The Polycystic Ovary Syndrome

A brief review of the medical background

This information sheet is a guide to the symptoms and treatment of PCOS. It outlines the issues of management developed in a specialist endocrine hospital clinic. In this setting, the emphasis is upon hormones and how they affect each individual. Alternative medicines, cosmetic treatments and psychological issues are also important for women with PCOS and are not covered here. Although every effort is made to achieve accuracy, errors and the results of new research may invalidate some of the information found below.

Definition of the polycystic ovary syndrome

The polycystic ovary syndrome is possibly the most common disorder affecting women with approximately 5% of all women experiencing a symptom at some time in their lives. Despite this commonness, PCOS remains one of the big enigmas of the female body as for the most part, we do not know how it comes about.

With the passage of years the definition of PCOS has changed depending on the technology of the time. The most accepted definition of PCOS in Europe is based on the ultrasound appearance of the ovaries. PCOS is the combination of ovaries which have more than ten follicles visible on ultrasound together with a symptom which can not be accounted for by any other process. The common symptoms of the polycystic ovary syndrome are irregular menstrual cycles, unwanted hair growth, acne, the scalp hair thinning and occasionally infertility.

Normal ovaries and their function

The ovaries, which are situated in the pelvis either side of the uterus, have two functions: to produce eggs and hormones.

- **Eggs - how they grow and where they come from**

In the normal menstrual cycle, about five follicles start to grow, each containing an egg. One of these follicles becomes 'dominant' and the rest die away. Ovulation occurs after the dominant follicle has grown to approximately 20 millimetres in diameter when it bursts open upon the surface of the ovary. The egg then passes down the fallopian tube where fertilisation occurs. The combined egg and sperm is called an embryo. The embryo completes the passage down the fallopian tube to the uterus where it implants into the lining or *endometrium*. If implantation is successful the embryo grows into can a placenta and foetus and the pregnancy continues. The placenta begins to make the hormone *human chorionic gonadotrophin* or hCG which can be measured in urine. This is the basis of the pregnancy test. If fertilisation or implantation does not occur, then the embryo comes away in the menstrual period about 14 days after ovulation.

All of the eggs that a woman has throughout her life are made before she is born. By the time that the foetus has been growing for six months about 3.5 million eggs are found in each ovary. Two thirds of these eggs are destroyed in the last three months of foetal life. Most of the remaining 1 million eggs in each ovary are slowly destroyed throughout life until only 1000 remain at the average age of the menopause at 50 years. Only a minute proportion of eggs is used in ovulation. If a woman ovulated every month between the ages of 15 and 45, fewer than 500 eggs are used. It is not known how the body chooses which eggs will mature to ovulation and which will be destroyed.

- **Reproductive hormones - where they come from and what they do**

The ovaries make three types of hormone - *testosterone, oestrogen* and *progesterone.* Testosterone is made by the cells which surround each follicles - *theca cells*. Some of the testosterone is released into the bloodstream but most of it is handed onto the cells which make up each follicle - *granulosa cells*. Granulosa cells take up testosterone and converted it to oestrogen. As the follicles grow bigger, more and more oestrogen is made and the level of oestrogen in the bloodstream rises. After ovulation the empty follicles turns into the corpus luteum which makes progesterone. Progesterone it is important as it prepares the uterus for implantation. Progesterone is only made in the second half of the cycle when it can be measured in the bloodstream to provide proof that ovulation has occurred. Progesterone causes the body temperature to rises by about half a degree and this change can be measured by careful temperature recording as another way to indicate that ovulation has occurred.

The whole reproductive cycle is controlled by two hormones made by the pituitary gland - luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH drives the theca cell to make testosterone and takes a major part in the timing of ovulation. At ovulation the concentration of LH in the blood rises sharply just before the egg is released. This rise in LH can be measured in urine and this is the basis of the ovulation monitoring kits available in chemist shops. FSH stimulates the granulosa cells to multiply for them and to make oestrogen. The hormone FSH is a good marker of the health of the ovary. When the ovary and begins to fail the level of the FSH in the bloodstream rises. A higher FSH measurement is found when the ovaries stop working as in the menopause.

