Polycystic Ovary Syndrome
Information for Patients
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This is a handout with some background information about Polycystic Ovary Syndrome. I have written it for my patients and others interested in this condition. My perspective is a long-term one – I am concerned about the art of living with PCOS for a lifetime. My colleagues in Reproductive Endocrinology can say more about infertility, so I don't address that extensively here. Here's what I do talk about:

- How PCOS is defined
- Common symptoms
- Insulin resistance and how it fits into PCOS
- Long-term metabolic problems
- Basics of preventive care

Polycystic Ovary Syndrome is a common condition that affects approximately 5-10% of reproductive-aged women. This makes it the most common endocrine condition in women of this age group. Despite being very common, it is currently under-diagnosed and under-treated. Only in the past ten to fifteen years have we begun to unlock some of the secrets of PCOS. While we still don't know enough, research efforts have intensified over those years, and we are learning important things about what it means to live with PCOS over a lifetime. The most important thing we've learned is that there are serious but preventable health problems that come along with PCOS. By learning as much as you can about how PCOS works, you can take steps to stay healthy.

How PCOS got its name: Initially, Polycystic Ovary Syndrome was named when it was recognized in its most severe form. It was originally called Stein-Levinthal Syndrome after the investigators who first described it. Women with Stein-Levinthal Syndrome had very dense male-pattern hair growth and some had hair loss over the scalp. They also experienced infertility because they ovulated infrequently -- their ovaries did not produce eggs on a regular monthly basis. In the absence of normal ovulation, their menstrual periods were unpredictable and irregular.

The ovaries seemed to be at the center of the problem. They looked remarkably different when examined during surgery. They were bulky and had tiny cysts around the edge. Ovaries can normally have cysts of different sizes scattered throughout, but the similarity in size and location set "polycystic ovaries" apart. In the absence of a good understanding of what caused Stein-Levinthal Syndrome, it was called Polycystic Ovary Syndrome based on the appearance of the ovaries.

Diagnosis: The hallmarks of PCOS continue to be irregular menses over a sustained period of time and signs of excessive male hormone levels (such as hair growth). "Male hormones" such as testosterone are also called androgens. Androgens are not strictly "male hormones" because women normally make testosterone. (And, for that matter, men normally make estrogen.) But androgens are the dominant sex hormones in men, and estrogens are the dominant sex hormone in women. The high levels of androgens, or an unusual sensitivity to the hormone can result in the male-pattern hair growth, acne and hair loss over the scalp that sometimes occur in women with PCOS. The androgen-related hairs are dark, coarse and usually black. However, women with light or red hair may notice that the hairs are unusually thick, but not black. These coarse hairs are called "terminal" hairs, and may grow over the upper lip, chin, side of cheeks, neck, chest, breasts, abdomen, inner thigh, back and buttocks. Many women have fine light hairs that grow in these areas, but these are probably not androgen-related.

In summary, the criteria for making a diagnosis of PCOS are these:

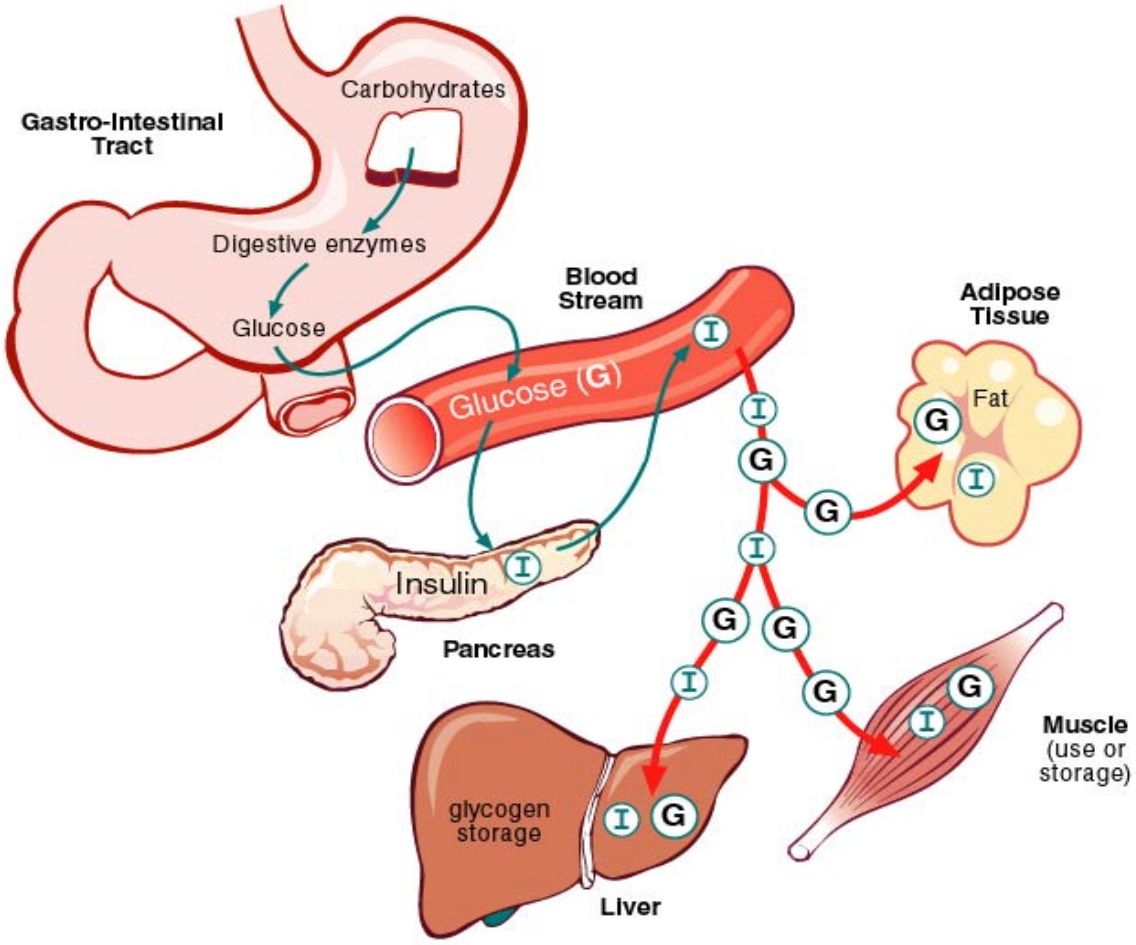
1. A long-standing history of irregular menstrual periods and
2. Signs of excessive androgen exposure

