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POLYCYSTIC OVARY SYNDROME

Polycystic ovary (or PCO) syndrome is often a loosely used term that describes a symptom complex characterised by irregular menstrual periods, mild androgen excess (or too much of the male-like hormones) and or the presence of a number of small cysts (or follicles) within the ovary.

It is important to recognise that not all women with a diagnosis of "PCO" will have all of the symptoms or problems. In fact the term 'polycystic ovaries' by its strictest definition describes only the ovaries as seen on an ultrasound scan. Many women have ovaries that are polycystic, but may never have any of the other symptoms or hormone findings of the PCO Syndrome. Overall, around 20% of women can have ovaries with this appearance. What is uncertain is whether this is one end of a long scale that includes the full polycystic ovary syndrome or a sign that some or all of the problems of PCO are more likely to develop in the future.

Menstrual Disturbance ie Irregular Periods

About 75% of those with the PCO disorder have infrequent, irregular or absent periods. Often the periods are particularly heavy when they do arrive. This menstrual disturbance is usually a sign that there is a problem with ovulation. This is very common in the teenage years even without any PCO disorder. If a teenager uses the contraceptive pill to control irregular or heavy periods then the diagnosis of PCO syndrome many not be made until the pill is stopped and it is noted that periods cease or become irregular and some of the other problems emerge.

Mild Androgen Excess

Androgens are a group of hormones found at high levels in men but present also in women at much

lower levels. Women with PCO syndrome often have higher than normal female levels of androgens. This is most often manifest as excess hairiness, but some women find acne or even male-pattern hair loss a particular problem.

Infertility

Given that the period disruption with PCO syndrome is due to irregular or absent ovulation it is not surprising that it is a common cause of infertility. It is not usually 100% absolute, and many women with PCO ovulate normally, albeit less frequently. This may result only in a delay in conception. Others do not ovulate at all and assistance to conception is required.

Obesity

Some 40% of women with PCO syndrome are overweight. In fact obesity itself will trigger the problems for some women who would not have otherwise suffered had they remained of normal weight. This interesting observation has led to speculation that such women are programmed to ovulate and conceive only in times of famine when the remainder of the female population would cease ovulating and reproducing. Unfortunately "famine" is rare in our modern world and the hormone changes associated with PCO make weight loss more difficult.

How is it Diagnosed?

PCO syndrome is a clinical diagnosis. That means it is the sum of a variety of problems and changes evaluated by a doctor and confirmed by a variety of tests. To visualise the ovaries it is frequent practice to perform a vaginal ultrasound scan. For this purpose a slender probe is placed just inside the vagina, giving the best views of the ovaries and pelvic organs. With PCO, the ovaries



are found to have multiple, small cysts around the edge of the ovary. These cysts are only a few millimetres in size and never in themselves a cause of pain. In fact they are partially developed follicles in which the microscopic eggs are prepared but not released.

Blood tests of hormones are also frequently done. One of the more important ones is a comparison of the two major pituitary hormones that regulate the menstrual cycle namely Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). Measurements of androgens such as testosterone and the carrier protein for testosterone may be required. Sometimes a progesterone blood test 7 days before a menstrual period can determine whether ovulation has occurred in that month.

Diabetes, Insulin and PCO

In recent years it has become clear that PCO syndrome is closely related to a problem with insulin. Insulin is a hormone released from the pancreas after a meal and it allows the organs of the body to take up energy in the form of glucose. In PCO syndrome there is a 'resistance' of cells in the body to insulin, so the pancreas makes more insulin to try and compensate. The excessively high levels of insulin have an effect on the ovary, preventing ovulation and causing a rise in androgen levels.

One study found that 30% of slim women with PCO syndrome have insulin resistance, but it affects as many as 75% of those who are overweight. This explains why overweight women with PCO are more likely to suffer with excessive hairiness and infertility.

