InfoSheet : POLYCYSTIC OVARIAN SYNDROME

INTRODUCTION

Normal Physiology

All women have two ovaries which are located in the pelvis alongside the uterus. At birth the ovaries are provided with thousands of eggs. So the ovaries are like "banks" of eggs – unlike the testes in men, which manufacture sperm continuously from puberty on. At puberty the ovaries contain about 150 -300,000 eggs. Each month, under direction from the pituitary gland in the brain (which releases a hormone called Follicle Stimulating Hormone or FSH which stimulates the ovaries), a number (or "cohort") of these eggs are "recruited" to develop. Until this time the eggs had remained dormant in the ovary, but now they start to grow, each one in a little blister of fluid called a follicle, (follicles are also sometimes called cysts, in that a "cyst" is a structure containing fluid, and hence a follicle is a type of cyst). Hundreds of eggs respond to the call, but most of them die (or become "atretic") within a couple of days. As you can see, hundreds of eggs from the "bank" are wasted every month.

By some process that we don't really understand, one follicle (very occasionally two) becomes "dominant" and continue to grow and mature, reaching a size of about 20 mm (or 2 cm). During its growth the cells which line the follicle release a hormone called estrogen. Estrogen is the dominant female hormone and is responsible for many functions, including sexual characteristics like breast development, vaginal lubrication and, importantly, for stimulating the lining of the uterus (the "endometrium") to grow and prepare for a possible pregnancy. As the dominant follicle grows the estrogen levels in the bloodstream increase. This process of follicle growth is called "folliculogenesis".

The brain recognizes when the follicle is mature and sends another message to the ovary and follicle by way of a hormone called luteinizing hormone (or "LH"), which triggers the final maturation of the egg and then makes the follicle rupture and release the egg..

Hopefully the egg is "picked" up by the fallopian tube and it travels down the fallopian tube to the site of fertilization in a region called the ampulla. If at this time sperm were to enter the uterus, they would travel up the fallopian tube, and if a sperm fertilizes the egg an embryo would be formed. The embryo then has to travel down the tube until it reaches the uterus where it would implant in the lining of the uterus – the endometrium- and grow into a pregnancy.

After the follicle has ruptured and released the egg a new type of cyst forms – the corpus luteum. The corpus luteum has the important function of manufacturing yet another hormone called progesterone, which acts on the endometrium and nourishes it. This is how the early embryo is nourished while it is growing in the endometrium. The corpus luteum has a life span of only 14 days, after which – if no pregnancy occurs – it dies and disappears. When the corpus luteum dies it obviously stops producing progesterone, so the support for the endometrium is withdrawn, and the endometrium then dies and is shed. This is menstruation.

With menstruation hormone levels fall the brain realizes this and, once again, responds by releasing FSH to recruit the next cohort of dormant eggs. And so the whole cycle is repeated.

Obviously this is a very simplified explanation of things. It is also important to know that the ovary makes another type of hormone, which is called an androgen. Although this is a male hormone, it is produced in small quantities by the ovarian tissue in which the eggs lie waiting. Normal ovarian function relies on a perfect balance between these three hormone groups – estrogen, progesterone and androgen.

POLYCYSTIC OVARIAN SYNDROME (PCOS)

PCOS is a common condition and around one-in-five women have polycystic ovaries as defined by ultrasound. About 5–10% of women will have symptoms of this syndrome which may include menstrual irregularities, acne, excessive hair growth and infertility. It is actually a poorly understood condition – but a

VICTORIA FERTILITY CENTRE – Dr STEPHEN HUDSON, OB/GYN
#207–4400 Chatterton Way Victoria, BC V8X 5J2
info@victoriafertility.com www.victoriafertility.com
☎ (250) 704-0024 (250) 704-0034

simplified explanation of what may happen follows below.

