) to frequent, almost continuous bleeding.

Irregular uterine bleeding such as this **can often become heavy**. This can result in depletion of the body's iron stores and in extreme cases, anemia (low blood). The other extreme can also develop where very few periods occur. This pattern is often associated with low estrogen levels (see below).

Prior to the recent change in the criteria for PCOS, it would be unusual to be diagnosed with PCOS and have regular menstrual cycles. What the new criteria recognize is that some women may have regular cycles but increased androgen levels and a polycystic appearance to their ovaries



### Infertility

Irregular ovulation or no ovulation usually means that **pregnancy is more difficult** to achieve. Sometimes, a pregnancy will occur in women with very irregular cycles because ovulation occurs occasionally. Fortunately, if ovulation is not occurring, giving medication to promote ovulation can often restore fertility. Many women with PCOS respond well to clomiphene citrate, which is inexpensive, safe and convenient to take. This is discussed in more detail under treatment.

### Hirsutism

Because the ovary has a tendency to produce more male-type hormones if ovulation does not occur, women with this condition often have more male hormone effect than they desire. Body hair exists over the entire body and the numbers of hair follicles are fixed at birth. Most of it is in the form of vellus hair, which is barely visible. In the male hormone sensitive areas of the body, exposure to male hormone converts the vellus hair into a terminal hair. Terminal hairs are coarser, longer and darker color. This can result in **male type distribution** of hair growth on the face, chest, lower abdomen, lower back and legs. Conversion of vellus to terminal hair is a one-way street so that hirsutism tends to become progressive if not treated. Good treatments exist for the treatment of hirsutism and are the subject of a different information sheet.

## Acne

The over production of male hormone may also cause acne. Severe cystic acne as a teenager or acne persisting past the teenage years is often predictive of PCOS. Aggravation of acne is probably due to the increased male hormone levels present in this condition. Treatment of the PCOS can often be very beneficial to the acne.

## Ovarian Cysts

The ovarian cysts common in this condition usually present no health problem but occasionally can cause problems. The ultrasound appearance of the ovary is sometimes very characteristic. More follicles (small fluid filled structures containing an egg) are usually present in an ovary of a patient with PCOS than are present in a normal ovary. Ovarian volume (the three dimensional size of the ovary) is usually also increased. The follicles can often be seen lining up around the margin of the ovary on ultrasound. This is referred to as “the ring of pearls” appearance.

There is also a tendency to form larger ovarian cysts. Ovarian cysts usually do not cause symptoms except if they leak or twist.

## Obesity

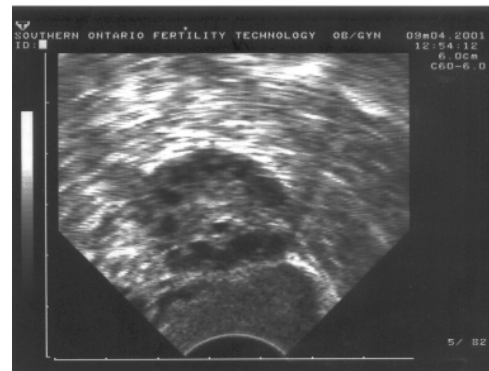
At least 50% of women with PCOS are overweight (although insulin resistance – see below – commonly associated with PCOS or obesity can make weight loss more difficult). Obesity is not necessarily caused by PCOS but likely the reverse is true. One of the most common causes of PCOS is obesity.

## Elevated LH/FSH Ratio

LH (luteinizing hormone) and FSH (follicle stimulating hormone) are two hormones from the pituitary gland, which are associated with the normal cycling of the ovary. Except briefly at the time of the LH surge, in almost all normal ovulatory cycles the level of FSH is higher than LH. If the LH is found to be higher than the FSH it may be a sign of PCOS. This is especially true if the blood test is timed to the beginning of a cycle (usually day 3). In investigating infertility or irregular cycles, you will often be asked to do “day 3 bloodwork”. If the cycles are extremely irregular or do not come, they can often be brought on by medication (Provera ®) after it is determined you are not pregnant.

## Insulin Resistance

Insulin resistance refers to the situation where the blood sugar is normal, but the body must make more insulin to keep it this way. It can develop because of the PCOS or it may be an underlying causative factor. It is significant because it is a marker for higher risk of maturity onset diabetes later in life.



**Polycystic Ovaries As Seen By Vaginal Ultrasound**

Insulin resistance is a bit difficult to diagnose as blood testing is not always reliable. A simple measurement of the insulin level when one is fasting is a reasonable screening test. Many physicians will look at the ratio of the fasting insulin divided by the fasting blood sugar. This is a bit more accurate but not totally reliable. There are also more complicated tests but most of these are reserved for research purposes.