Longer-term Problems

The long-term problems with the PCO syndrome are related to insulin resistance, repeated absence of ovulation and the mild excess in androgens. High levels of insulin are associated with an increased risk of developing diabetes. This is of the type that requires strict diet control or possibly tablet medication. Up to 35% of overweight women with PCO show signs of diabetes by their 30's and becomes even more common in the 40's and beyond.

The other hormone changes increase the chance of developing high blood pressure and high cholesterol levels, both of which can lead to a greater risk of heart disease.

Irregular or infrequent periods over a long period of time lead to an increased risk of cancer of the lining of the uterus (endometrial cancer). This is, in part, due to higher and sustained levels of the hormone oestrogen, which over-stimulates the lining of the uterus. Absence of ovulation, and the resulting progesterone deficiency, also contributes to this risk.

Control of Irregular Periods

Irregular and heavy periods can occur due to problems with ovulation. Whilst it would seem that restarting ovulation would be the best treatment, this is generally reserved for when a pregnancy is desired. This is because the drugs required have potential side effects that makes their long-term use inappropriate.

Excess weight is a cause of menstrual problems in both women with and without PCO syndrome. This is because androgens are converted to oestrogens in fat tissues. This in turn interferes with ovulation and leads to over-stimulation of the lining of the uterus and heavier periods. Weight reduction will improve cycle control and reduce the heaviness of menstrual flow.

Periods may be controlled by the use of the contraceptive pill, which is most suitable for women under the age of 35 who also require a good form of contraception. The other type of drug used is a progesterone-like hormone. Progesterone is an important hormone released only in the second half of the menstrual cycle after normal ovulation. It regulates both the length of the cycle and the shedding of the lining of the uterus during menstruation. Progestagens are taken as tablets in a cyclical way, for example between days 12-26, the exact type and timing depending upon a woman's individual cycle problem.

Some women have no periods at all, and either the contraceptive pill or cyclical progestagens are advisable to avoid the risk of endometrial cancer. Around 6 periods per year is adequate to protect against this.

Infertility Treatments

Polycystic ovary syndrome is found in around 70% of women who have ovulation difficulties leading to infertility. This is more common in women who are overweight and weight reduction alone has consistently been shown to be as effective as drugs in restarting spontaneous

ovulation. The amount that needs to be lost is less than most women might expect - around 5% of their current weight is associated with an increased number of ovulatory cycles.

Clomiphene

Clomiphene citrate is the most commonly used drug to stimulate ovulation. It is taken in the early days of the cycle (usually days 4-8) and results in ovulation in around 80% of women overall, and a 6 month successful pregnancy rate of 45-50%.

Ovarian stimulation

When clomiphene is unsuccessful, there are two main approaches. The first is to use injectable hormones to stimulate the ovary to produce eggs. This is known as ovarian stimulation and, where there is an additional sperm problem, is combined with insemination of sperms through the cervix around the time of ovulation (intrauterine insemination, or IUI). The hormone treatment must be monitored by blood tests and ultrasound scans to avoid over-stimulation.

Multiple pregnancy is always a risk with this type of treatment, but especially so for women with PCO because their ovaries are particularly sensitive to stimulation.

If ovarian stimulation is unsuccessful, many women resort to in vitro fertilisation (IVF), the success rates of which depend very much upon individual circumstances. The most important of these is the age of the female partner.

Laparoscopic Ovarian Diathermy

The alternative to ovarian stimulation is an operation called laparoscopic ovarian diathermy (LOD), also known as 'ovarian drilling'. This is a day case operation, a short general anaesthetic, and a "telescopic" look into the abdomen. The ovaries are identified and several small holes made in each ovary, either with a fine hot diathermy probe or with laser. It is not actually known how this works, but it can restore regular ovulation, or make the ovary more sensitive to clomiphene.

Advantages of LOD include the fact that it may improve other symptoms of PCO syndrome, such as menstrual disturbance, as well as avoiding the

need for stimulatory drugs and their increased risk of over-stimulation and multiple pregnancy.