The diagnosis of PCOS can be made purely on the basis of history and clinical observations. However, lab testing can SUPPORT the diagnosis, make sure there is nothing else going on, and evaluate for other metabolic problems associated with PCOS.

More problems? Yes. We now know that PCOS affects more than just the ovary and that is it associated with a higher risk for certain metabolic conditions. What are these other metabolic conditions? One major condition is called insulin resistance. I'll explain what this is below.

Insulin Resistance: Insulin is the protein hormone that is secreted from the pancreas into the bloodstream in response to rising blood glucose (sugar) levels, such as occurs after eating a meal. Insulin is responsible for ensuring that the glucose gets to where it needs to be in the body. Glucose needs to be inside cells where it can be made into energy, stored as a readily available fuel source or stored as fat.

So, let's say you just ate a piece of toast (see the diagram on the next page). The toast is primarily carbohydrate. Carbohydrates are broken down into sugars in the intestine and absorbed into the bloodstream as sugars. After you eat this toast your blood glucose will gradually rise over the course of about 2 hours. If insulin were not released from the pancreas, blood glucose levels would rise and would simply stay elevated. Body tissues would not get any nutrition from the glucose and no energy could be produced. This would literally mean that your muscles would not be able to move. Nor would you be able to store the excess glucose for later use. It would simply be left circulating in the bloodstream, resulting in the symptoms of diabetes, which I will describe later.


Gastro-Intestinal Tract
Carbohydrates
Digestive enzymes
Glucose
Blood Stream
Glucose (G)
Adipose Tissue
Fat
Insulin
Pancreas
Muscle
(use or storage)
glycogen storage
Liver

So back to the piece of toast. What happens is this: the toast is converted eventually into glucose in the stomach and intestines. The glucose is absorbed into the bloodstream. The rising levels of glucose signal to the pancreas that it should begin producing insulin to take care of this “glucose load.” The glucose and the insulin meet up at the surface of a cell, such as a muscle cell. Insulin attaches itself to a specific part of the cell surface. When it attaches, insulin sends a signal to the inside of the cell telling it to let the glucose cross through from outside the cell, to the inside. Insulin’s job might be similar to a taxi driver, who is dropping off a passenger, beeping its horn to signal the bellman to open the door for the taxi’s passenger to go in. The taxi is insulin that signals the doors to open allowing sugar to get into the cell. Without insulin, glucose cannot get inside the cell. Like we talked about before, it would just circulate in the bloodstream with nowhere to go. So, insulin’s job is to send the message that lets glucose enter the cells.

Using slightly more biological terms, I can describe the process this way. Insulin binds to a protein on the cell surface called an insulin receptor. This insulin receptor extends from the outside to the inside of the cell. Insulin and its receptor fit together like a lock and key. When insulin binds to its receptor on the outside of the cell, the receptor changes shape slightly to accommodate the insulin. This change in shape triggers changes inside the cell, which then trigger other changes, which then trigger other changes, etc. Much of this process is not well understood, but eventually, all these changes finally signal proteins that are in “storage” inside the cell to move to the cell surface. These proteins are called “glucose transporters,” and essentially form channels that the glucose can move through. So, you can see how an event that occurs on the outside of the cell can signal changes in the inside of the cell. In this scenario, insulin does not need to get inside the cell to do its job. It just needs to rest on its receptor and the cell does the rest!