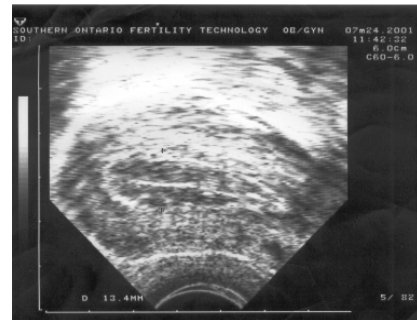
Some controversy exists about whether women with PCOS without documented insulin resistance might also benefit from insulin resistance treatment. Recent papers have demonstrated improved ovulation and higher pregnancy rates in these women despite no clear-cut demonstration that they were insulin resistant in the first place.

Its treatment can sometimes restore normal menstrual function or make women who were previously resistant to clomiphene be more responsive to it. It is also associated with a much higher risk of cardiovascular disease. Whether treatment of insulin resistance can decrease the chance of maturity onset diabetes or decrease the risk of heart disease is not known because no long-term scientific studies have been done yet. However, it does make sense that it would; especially if it can be accomplished with diet, exercise and weight loss.

Treatment of insulin resistance involves exercise, weight loss, diet or medication. The most common medication is metformin. Metformin is taken three times per day. A newer medication, rosiglitazone has become available in Canada and only has to be taken once per day.

### **Endometrial Hyperplasia**

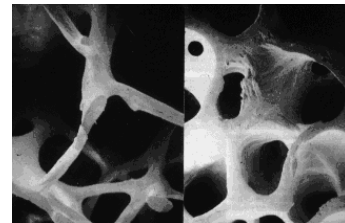
Because ovulation does not occur, progesterone is not produced in high concentrations in the second half of the menstrual cycle. This means that the lining of the uterus (the endometrium) is exposed to **continuous estrogen stimulation**. Continuous estrogen stimulation presents no problem in the short term, but if it continues for years may cause the endometrium to “overgrow” in the form of polyps, endometrial hyperplasia and even a low-grade type of uterine (endometrial) cancer.



**Ultrasound Picture of endometrium is often used to determine if an endometrial biopsy should be done**

### **Low Estrogen**

Women with PCOS, who tend to have less menstrual bleeding, have lower estrogen levels. Lower estrogen levels have been linked to osteoporosis and



**Normal and osteoporotic bone**

premature cardiovascular disease. Good evidence does exist that bone density is well maintained in this pattern of PCOS because of the higher chronic male hormone levels. Whether the lower estrogen levels contribute to the increased risk of heart disease is not known.

## Heart Disease

Obese women with polycystic ovaries are at greater risk of heart disease. Much of this increased risk **may be due to the obesity or insulin resistance**. Hypertension (elevated blood pressure) and increased cholesterol are also more common.

A small subgroup of PCOS patients have “cardiovascular dysmetabolic syndrome”. This syndrome usually includes severe insulin resistance and increased blood lipids (hyperlipidemia) and drastically increases the risk of premature heart disease. It is therefore important that women with PCOS be investigated for insulin resistance and hyperlipidemia.

## Diagnosis

PCOS is defined as chronic anovulation with clinical or biochemical hyperandrogenism and ultrasound appearance of polycystic ovaries. It is also important to exclude other causes of anovulation (ovarian failure, hypothalamic or pituitary failure). Other factors such as insulin resistance, elevated LH to FSH ratio, ultrasound evidence of polycystic ovaries, and the onset of obesity or hirsutism at puberty also help to confirm the diagnosis.

## Treatment

Whether to treat PCOS by regulating the menstrual cycle should be an individual decision on the part of each woman in consultation with her physician. Many women with this condition are unaware that they have it.

The treatment of PCOS also **depends on the goal of treatment**. The goal of treatment may be to produce a pregnancy or to control any or all of the symptoms of PCOS without producing a pregnancy.

Women **with symptoms such as infertility, severe menstrual problems, progressive hirsutism, male-pattern baldness or severe acne** will be helped by treatment. Treating to prevent endometrial hyperplasia or increased heart disease risk is less immediate and should be an **individual decision**.

Over 50% of patients with PCOS are overweight. Sometimes even modest weight loss can have a substantial impact on some symptoms. Proper diet and exercise are also beneficial.

## Treatment to Control Symptoms

As stated above, the ideal treatment of PCOS is **weight loss** if you are overweight. **Diet and exercise** can be used to accomplish this. Exercise may also be beneficial for normal weight PCOS. Although this is the ideal treatment, in a perfect world – in the real world this is often difficult to accomplish!

The first line medical treatment of PCOS is an **oral contraceptive**. Recently some oral contraceptives have been marketed specifically to treat hirsutism or acne. They contain very non-androgenic progestins. Although they may control acne faster, all oral contraceptives will eventually improve both acne and hirsutism in PCOS women. This restores normal menstrual period and prevents heavy irregular bleeding. It also decreases

the production of male hormones thus helping conditions like hirsutism, acne or male-pattern baldness.

At S.O.F.T., we have developed a protocol for “continuous” oral contraceptive use which is excellent for controlling cycles and minimizing symptoms. A detailed information sheet is available on this but will be summarized here briefly.