The average length of the menstrual cycle is 28 day but this length commonly varies between 21 and a 35 days. The first day of the menstrual cycle is counted from the first day of a period. The first half of the menstrual cycle is called the *follicular phas*e because it is during this time that the follicles grow. Ovulation occurs midway through the cycle or more accurately, 14 days before the menstrual period. The second half of the menstrual cycle is called the *luteal phase* when the *corpus luteum* is active in making progesterone.

The normal range of each hormone will vary slightly in each laboratory. As a guide, the normal ranges for hormone measured at the Middlesex Hospital are listed here:

LH	1 - 10 mU/L
FSH	1 - 10 mU/L
Testosterone	0.2 - 2.8 nmol/L
Oestradiol	40 - 1300 pmol/L - very variable depending on day of sample
Progesterone	< 1.0 nmol/L before ovulation >30 nmol/l if taken one week after ovulation

In a fertility screen the following hormones are also checked routinely - other tests for thyroid function might be included

Prolactin	<700 mU/L
TSH	0.5 - 5 mU/L
Free Thyroxine	9.1 – 23.8 pmol/L

In a metabolic screen the following tests may be included

Fasting Glucose	3.3 - 5.6 mmol/L
Fasting Insulin	10 – 80 pmol/L
Total cholesterol	2.3 - 6.9 mmol/L
HDL cholesterol	1.0 - 2.0 mmol/L
Triglycerides	0.5 - 1.8 mmol/L
LDL cholesterol	1.5 - 4.1 mmol/L

The polycystic ovary

In comparison to the normal ovary, the polycystic ovary is larger, has more follicles can and has a particularly dense centre - the stroma which is where testosterone is made. On average the normal ovary contains five follicles and is about the size of a walnut. The polycystic ovary contains 10 or more follicles, usually these are small follicles measuring between 2 and 10 millimetres in diameter. The polycystic ovary is usually the size of a hen's egg but occasionally they may be the size of an orange. The increased size of the polycystic ovary is mainly due to an increased amount of stroma and not, as may be expected, because of the extra follicles or cysts. Usually, the follicles are too small to contribute much to the ovary size.

The description of the polycystic ovary above is derived from their appearance on ultrasound. When ultrasound is used in the general population it has been found consistently that 20 - 25% of all women polycystic ovaries - only a proportion of women with polycystic ovaries also have some of the symptoms below and therefore have the polycystic ovary *syndrome*.

History of PCOS

PCOS was first recognised in the 1930's when Stein and Leventhal described a severe form of the syndrome in women who were very over weight, had unwanted hair growth and no periods. At surgery, these women were found to have large cystic ovaries. In fact, we now understand the cysts to be enlarged follicles which are a normal part of the ovary and this syndrome might more accurately, and less frighteningly, be called the *polyfollicle ovary syndrome!*

In the 1960s and 1970s it became possible to measure performance first in urine and then in blood. The most consistent hormone changes were found to be raised measurements of ultrasound hormone and testosterone. In the 1980s high resolution ultrasound was used to define the typical polycystic ovary picture. It became apparent, when stimulating the ovary with fertility hormone treatment, that ovaries with fewer than eight follicles usually be produced a single egg whereas treatment with ovaries containing more than 10 follicles often resulted in more than one ovulation. Using ultrasound, it has been shown one in five of all women have at polycystic ovaries even though many will never have the slightest symptom. When considering women with unwanted hair growth, we find that more than 95 per cent have polycystic ovaries.

In the 1990s, to new aspects of PCOS became apparent. First, in many instances polycystic ovaries are inherited and this could be through either the mother or father. The polycystic ovary, therefore, can be considered part of an individuals genetic make up and remains so for life. The symptoms of PCOS however, may changes at different times of life. Second, some women with PCOS have raised circulating insulin concentrations and are at risk of becoming diabetic later in life - *a metabolic syndrome*.

The symptoms of PCOS

- **Hair growth and skin**

Hair growth on the face and body and the making of grease on the skin is driven by the male hormone, testosterone. Under the influence of testosterone the hair follicle produces thicker, pigmented terminal hair at a faster rate causing *hirsutism*. On the scalp however, testosterone switches hair growth off, so scalp hair thinning, or *alopecia*, can accompany unwanted hair growth on the body in women with PCOS. The sebaceous glands of the skin produce more sebum or skin grease in response to testosterone. One result of an excess of sebum, is that skin pores become blocked causing *acne*. Eighty five percent of women troubled by acne after the age of 20 have PCOS.