So, that’s the basic lesson of how insulin works. Insulin aids in the everyday metabolism that keeps you moving, going to school, going to work, driving home and taking the kids to soccer. What happens then if you have “insulin resistance”? Insulin gets as far as the cell surface and binds to its insulin receptor normally, but then nothing happens. Only very weak signals may get through to the inside of the cell. No glucose transporters are sent to the cell surface, and glucose is stuck outside the cell. Therefore, even though there is enough insulin, it doesn’t work well. Something inside the cell’s machinery is ineffective and insulin‘s ability to trigger the normal events is blocked. It is inefficient. In this case, the body has two options. It can either leave the glucose outside the cell where it is not doing anything useful or it can respond by producing more insulin. Doing nothing will essentially lead to starvation – glucose is one of the major food options for a cell. Without glucose then, the cell would die. To overcome the resistance to insulin, the body makes more insulin. If a little insulin doesn’t work perhaps more will. So the pancreas begins producing more insulin in an effort to get the glucose in the cells and to maintain the blood glucose levels in the normal range. So, in insulin resistant states, blood glucose levels may be normal but the big clue is that insulin levels are high.

> In the early stages of insulin resistance, blood glucose is normal, but insulin levels are high.

Continuing just a bit further with the biology, if this state of affairs continues, the pancreas may become “exhausted.” This does not happen in everyone with insulin resistance but it does happen to a fair number. After long years of producing excessive but necessary amounts of insulin, the pancreas begins to fail. Although the insulin produced may be elevated, this level will eventually be insufficient to keep blood glucose normal. This is the stage where we start to see blood glucoses rising. They rise only when the pancreas begins to slow down. As you can guess, this is a fairly late phase in the process of insulin resistance. Once this occurs most patients will go on to develop type 2 diabetes. However, if we

can catch this process in its very earliest phases we have a good chance of preventing, or at least greatly delaying, the progression that I describe here. So, the clinical lesson here is that early detection is absolutely critical.

Insulin Resistance and PCOS: How does all of this relate to Polycystic Ovary Syndrome? It turns out that about 80% of women with PCOS have this condition called insulin resistance. It is particularly common among women who are carrying extra weight. If you'd like more numbers, here's another set: 40 % of women with PCOS will have consequences of insulin resistance (impaired glucose tolerance or type 2 diabetes) by the time they are age 40! Those are serious numbers! This is of course in untreated women, not in women who are fortunate enough to learn about their condition early.

So, what is the connection between insulin resistance and irregular periods? And how does the elevated androgen level come into play? In a nutshell, the high insulin levels that occur in insulin resistance tell the ovary to make too much testosterone. It doesn't work this way in all women. It seems that just the ovaries of women with PCOS respond to high insulin levels by making testosterone. At least for some women, the insulin *drives* the ovary to make excessive testosterone. And the high testosterone is a major factor in disrupting the ovary's ability to make an egg. After I describe how we test for insulin resistance, I'll discuss this in more detail.

Testing for Insulin Resistance: So, how do you know if you have insulin resistance? Fortunately, the test that you need, called an oral glucose tolerance test, is pretty simple and can be done in almost any lab. It doesn't require any particularly special tools. The basic procedure is that you come in after an overnight fast and have a fasting glucose level and a fasting insulin level drawn via a blood test. An important part of preparing for the test is to not restrict your dietary carbohydrates for at least three days beforehand. A low-carb diet can skew the results of the glucose tolerance test. After the first blood draw, you will be given a very syrupy solution that contains 75 grams of glucose. Many people find this a bit difficult to drink because it is so sweet. Drinking it cold makes it a little easier. At any rate, you drink it down within 15 minutes and then two hours after you finish the drink, you have your blood drawn for the 2-hr glucose level and a 2-hr insulin level. That's it! In a full-fledged glucose tolerance test you would have labs drawn at 30 minutes, 60 minutes, 120 minutes and 180 minutes. However, I can get all the information I need from just two blood tests. What's important is that both the insulin and the glucose levels are obtained during this test. That's the unusual part. Insulin is not usually drawn during a typical glucose tolerance test but it is a readily available test. Because I recommend a slight variation (like getting only one set of labs after drinking the sugar, and by adding insulin to the test) some lab technicians are confused by the test. It is frequently helpful if you have a good understanding of what needs to be done so that you can coach the lab technician if necessary. It never hurts to be your own advocate!

> If you are having a glucose tolerance test: Don't eat a low-carbohydrate diet during the three days before the glucose tolerance test. For an accurate test, eat a "full carb" diet during those three days.

Interpretation of the glucose tolerance test: In a normal glucose tolerance test, fasting glucose should be less than 100 mg/dl and the 2-hr value should be less than 140 mg/dl. If the fasting glucose is greater than 100 but less than 126 we say that you have impaired fasting glucose. This is a pre-diabetic condition. If your 2-hr glucose value is between 140 and 200 we say that you have impaired glucose tolerance (IGT). This is also a pre-diabetic condition. If your fasting glucose is greater than 126 mg/dl or your 2-hr value is greater than 200 mg./dl, we say that you have type 2 diabetes.