At the start of a cycle many eggs respond to the messages being sent from the brain (i.e. FSH). Whereas normally a number of follicles would start developing but most die, leaving only one to grow to maturity, in PCOS many follicles continue to grow but do not develop to full maturity. After growing to an intermediate stage of development they stop: but they do produce estrogen, and the rising estrogen levels make the brain think that a follicle is ready to release. But there is no mature follicle ready to release an egg. The reason the estrogen levels are high is because there are many follicles making estrogen, and hence the brain "thinks" that a follicle is ready. The brain therefore causes the release of LH – but, because there is no mature follicle, no egg is released. However, the LH stimulates the ovarian tissue to release more androgens (the male hormone), which further upsets the balance and can result in excessive hair growth and acne. This situation continues, and the estrogen levels remain high, no follicles mature, no eggs are released, and the male hormone levels remain high. The high estrogen levels stimulate the endometrium to grow, and it gets thicker and thicker until, eventually, it outgrows its blood supply and breaks down and is lost. Such a menstrual bleed is not a well orchestrated one, and can be irregular and heavy.

On ultrasound these ovaries have numerous small follicles – hence the name Polycystic Ovarian Syndrome. These small follicles are typically just beneath the surface of the ovary – and on ultrasound appear like a "ring of pearls". Blood tests show higher than normal levels of estrogen and high levels of LH.

Patients who are overweight may be more predisposed to PCOS. This is because fat tissue tends to increase the blood levels of estrogen , thereby contributing to the hormone imbalance which leads to PCOS. In fact, obesity is a feature in about 2/3 of women with symptomatic PCOS.

Another important imbalance to understand is that of Insulin Resistance. Insulin is a hormone produced by the pancreas to regulate sugar levels. When sugar levels go up, like after a meal, more insulin is released. But in patients who are overweight and in patients with PCOS there appears to be a resistance to insulin. In other words, more insulin needs to be produced to keep the sugar level under control. Higher insulin levels stimulate the ovarian tissue to make androgens, which upsets the normal hormone balance and leads to PCOS. Insulin Resistance can also lead to diabetes and hypertension.

Among the approximately 40% of subfertile women who have a disturbance of ovulation, PCOS is the most common cause.

DIAGNOSIS

In the majority of cases the diagnosis of PCOS is made from taking a woman's medical history and performing a clinical examination. Such women tend to complain of irregular periods, hair growth, acne, infertility and a chronic watery discharge. (The high estrogen levels stimulate the cervix to produce mucus which discharges from the vagina.) Physical findings on examination may include high blood pressure, obesity, hair growth, acne, watery vaginal discharge and sometimes a skin condition called "Acanthosis Nigricans". This skin condition is related to high insulin levels – and results in a velvety brown discolouration occurring at the base of the neck, under the breasts, in the armpits and on the inner thighs.

Blood tests might show higher levels of LH and testosterone (as well as other androgens). Ultrasound may show the "string of pearls" sign. Because PCOS is associated with diabetes and high cholesterol levels these can be tested too, usually by checking a fasting blood sugar and lipid profile. If the fasting glucose is greater than 7.8 mmol/l then a "glucose challenge test" is done.

Treatment Options

Irregular Periods.

Irregular infrequent periods (oligomenorrhoea) or absent periods (amenorrhoea) are common problems with PCOS. The reason for this is anovulation – meaning that ovulation is not taking place – so no corpus luteum is ever produced – and therefore no progesterone is every produced. This means that the higher levels of estrogen stimulate the lining of the uterus to grow – endometrium – until it outgrows its blood supply – at which time it sheds. This bleeding may occasionally be very, very heavy and unpredictable. A risk of constant estrogen stimulation on the endometrium (without progesterone) is endometrial cancer. Therefore it may be suggested to you that at the start of treatment you have an endometrial biopsy to exclude cancer.

The different options to control this problem are:

1. Weight loss – which may be enough to allow spontaneous regular ovulations again, and thereby regular periods.
2. The birth control pill. This is very effective. It will regulate periods and also provide the necessary progesterone to protect the endometrium against cancer.
3. Cyclical progesterone – in other words taking progesterone pills for 2 weeks every month – like a corpus luteum would normally do. There are different types of progesterone available. Some of these progesterone preparations may cause PMS-like side effects – such as bloating, headache and mood disturbances.
4. Metformin. Metformin is a drug which reduces the production of glucose by the liver – and thereby reduces blood sugar levels. Less insulin then needs to be produced to control sugar levels. The drop in insulin levels that occurs may sometimes allow ovulation. Metformin also makes the cells more sensitive to insulin meaning that less insulin needs to be produced by the pancreas to control blood sugars. Metformin is usually used in certain diabetic patients to control blood sugars. It will **not** cause sugar levels to fall and make you hypoglycemic. It is most useful in overweight patients as it can also help in losing weight. The usual dose is 500 mg 2 to 3 times daily. Early common side effects are nausea and diarrhoea. The diarrhoea usually settles down after a month or so. These medications may be taken for years. The medication should be stopped if and when you become pregnant. Although it is used in some countries to manage gestational diabetes, we do not routinely use it in pregnancy in Canada. The only dangerous risk related to the use of Metformin is called Lactic acidosis. This is very rare. However there may be a risk of lactic acidosis if you become dehydrated. You should be aware of this.