- **Irregular menstrual cycles**

The monthly timing of the menstrual cycle is controlled by a complex balance of hormones made by pituitary gland and ovary. This reproductive cycle controls oestrogen and progesterone production from the ovary which acts on the uterus to bring about a menstrual bleed. If there is any imbalance in this hormone cycle, then the period can be delayed or missed completely. A complete lack of periods for more than 6 months is called amenorrhoea. Long gaps between periods of between 35 days and six months is called oligomenorrhoea. The normal menstrual cycle can vary between 21 and 35 days although women with normal ovaries on ultrasound do not usually experience much variation in their cycle timing.

In some women with oligomenorrhoea the lining of the womb can build up to lead to a heavy painful period. Occasionally the lining of the womb can become very thickened - endometrial hyperplasia - and if left for years there is a risk that cancer might develop as a result of this build-up. For this reason, long gaps between periods should be taken seriously although cancer of the uterus in women with PCOS is a very rare event.

- **Infertility**

PCOS causes infertility by preventing ovulation taking place. Usually the egg is released 14 days before a period. If the periods are very irregular then ovulation may be unreliable or indeed - it make not take place at all. As a general rule, if periods are regular then ovulation and fertility will be normal. It is rare for periods to occur without ovulation - but it can happen. The event of ovulation can be confirmed in a variety of ways (see treatment) and if ovulation is proven to be reliable, then PCOS is not the cause of infertility.

- **Miscarriage**

Once the sperm has fertilised the egg, if embryo development is abnormal a miscarriage occurs. That is, most miscarriages come about because of an abnormality of the embryo. Usually miscarriage is a random event which does not happen repeatedly. Some couples, however, experience several miscarriages in a row - recurrent miscarriage. Women with PCOS who also have a raised LH measurement are at an increased risk of miscarriage. The mechanism of this association is unknown. No treatment has yet been found to be effective in preventing miscarriage which is particular to PCOS. There are however, other causes of recurrent miscarriage which can be treated effectively so careful investigation is worthwhile.

- **Over weight**

Being overweight occurs more commonly in women with PCOS in than average. There are a variety of explanations why women with PCOS can be obese. Some believe that the hormone imbalance made by the polycystic ovary in some way causes weight gain. There is little evidence to support this notion. For instance, when ovaries are removed from women with PCOS,

weight loss does not follow. Raised insulin levels might, however, be a drive to the appetite centres of the brain. The most plausible link between obesity and PCOS is that an individual inherits both a low metabolic rate and a polycystic ovary separately. One or the other condition might be innocent but the two together results in the symptoms of PCOS.

The while the cause of obesity may uncertain the fact of being overweight is clear. Weight gain results in higher insulin levels which in turn drives the ovary to make more testosterone. Thus, as women gain weight the concentration of testosterone in the blood rises. Conversely, as women are lose weight, the concentration of testosterone falls and the symptoms of PCOS improve.

What should my weight be? The ideal weight range for any given height is estimated by the **body mass index** or BMI which is your weight in kilograms divided by height in metres squared (kg/m^2). The normal range for BMI is 18 – 25 kg/m^2.

- **Health in later life**

Recent studies have shown that women who were diagnosed as having PCOS 30 years ago have a completely normal life expectancy. An inspection of more than 700 death certificates from women with PCOS has shown that there is no excess risk of cancer in any organ or of heart disease. Other studies have shown that diabetes later in life is much more common in women with PCOS than average. As diabetes san be prevented by attention to diet and body weight it seems sensible to take avoiding action early in life.

Women who have very infrequent periods are at a greater risk of cancer of the endometrium - the lining of the womb - than women with regular periods, particularly if they are over weight. For this reason, amenorrhoea in women with PCOS should not remain untreated even though this type of cancer is quite rare.

It is reassuring that PCOS offers so little risk to long term health. With this in mind, all treatments must be considered to be optional and the safety of treatment must be a priority.