	Fasting glucose	2hr glucose	Fasting insulin*	2 hr insulin*
Normal	< 100 mg/dl	<140 mg/dl	< 10 uIU/ml	<40uIU/ml
Insulin Resistance	<100 mg/dl	<140 mg/dl	>10mg/dl	>40-80 uIU/ml
Impaired Fasting Glucose	>100 mg/dl			
Impaired Glucose Tolerance or "Pre-diabetes"		>140 mg/dl but < 200 mg/dl		
Diabetes	>126 mg/dl	>200 mg/dl		

* these insulin values are guidelines. There is no consensus about cut-points for normal and abnormal insulin levels.

To diagnose insulin resistance, we need to look at the insulin levels. Normal fasting insulin should be less than about 10-15 uIU/ml. The 2-hr insulin should not be greater than 40-80 uIU/ml. The cutoff between what is high and what is normal is a little bit fuzzy but these are good guidelines.

> The modified glucose tolerance test:
>
> Fasting blood work: fasting glucose and insulin level. After the blood is drawn, drink a solution containing 75 grams of glucose
>
> Two hour blood work: At the 2hour mark (120 minutes) draw another glucose and insulin level

Laboratory testing for PCOS: In addition to the glucose tolerance test, there are other lab tests that I commonly get. The diagnosis of PCOS, as I said, requires a long history of irregular menses and evidence of excessive androgen exposure. The other part of the definition is "the exclusion of other disorders that could cause a similar set of symptoms." There aren't many disorders that do this, so the list is pretty short. I generally make sure that a thyroid test has been done and that there is a test to determine the level of a hormone called prolactin. Abnormalities of both thyroid and prolactin can cause irregular menstrual periods. I also might get a lab test called a "17-hydroxyprogesterone". This is to screen for a very rare condition called "late onset congenital adrenal hyperplasia" or CAH. If the screening test is high, further testing is done. I don't always do this because the condition is so rare. Then, if certain other signs are present, like high blood pressure, purplish stretch marks on your abdomen (rather than pale, whitish-pink or brown stretch marks), easy bruising and thin skin, then I might look for another rare condition called Cushing's Syndrome. This is a syndrome caused by the adrenal gland producing too much cortisol, a prednisone-like steroid. This test can also be done fairly simply with either a 24-hour urine collection or an overnight dexamethasone suppression test. It's not super important that you know what these are just now, just what they are called. Finally, I usually draw a testosterone level. This can be normal in women with PCOS and what I am looking for is extremely high values to look for an androgen-secreting tumor. Usually, androgen-producing tumors produce more testosterone than the ovaries of women with PCOS do. So if testosterone values are extremely elevated, I might look for a tumor. The timing of the development of androgen-related symptoms helps tell the difference. With androgen secreting tumors, there is usually a rapid change from having regular menstrual periods and no male pattern hair growth and no acne to the sudden appearance of all of these. As you know, this is not the typical pattern of PCOS, which tends to occur much more slowly.

At this point we've looked for other conditions that can mimic PCOS, and we've done a glucose tolerance test to look for insulin resistance. The final issue is to look for signs of other problems that can develop in people with insulin resistance. In particular, I check a lipid (cholesterol) profile and liver function. Women with PCOS frequently have abnormal cholesterol levels. The laboratory test that is most helpful is a "lipoprotein profile." This measures the total cholesterol level as well as the

components of the total cholesterol. These include high-density lipoprotein (HDL-the good cholesterol), low density lipoprotein (LDL-the bad cholesterol), and trigyclerides. The most common pattern seen in women with PCOS is high triglycerides and low HDL values and sometimes elevated LDL. Although one's triglycerides can be quite elevated, this condition usually responds very well to exercise and diet modifications. The reason I check liver function studies is to look for signs of general liver "inflammation". The specific tests that I find most useful are the SGOT (AST) and the SGPT (ALT). If these are elevated they may point to a diagnosis of "fatty liver". Like high triglycerides/low HDL, fatty liver is a common companion to insulin resistance and responds well to small changes in diet and exercise.

To summarize, the purpose of lab testing is two-fold:

1) to make sure that we aren't missing any other underlying conditions that might be mimicking PCOS
2) to determine if you have insulin resistance, high triglycerides, or fatty liver.

<u>The reproductive system in PCOS:</u> Now that we've reviewed some of the metabolic problems that may be associated with PCOS, let's turn to the reproductive system. We said that PCOS is diagnosed on the basis of a lack of ovulation ("anovulation") resulting in irregular menses, and male pattern hair growth (hirsutism). (Note that the "definition" doesn't say anything about insulin resistance. That's because we've only investigated the insulin resistance connection recently.) What is behind the irregular periods? And how is this related to the hirsutism?