### **“Continuous” Oral Contraceptive Protocol**

(This protocol can be beneficial in many circumstances where one wants to regulate the menstrual cycle and avoid as many periods as possible)

Any oral contraceptive which is monophasic can be used. Monophasic means that all the pills in the package contain the same dose. The first pill can be started at any time during the cycle. A single pill is taken every day. The pills are stopped only if there are 5 days of spotting or 3 days of bleeding. Spotting means the bleeding can be controlled by panty liners; bleeding means that a pad or tampon is required. When the pills are stopped, they are only stopped for 5 days and then immediately restarted.

**Spironolactone, cyproterone acetate and finasteride** are androgen blocking agents (block the action of testosterone) and can also be beneficial if hirsutism or other signs of androgen excess that persist despite oral contraceptives.

**Electrolysis or laser hair removal** can be beneficial in PCOS women with severe hirsutism. Waxing, pulling and dying although not permanent can help with the promotion of a better self-image.

### **Treatment to Promote a Pregnancy**

**Clomiphene citrate** is used to induce ovulation when infertility is a complaint. Approximately 80% of patients with PCOS will ovulate on clomiphene. However, only 50% of those that ovulate will get pregnant. Clomiphene is indicated for six ovulatory cycles. It is important to demonstrate ovulation on clomiphene and this is done using a luteal phase progesterone level. A complete description of clomiphene is available on the clomiphene information sheet.

A newer medication sometimes used in a similar fashion to clomiphene is letrozol (**femara**). The initial results with this drug have been very exciting. We use it at S.O.F.T. when clomiphene has not produced a pregnancy with six cycles, when clomiphene causes excessive thinning of the endometrium or when higher doses of clomiphene have been necessary to induce ovulation.

**Metformin** can be beneficial to treat insulin resistance. When insulin resistance is present, use of metformin will sometimes allow the resumption of normal ovulatory cycles and sometimes a spontaneous pregnancy. Three such pregnancies occurred in the first year of operation of S.O.F.T.

It is also very helpful in PCOS, which is resistant to ovulation induction with clomiphene. Early results of a clinical trial demonstrated that in 19 consecutive patients with infertility, PCOS and insulin resistance who did not ovulate with clomiphene citrate in a dose of up to 150 mg., metformin 500 mg. p.o. t.i.d. allowed 4 patients to ovulate at 100 mg and 2 patients at 150 mg. (31.6%). Two pregnancies occurred. Since then many more pregnancies have occurred in the same circumstances.

Metformin is given in a dose of 500 mg. This is begun at once a day for a week, then twice a day for a week, then three times a day for a week to avoid the side effects of heartburn and diarrhea. The insulin resistance test is usually repeated at the end of the first week of the three times a day dosage. Other medications are available if the insulin resistance does not respond to metformin.

#### **Treatment with Metformin**

To start Metformin you will be given a repeating prescription of 100 tablets. Metformin will often cause diarrhea and to a lesser extent, heartburn. Introducing the medication slowly can minimize these side effects. To do this you will be asked to start a single tablet once per day. After a week, any side effects should have just about gone. If this is the case, you should increase metformin to two tablets per day. If the side effects at the end of the first week are still continuing, don't increase the dose but wait until things do settle down. Similarly, increase metformin to three per day after another week as long as the side effects are minimal. After taking metformin at three per day for a week the fasting blood sugar with insulin level should be repeated. You will be given a requisition for this blood

Once a pregnancy has occurred, Metformin is usually stopped. This does not have to be done quickly. There is no indication that Metformin is dangerous in pregnancy. In fact, in much of the world (India, China) it is used to help control blood sugars in pregnancy. Also recent evidence indicated that the spontaneous miscarriage rate and even the congenital abnormality rate may be lower in PCOS women who become pregnant while on Metformin. In North America, however, it is the standard of care to stop Metformin once a pregnancy has occurred. At S.O.F.T. we usually will stop Metformin at the time of the luteal day 40 ultrasound.

Rosglitazone (advandia ®) is often used if too many side effects occur with metformin or occasionally will be used with metformin for more profound treatment of insulin resistance.

Treatment options after a trial of clomiphene ± treatment of insulin resistance include **injectable fertility medications or laparoscopic ovarian cautery**. Patients with PCOS tend to under or over respond to injectable fertility medication creating a higher risk of multiple pregnancies or ovarian hyperstimulation syndrome. Very careful monitoring is necessary to avoid these complications. Ovarian cautery or drilling will sometimes cause the resumption of ovulatory cycles. If this does not occur it does make ovulation induction more successful and treatment with injectable infertility medications more predictable and controllable.

A complete information sheet is available on decreased ovulation.

#### **A Final Word**

PCOS is **not a disease**. It is an imbalance of the hormones controlling normal ovarian cycling. It causes other unpleasant symptoms, which can be controlled. Pregnancy can occur but usually require some medical intervention to cause ovulation.

Maintenance of ideal weight, exercise and a healthy diet should always be the first treatment attempted in this condition. In the case of infertility, it has been demonstrated that even modest reductions of weight can cause ovulations to occur and pregnancy to be possible.

However, PCOS presents an opportunity for good preventative medicine. Steps should perhaps be taken early to control the sometimes-progressive symptoms before they affect the overall quality of life.

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