The hormone changes

- **Testosterone and other androgens**

The ovary makes several androgens of which testosterone is the most prominent - others include androstenedione and DHEAS. The most typical feature of the polycystic ovary is that the stroma and theca cells make an excess of testosterone. The adrenal gland is another source of testosterone but the function of this gland is usually normal in women with PCOS.

- **The gonadotrophins, LH and FSH**

The monthly timing of the menstrual cycle is controlled by a complex balance of hormones from the hypothalamus and pituitary gland which is situated behind the eyes. The gonadotrophins, LH and FSH are made by the pituitary gland. LH, luteinising hormone, drives the theca cells of the ovary to make testosterone. Testosterone is then passed to the granulosa cell of the ovarian follicle where it is turned into oestrogen under the influence of FSH, follicle stimulating hormone. In one third of women with PCOS the level of LH is raised and there is a rough association between this finding and a tendency to infertility. Concentrations of FSH are normal in women with PCOS.

- **Insulin and the metabolism**

The main role of insulin in the body is in regulating the level of glucose in the blood. In some individuals, high concentrations of insulin are required in order to maintain normal glucose levels - insulin resistance. When insulin fails in this effort, diabetes ensues. Raised insulin concentrations have a side effect in the body of stimulating the ovary to produce more testosterone. About one third of lean women with PCOS have raised insulin levels and this proportion rises in those who are over weight. In obese women with PCOS about half have raised insulin levels and 10% have mild diabetes. Raised insulin levels are part of a *metabolic syndrome* which also includes high blood pressure and an adverse cholesterol profile - low HDL cholesterol and raised triglycerides.

The treatments

In many instances, when a women with PCOS has several symptoms, a choice has to be made as to which symptom gets priority. For instance, it is impossible to suppress unwanted hair growth and to stimulate ovulation for infertility at the same time. For this reason, each treatment program has to individually tailored.

Hirsutism and the skin

Many women use physical treatments for unwanted hair growth such as shaving, plucking, waxing or electrolysis. These are all acceptable and do not increase the growth of hair - a common myth! Recently, laser hair removal has been introduced but the long-term success of this treatment has not been seriously studied. Drug treatment reduce the rate of hair growth and make hairs which grow thinner an less pigmented. This effect takes months to have a noticeable effect. Often little improvement in hair growth is seen inside of six months of treatment whereas acne can improve in 8 weeks of treatment. Alopecia, on the other hand, is the slowest symptom to respond and often improvement is only partial.

- **The pill**

The most common treatment for acne and unwanted hair growth is the combined oral contraceptive pill. The pill acts to suppress the ovary and while effective in this way as a contraceptive it also suppresses testosterone production by the ovary. The pill 'Dianette' is specially formulated to be a most favourable combination of oestrogen and cyproterone acetate for women with PCOS. Pills vary in their strength and progesterone content and experimentation may be needed to find the bast one for an individual. The main hidden side effect of the pill is thrombosis and this is most common in smokers and in the obese in whom alternative treatments might be chosen.

- **Anti-androgens**

The pill on its own is frequently not strong enough to clear unwanted hair growth. When this is the case, the addition of an anti-testosterone compound - anti-androgens - improves the effect of treatment. Most anti-androgens act by blocking the action of testosterone at the hair follicle. The most common anti-androgen is cyproterone acetate, *Androcur*. A dose of 25 - 50 mg is given for the first ten days of each calendar pack of the pill. Side effects include weight gain, lethargy and headache.

The second most common anti-androgen is spironolactone, *Aldactone.* This mild diuretic has almost no noticeable action on urine flow but does effectively block testosterone. Unlike, cyproterone acetate, spironolactone can be used on its own - without the pill - and this can be useful in smokers or obese women who might choose not to take the pill. The dose of spironolactone is 50 -200 mg per day in divided doses. The main side effect is to make periods more irregular and heavy.

Flutamide and finasteride are alternative anti-androgens which are generally only prescribed in specialist units.

- **Other treatments**

Steroids such a Prednisolone have been used in the past to treat PCOS. In general the side effects of this treatment are considered to be too great for long term treatment. Anitbiotics, such a Minocycline are often used to treat acne but this treatment does nothing for other aspects of PCOS such as hirsutism which son often accompanies acne. If acne does occur on its own then Roaccutane is very effective treatment prescribed in dermatology clinics.