The menstrual periods are irregular because ovulation, or the production of an egg, does not occur on a monthly schedule. In regularly ovulating women, the usual pattern of events occurs because the brain and the ovary are communicating with each other in a carefully orchestrated way. The hypothalamus, a part of the brain, produces a hormone called GnRH, and secretes it in little pulses. This hormone stays in the brain and cannot be measured in the bloodstream. These little pulses of GnRH signal the pituitary, a gland located near the hypothalamus in the brain, to send out hormones called FSH and LH. Again, these hormones are also sent out in little pulses. They travel via the bloodstream to the ovary, where they stimulate the maturation of an egg. After about 2 weeks of these carefully patterned pulses (kind of like Morse code), the mature egg is released from the ovary at mid-cycle. It then travels through the fallopian tube where it is may be fertilized by sperm. After ovulation (release of the mature egg), the system is maintained in a state of readiness for fertilization by a structure in the ovary called the corpus luteum. This structure develops from the cells left behind when a mature follicle extrudes its egg and is only present if ovulation has occurred. The corpus luteum makes progesterone, which is the hormone that keeps the lining of the uterus ready to support a pregnancy. The corpus luteum lasts about two weeks. Then it stops making progesterone, and progesterone levels fall quickly. This drop is what triggers menstruation. The uterine lining is no longer supported by progesterone, so it is shed, completing a normal, ovulatory cycle. When menstruation begins, the whole cycle starts again with the maturation of another egg.

In women with PCOS that Morse code-like communication does not happen in the usual way and the ovary does not get the right signals in the right pattern to create a mature follicle (a follicle is the egg plus the surrounding supporting cells). Why this fails to occur is still a mystery. Some people think that the pattern is scrambled while still in the womb and others feel that there is a genetic or hereditary basis for this. At any rate, we don't think that there is anything that you or your mother did to make this happen and we don't know of any precautions that can prevent it from happening (in case you are thinking about your own children). The net result is "anovulation" which means that ovulation does not occur. Without the production of an egg, of course, pregnancy cannot occur and infertility results.

Of course, women with PCOS do get pregnant. A better (and more hopeful!) description might be "subfertlity" instead of "infertility" because ovulation does occur – just not in a predictable pattern and

sometimes not very frequently. Since women with PCOS tend to have an easier time getting pregnant in their twenties, I'm guessing that ovulation happens more frequently early in life and decreases in frequency as women mature. It seems hardest for women with PCOS to get pregnant in their thirties and forties.

If we measured hormone levels in regularly cycling women and women with PCOS, what would we find? First, let's consider women who ovulate every month. The two major hormones are estradiol (an estrogen) and progesterone. Estradiol is produced by cells in the follicle, a structure that contains the egg. Progesterone is made by the cells that are left after ovulation, the corpus luteum. Estradiol kevels tend to be highest in the first two weeks of the cycle and lower in the second half. (Remember, during the first two weeks the egg is maturing within the follicle, and about two weeks after the first day of the last menstrual period the egg is released). On the other hand, as you would guess, progesterone levels are lower in the first two weeks of the cycle and highest in the final two weeks, when the corpus luteum is working. The progesterone levels remain high for two weeks post-ovulation and then they fall as the corpus luteum "retires". With the fall in hormone levels, the lining of the uterus is no longer supported and is shed, resulting in menstruation. The cycle that I am describing starts all over again with the first day of your menstrual cycle. Another hormone called testosterone is also made by the ovary. Women normally have a small amount of this hormone throughout the cycle and there is not much variation.

The process is different for women with PCOS. Since ovulation usually does not occur, hormonal levels (such as estradiol and testosterone) are actually quite stable. The levels may also be unusually high for these hormones. And if ovulation does not occur, progesterone levels remain low. In fact, one way to check for ovulation is to measure the progesterone level during the third week of the cycle. If ovulation has occurred, the progesterone level should be high.

The constantly high level of estradiol poses a problem. If the lining of the uterus – the endometrium - is exposed to estrogen without the shedding effect of progesterone, it will continue to grow. Eventually, abnormal cells may develop, which can lead to cancer. This is the main reason that it is important for women with PCOS to take medicines to induce a period if one doesn't occur by itself. If the lining is shed regularly, at least every three months, abnormal cells are much less likely to develop. One strategy to start a period is to take a progestin (such as Prometrium or Provera) for 10-14 days. Within 5 days of the last dose, a period should start. Another alternative is to take oral contraceptives (birth control pills).

In women who ovulate normally, a period usually signals that ovulation has occurred. But, in women with PCOS, does having a period mean that ovulation has occurred? The answer is not always. Sometimes a period occurs because the endometrial lining builds up to a point where it just breaks off. Other times, it may happen because for some reason there is a temporary drop in estradiol levels. If you want to know for sure whether a period means that ovulation occurred, you can wait 21-23 days after your last cycle and have a progesterone level drawn. If it is low, ovulation did not occur. If it is elevated, ovulation did occur. To summarize, women with PCOS can have menstrual bleeding for a variety of reasons. It may be because of ovulation, a minor change in estrogen levels, or it may simply indicate that the uterine lining has built up so much that it is simply breaking off.