Hirsutism (excessive hair growth) and Acne

1. Birth control pill. The birth control pill keeps periods regular by mimicking the normal ovarian cycle. The BCP suppresses ovulation and also suppresses the production of LH by the pituitary gland in the brain. It is the increased levels of LH that stimulate the ovary to produce more male hormone. So the BCP helps reduce male hormone levels – and thereby reduces hair growth.
2. Anti androgen drugs. These medications reduce the efficacy of the male hormones in the body – and thereby help relieve some of the side effects such as hair growth. Drugs often used include:
   Spironolactone: The usual starting dose is 100-200 mg daily, which is then reduced over the next couple of months to 25-50 mg daily. Side effects are minimal – and may include diuresis (voiding of lots of urine as this is a diuretic), fatigue and irregular bleeding. It should not be taken in pregnancy – so extra forms of birth control are essential when using it.
   Cyproterone acetate. This is a powerful progesterone which is also effective in treating excessive hair growth. It is best used in a birth control pill called **Diane**. This will kill two birds with one stone – in helping treat hirsutism and regulating periods. It will of course also provide contraception.

There are other medications which can be tried – such as cimetidine, flutamide and finasteride – but they are not used much. The most effective therapies are either Diane or Spironolactone combined with a regular birth control pill. It should be remembered that it will take months before you notice any change in hair growth. The first changes will be that the facial and other undesirable hair growth becomes softer and finer.

3. Waxing and electrolysis.

Hyperinsulinaemia

1. Weight loss is very important – and the aim should be to get your body mass index to a normal range – that is between 20 and 25.
2. Metformin. This will help treat associated diabetes. I have explained how this works.
3. Rosiglitazone. This is a drug which increases the body cells sensitivity to insulin. We explained above how in PCOS there is a resistance in the cells to insulin – so more insulin has to be produced to be effective in controlling sugars. .

Infertility

Anovulation is a common cause for infertility in patients with PCOS. However, it is important to exclude other possible contributing factors as well. Ways in which ovulation may be induced include:

1. Weight loss (Low carbohydrate,high protein diets are useful)

2. Metformin
3. Ovulation induction agents – such as Clomiphene, tamoxifen and gonadotrophins. These are discussed in the handout on Subfertility. We normally start with Clomiphene – and move on to stronger drugs if necessary. The main risk is of multiple pregnancies.
4. Surgery. This is done by way of a laparoscopy – and involves burning small holes in the ovary – and thereby destroying some of the tissue which is responsible for producing excessive estrogen and male hormone. This can result in spontaneous ovulation again. There are some risks – specifically of adhesions or scarring in the pelvis from the surgery. Secondly there may be a very small risk of damaging the ovaries and causing premature ovarian failure – or menopause.
5. If medications are not successful – then IVF is a possibility.

Miscarriages

Miscarriages may be more common in women with PCOS. This may be related to hormone imbalances which effect the development of a healthy endometrium. Management is aimed at improving the hormone levels through the ovulatory cycle. In certain circumstances the use of metformin may reduce the risk of miscarriage.

Hypertension

Hypertension, diabetes and high cholesterol levels are on many occasions influenced by weight. The first line of treatment would be aimed at diet and losing weight – perhaps helped with drug therapy. Treatment would be individualized to an individual's needs.

Summary

Many long term related health problems are related to being overweight – so a healthy diet, weight loss and regular exercise are important. Management options have been discussed – and it is important for you to be well informed and with your doctor choose a treatment plan which is acceptable to you – which addresses your needs.

More information can be had by visiting website: www.pcosupport.org.