Weight Loss

This is a very difficult area for women who are constantly told by their care providers that they must lose weight. The very disease that is worsened by the excess weight conspires against them in this quest, making weight loss more difficult than usual. There is no simple answer and the key is a combination of strict calorie reduction combined with aerobic exercise as part of a supervised programme.

Weight loss will regulate periods, lead to more ovulatory cycles, reduce hairiness, reduce the risk of heart disease and lower insulin levels. A dietician is often useful to discuss the optimum diet, which is particularly important considering the tendency toward high cholesterol and unhealthy blood lipids that comes with PCO syndrome. Getting weight into the normal range and maintaining is a lifelong process, rather than a short-term fix. It will help to ensure that you maintain the weight you lose and the healthy lifestyle that helped you achieve it.

Hirsutism (hairiness)

This is usually due to above average levels of androgens, the male hormones that are normally present in women at low levels. Some women do not find the excess hair a problem, particularly if it does not affect their face, or if it is pale in colour. Sometimes excess hairiness is not abnormal and is a racial or genetic variation.

Initial treatments include bleaching and electrolysis. If these do not produce an acceptable result then drugs may be used to reduce the high androgen levels, if that is the cause.

The contraceptive pill contains oestrogen, which reduces androgen levels and will improve hirsutism. A particular formulation, known as Diane, is available that includes a specific drug that reduces androgen levels. This drug is called cyproterone acetate, and it can be given in a larger dose than is present in Diane to produce a greater effect.

Spironolactone is another drug alternative, but because it often results in erratic periods. It is usually given with a low dose contraceptive pill.

Side effects of the anti-androgens include tiredness, mood changes and reduced sex drive. Higher dose cyproterone acetate has a rare but serious side effect of causing problems with liver function, and so regular blood tests may be required.

All hirsutism treatments must be continued for 8-18 months before a response can be expected, due to the slow rate of hair growth. At that time, electrolysis can be performed to remove the unwanted hairs already present. Thereafter less return growth can be expected.

Long-term Monitoring

Given the longer term risks that have been identified, particularly in women who are overweight, such as high blood pressure, high cholesterol, the increased risks of diabetes, heart disease and cancer of the lining of the uterus, it is important that a doctor keeps an eye on these and provides appropriate counselling to reduce the risks as much as possible. Extra risks arise in smokers. The avoidance of excess fatty foods and weight control is important. Blood tests for cholesterol levels and diabetes should be considered, perhaps every one or two years from age 35 and even earlier if there is a family history.

Insulin-sensitising Drugs - Metformin

Because PCO is often associated with resistance to insulin, the body produces excessively high levels in an attempt to compensate. This higher level of insulin is known to cause abnormal cholesterol and lipid levels, obesity, irregular periods, higher levels of androgens, infertility due to disturbance of ovulation and an increased likelihood of diabetes.

Metformin is a type of drug known as an "insulin-sensitising agent", which lowers the blood sugar

level and, in turn, reduces the requirement for excessively high insulin levels.

There are actually very few studies that have been carried out and published concerning the use of insulin sensitising drugs as a treatment for PCO syndrome. These suggest that it may well be useful in several areas:

weight reduction, improving irregular periods (70%), normalising blood cholesterol and leading to ovulation.

One study looking at ovulation in particular found that compared to no treatment, 34% of women ovulated taking metformin (compared to 4% who did not receive it) and, when this was combined with clomiphene it was as high as 90% (as compared to 8% in those who only received clomiphene). These studies involved only overweight women with PCO - its role in treating women of normal weight has not been investigated.

The most common side effects during treatment were diarrhoea, nausea, vomiting and abdominal bloating. The long-term effects are not known - the longest follow up so far is for around 6 months of use.

Because of the lack of research using these drugs, many doctors are awaiting further studies to confirm their initial apparent success and to identify potential side effects before jumping in and prescribing them.

This is a safe and sensible approach. There may be specific cases when their use is considered appropriate, and this is something for an individual doctor to decide with the patient's full understanding of the present situation.