A menstrual period can occur because:

- ovulation has occurred
- estradiol levels dropped temporarily
- "breakthrough" bleeding has occurred

Now we come to the question of why the hormonal levels are what they are. Progesterone is low because ovulation does not occur. Estrogen levels remain in the high range again because ovulation

does not occur and the brain is still sending out signals, though somewhat disordered, to stimulate the ovary. The ovary is just unable to interpret the signal because it comes in the wrong "Morse code". What about testosterone? This is a little more complicated. And, we don't have it all very well worked out. But I will tell you what we know.

Normal ovaries produce some testosterone. However, in women with PCOS the testosterone-producing cells are abnormal. For some reason, if they are exposed to high levels of insulin, they respond by making testosterone. Conversely, the ovaries of normally cycling women do not do this. An interesting lab experiment showed this very clearly. Cells from a normally cycling ovary were placed in one dish, and cells from the ovary of a woman with PCOS were placed in another dish. They were both incubated with insulin and, after a while, testosterone production in each dish was assessed. As expected, normally cycling ovaries did not make much testosterone in response to insulin. In contrast, PCOS ovaries made lots of testosterone. Insulin drives testosterone production in PCOS ovaries, but not in normal ovaries. This is the connection between the insulin resistance and the elevated testosterone levels. That is, insulin resistance results in high insulin levels. The insulin in turn has the unusual effect of making the ovary produce excessive amounts of testosterone. The testosterone interferes with normal ovulation. This is at least one way in which we think hirsutism (hair growth) and irregular menstrual periods, the hallmarks of PCOS, are connected to insulin resistance. This can't be the whole explanation since not every woman with PCOS has insulin resistance, but it may explain some part of the problem in some patients.

Treatment: Treatment begins with a candid discussion of lifestyle. What is your diet like? Where are the rough spots? What sorts of physical activity do you get in the course of the day? What is your stress level and how do you manage stress? Stress is important because it can raise blood glucose levels in people with insulin resistance. After thinking hard about the factors in your lifestyle that contribute to insulin resistance, we start thinking about what realistically can be changed to help your metabolism. This is of course not easy, but it is critical.

When you think about the lifestyle that most of us live, or at least are encouraged by our surroundings to live, it is clear that it is not ideal for someone with insulin resistance, or the dysmetabolic syndrome. We depend on cars for almost every task. We may live in the suburbs and drive to work and to shop. In many communities, it is not easy to walk or ride bikes. Our work lives are often very demanding, with what seems like a lot less "down time" than we might need. So, many people pack their days with too many things to do and don't have enough time to plan out healthy and satisfying meals, or to shop for food to make those meals. We rely on prepared foods that tend to be high in fat, salt and sugar. And when we do have down time how do we fill it? We may "veg-out" in front of the TV. But is that really relaxing? Physically you may be doing nothing but your mind is being stimulated and in some cases "stressed" by the story on TV. We may even find our sleep disrupted if that is the only time left to wrestle with the problems of the day! So, the 21st century doesn't present the best living environment for people with the insulin resistance. In fact, if you think about life in the 19th century, with fewer cars or other machines to help with physical labor, and with no fast food chains-maybe that would have been a better environment in some ways!

So, spend some time thinking about your environment and how you live your life. Think "outside of the box." Don't think about what other people are doing as a measure of what you should be doing. Instead, fantasize about the kind of life that might be healthiest for you. Imagining it is the first step toward making it real.

Some practical suggestions that some of my patients have found helpful are as follows:

- Wear a pedometer. This is a device that measures the number of steps you take in a day. Try to get at least 10,000 steps per day and increase this periodically to meet your goal.

•Find alternatives to eating out. Many of us buy our lunch at a cafeteria at work or go out for fast food. Instead, try packing your lunch, or taking frozen meals.

•Switch from regular soda or sweet tea to unsweetened drinks. Better yet, switch to water.

•Eat regular meals. Skipping meals only makes you grumpy and apt to eat more at the next meal.

Medical Therapy: The most critical part of any therapy is lifestyle. That is the first part of any therapy. The next step in designing a plan for you is to decide whether medication is right for you. Therapy will depend on whether or not you are trying to become pregnant.

For those who are trying to become pregnant: Many women with PCOS do not have trouble conceiving. But for those who do, you will need to enlist the help of an Obstetrician/Gynecologist -either a generalist or a Reproductive Endocrinologist. They will do a thorough evaluation to determine why you are not getting pregnant. If it all comes down to Polycystic Ovary Syndrome, the first step is usually diet and exercise. Both of these improve insulin sensitivity, lower insulin levels, result in lower androgen (testosterone) levels and enhance ovulation. Chances are that most of you have already considered this. First line medical therapy may be a medicine called Clomid, which can be given in increasing doses. This medicine makes your pituitary gland produce more of the egg-maturing hormone FSH. The result of successful therapy is the production of one or more mature eggs. This therapy can frequently result in conceiving twins because it is difficult to control exactly how many eggs become mature. The next line of therapy would be injections. These injections contain pituitary hormones, such as synthetic FSH, in doses higher than your own pituitary can make. They work to stimulate the ovary with very high levels of these stimulating hormones and “force” it to make mature eggs. As you might guess, with this therapy, like Clomid therapy, multiple eggs can mature and twinning can result.

There are some other strategies that reproductive endocrinologists use that are beyond the scope of this article and I urge you to discuss them with a specialist if you are trying to conceive.

Where a medical endocrinologist may come in is with the use of insulin sensitizing drugs. These are drugs that are usually used to treat diabetes. Diabetes is considered to be the end result of long-standing insulin resistance. These drugs act by improving the body’s sensitivity to insulin allowing it to use glucose more efficiently. With improvement in insulin resistance comes a reduction in the amount of insulin needed to maintain normal sugars. With lower insulin levels comes decreased stimulation of the ovary to make testosterone. The fall in testosterone levels enhances the body’s natural ability to ovulate, or make a good egg. The ideal outcome here would be the production of a single egg, thus avoiding the potential problem of multiple gestation (twins, triplets, etc).

The insulin sensitizing drugs are not FDA approved for this purpose and we have only a little experience with these drugs. For instance, not everyone with PCOS responds to them drugs but we think that those with significant insulin resistance have the best chance of responding. There are two types of drugs. The first is the drug metformin, known by the trade name of Glucophage. The second class of drugs is called the thiazolidinediones, abbreviated TZD’s. The two drugs in this class currently available are rosiglitazone known by the trade name Avandia, and pioglitiazone known by the trade name Actos. Since Metformin is an older drug and has been used for many years, it tends to be the first line drug in this type of treatment. We know that it is safe in patients with normal kidney and liver function. We have less experience with the TZD’s as they have only been available for a few years. Earlier versions of these drugs caused major liver problems in a very small number of people. This earlier version (troglitazone, or Rezulin) was pulled off the market. The newer drugs, Avandia and Actos, are probably much safer, but we still use them cautiously in individuals who do not have diabetes. We are less certain about the risk-benefit ratio but sometimes it is worth the chance if you’re having difficulty with infertility. This is something that needs to be discussed candidly between you and

the prescribing provider. It is also important to have liver tests done at least every two months while taking these medicines. Future recommendations may change as more research accumulates in this area.

For those not wishing to get pregnant right away, the options for medical therapy are broader. The therapies are aimed at the different problems that can occur with PCOS. The problems are these: 1) hair growth, hair loss and acne, 2) the need for regular shedding of the uterine lining (menstruation), and 3) insulin resistance. I will discuss each one separately.

Hair growth (hirsutism): Hirsutism or excessive male-pattern hair growth is usually caused by excessive amounts of the male hormone testosterone. It is also influenced by your skin's sensitivity to testosterone. Some women with PCOS have normal testosterone levels but significant hair growth. This is because their hair follicles are particularly sensitive to testosterone. The first strategy to reduce hair growth is to reduce testosterone secretion. This is best accomplished with oral contraceptives. The Pill works by "resting" the ovary, resulting in decreased hormone production. Testosterone levels fall dramatically when oral contraceptives are used. There is no one oral contraceptive that is particularly better than others. These days, most of them work very well. By decreasing testosterone the rate of hair growth slows down and the hairs become finer. It does not stop hair growth completely, but it can significantly slow it down. It can also help control acne.

The next therapy that is frequently used is spironolactone, known by the trade name Aldactone. This is normally used as a diuretic, or water pill. However, it has another effect that we can make use of. It works at the hair follicle to prevent testosterone action. It is an "androgen blocker". Again, many women notice a decrease in the rate of hair growth and a decrease in the coarseness of their hair with Spironolactone. Many people also notice an improvement in their acne.

There is a new topical agent on the market called Vaniqa cream. Like the others, it slows hair growth but does not stop it entirely. It is used twice a day and needs to be left on for at least four hours each time. Most people don't have side effects but when they do it is usually a rash from the cream. The manufacturer recommends that you continue with your usual treatments (electrolysis, laser, shaving, etc.) while using this product.

Some people have tried using another medication called finasteride that goes by the trade name Proscar, or Propecia. This is an interesting medicine that is usually used to decrease the size of the prostate. When used in men it works in the prostate to prevent the conversion of testosterone to a more powerful form of testosterone called di-hydro-testosterone (DHT). DHT is made from testosterone by an enzyme called 5-alpha reductase. This enzyme is present in the prostate and the hair follicle. That means that the hair follicle can take testosterone and convert it to a more potent version of testosterone which then really stimulates hair growth. Proscar and Propecia essentially inhibit that process so that the more powerful testosterone is not made. It turns out that this works very well on the prostate but not so well on the hair follicle. Some women use it to slow hair growth, but I would suggest that it be used on a trial basis and only continued if it is helpful.

All of these therapies are ones that you absolutely should not take if you are pregnant or trying to become pregnant. They can cause abnormal development of the fetus.

All of these therapies slow hair growth and decrease the coarseness of hair. They do not work right away, unfortunately. They take several months to have a noticeable effect because hair growth is so slow. The only way to permanently remove hair is by using electrolysis or laser therapy. Electrolysis is a process in which a small needle is placed in the hair follicle (this part doesn't hurt) and a small electric current is passed into the needle, heating it up (this may hurt). The purpose of this is to destroy the hair follicle. Actually, it usually takes several treatments for the hair follicle to die completely so you will notice the hair growing back initially. However, with repeated treatments, the hairs will become finer and finer until eventually growth stops. Electrolysis itself can be a long and tedious process if you have

a large area that you would like treated. Laser therapy may be better for this as it can cover a larger area. However, this therapy too requires many treatments. In addition, the current lasers work best in women who have light skin and dark hair. The contrast is important for the laser to work. Therefore, it may not work well in women with dark skin and dark hair. This may change as new laser technology designed for dark skinned individuals becomes available.

Insulin resistance: If laboratory testing shows that you have insulin resistance or impaired glucose tolerance or diabetes, one of the insulin sensitizing drugs may be helpful for you. I'll start by saying that absolutely the most important therapy is physical activity and a healthy diet. None of the medications work very well without this. Lifestyle therapies are probably the most powerful therapies we have, even more powerful perhaps than the medications. It is also important to point out that neither metformin nor the TZD's are FDA approved for the treatment of insulin resistance. They are approved for use in patients with Type 2 Diabetes. These drugs may help to prevent or at least delay the onset of Type 2 diabetes in susceptible individuals. By reducing insulin resistance and therefore reducing testosterone levels these drugs may also be beneficial in reducing hair growth and promoting ovulation. However, the other medications I mentioned above, specifically oral contraceptives and Spironolactone and Vaniqa, are the most powerful agents we have for reducing hair growth and we are not certain that adding the insulin sensitizers will provide additional benefit in terms of hair growth.

Having said that, my usual approach is to test for insulin resistance before prescribing an insulin sensitizer. In women who have significant insulin resistance and who wish to try after understanding the rationale for using it, I frequently do prescribe it. Some women report that they have fewer carbohydrate cravings while taking metformin. They notice a decrease in appetite and begin to lose weight. Some people also notice that their menstrual periods become more regular and this can be useful in people who choose not to take or can't tolerate oral contraceptives. In this way metformin can be a way of regulating menses. Not all people respond to metformin so if you try it, it is important to plan a follow-up visit to discuss whether the medication is working. Usually that means further glucose tolerance testing. Although I usually prescribe metformin for the insulin resistance problems associated with PCOS, I occasionally use the TZD's in someone who is severely insulin resistant and cannot tolerate metformin.

About the medications: Metformin works by decreasing the amount of sugar produced by the liver and by enhancing the body's sensitivity to insulin. Its side effects are usually temporary gas, bloating and diarrhea. These symptoms usually resolve in two weeks but occasionally they do not. For this reason we usually start the medication very slowly with one pill a day, gradually increasing to the full dose as tolerated.

Metformin is generally safe and well tolerated. However, some people should not use it. These include people who have reduced kidney function or poor liver function. "Fatty liver" is usually not a reason to avoid metformin. Most young, healthy individuals can safely take metformin. In addition, we recommend that the medication be stopped if you become dehydrated. This may occur during a serious illness where you are not drinking much or you have nausea and vomiting. This might also occur during a hospitalization during which you are ill. Because intravenous contrast dye can cause mild dehydration in the kidneys, we recommend that you stop the metformin for 48 hours if you are having an x-ray study that requires intravenous contrast (oral contrast is okay).

Again the TZD's are generally safe. The package insert recommends that people taking the TZD's have liver function studies (a blood test) done every two months for the first year of use. After that, liver tests should be done periodically. This is because in rare instances serious liver damage has occurred with this class of drugs. Other side effects may include water retention with swelling and weight gain.

This has been a brief tour of one provider's approach to Polycystic Ovary Syndrome. Other providers may have different approaches and recommendations will differ based on your individual needs. Also, this is an active area of investigation so therapies and ideas about what causes PCOS are likely to

evolve over time. Therefore it is in your best interest to stay tuned and read a lot. There is a lot of information available about Polycystic Ovary Syndrome. As with every other condition, there is also a lot of misinformation out there. Discuss what you have read with your provider. Between the two of you, you should be able to sort out the good information from the not so good information. Consider joining a support group as a way of keeping up-to-date on current medical advances and sharing ideas about what works and doesn't work with other women who have the same condition. If you have family members that have symptoms similar to yours, consider suggesting that they undergo some metabolic testing especially to look for insulin resistance. If you have daughters, realize that they may develop this syndrome too because it is hereditary. Early therapy is the best therapy and early use of oral contraceptives can prevent a lot of the hair growth and acne that can have such a negative effect on self-image, especially for adolescents.

Here are some other references you might want to look at:

Living with PCOS by Angela Best-Boss
A Woman's Guide to Dealing with Polycystic Ovary Syndrome, by Collette Harris
PCOS: The Hidden Epidemic, by Sam Thatcher MD

http://www.pcosupport.org

http://ncpco.org