Menstrual disturbance

If periods occur more frequently than four times and then a medical treatment may not be absolutely necessary. An occasional ultrasound scan can be used to screen for any abnormality of the uterus is no treatment is chosen. The most common method of providing regular periods is the use of the pill. The pill has the added benefit of improving hirsutism at the same time as making periods regular. The pill has no lasting effect on the reproductive system. That is, the pill does not 'kick start' the periods and neither does it directly cause a lack of periods. If the pattern of periods is different after taking the pill then this is most likely due to natural variation in the symptoms of PCO or because of a change in weight while taking the pill.

If, for any reason, the pill is not suitable then an alternative way of bringing on the periods is with progesterone. Progesterone is given in a short course of seven to 12 days each month and a period usually follows each course. Three types of progesterone are commonly available, dydrogesterone (*Duphaston*), medroxyprogesterone (*Provera*) and norethisterone (*Primulot and Micronor*).

Infertility

While the usual reason for difficulty in conceiving is the failure to ovulate, in many couples there is more than one reason for infertility and a full check-up is usually required. In particular, a check of the fallopian tubes and a semen analysis is advisable before treatment is started. In women with regular menstrual cycles, ovulation occurs midway through the cycle. Counting the first day of a period as day one of the cycle, ovulation usually occurs near day 14. Knowing that this detail, it is possible to time intercourse for the most fertile time. In women who have menstrual cycles which vary in length, it can be difficult to know when ovulation occurs and mistiming of intercourse is a simple cause of infertility. Ovulation monitoring can be the remedy in the situation.

The single most important factor in predicating the success of fertility treatment is body weight. All treatments are less successful in women who are over weight. Weight loss must be the first action for infertile women with PCOS - in fact many can avoid fertility treatment if successful!

- **Ovulation monitoring**

There are simple changes in the body which can be used to time ovulation. For example the body temperature rises by half a degree at the time of ovulation and by keeping a careful temperature chart every day the fertile time can be predicted. Alternatively, a slight lower abdominal pain and a thinning of survival mucus can indicate ovulation. Many women find these changes are not reliable enough to be useful.

Ovulation prediction kits are available from pharmacies and are reliable in some women with PCOS. These kits however, work by measuring the hormone, LH, in the urine and in women who have a high circulating level of LH they are unreliable.

Lastly, ovulation can be predicted by using ultrasound to measure the development of follicles in the ovary starting from a bout day 8 of the cycle. This form of monitoring is only available from experienced specialist fertility unit and it may take several visits every few days before ovulation can be identified.

Whatever method is used to predict ovulation - confirmation that ovulation was successful comes from a measurement of progesterone in the blood about one week after ovulation. Progesterone is made by the corpus luteum in the ovary which only forms after ovulation has taken place so the timing of this blood test is critical. In a 28 day cycle - progesterone is best measure on day 21. In women with an irregular menstrual cycle - the timing of the test can only be made by ovulation monitoring and by keeping a record of when the following period occurs - it should be one week later.

- **Clomiphene Citrate (*Clomid, Serophene*)**

Clomiphene is an anti-oestrogen which is used to treat infertility in women with PCOS by inducing ovulation. The overall pregnancy rate in women treated with clomiphene is over 50%. The starting dose of Clomiphene is 50 mg on days 2-6 of the cycle and if the treatment is unsuccessful the 100 mg is given over for the same 5 days. Side effects include bloating, dizziness, breast discomfort and blurred vision. By stimulating ovulation, the chance of twins is increased from 1:80 in natural cycles to about 1:20.

There has been some concern that treatment with clomiphene citrate might increase the risk of cancer of the ovary later in life. For this reason, the Royal College of Obstetrics and Gynaecology have suggested that no more that 6 cycles of treatment be given. Recently, the strength of the link between ovary cancer and clomiphene treatment has been estimated to be very slight.

Cyclophenil (*Rehibin*) and tamoxifen (*Tamofen, Noltam, Nolvadex*) are alternatives to clomiphene which a favoured in some instances. Randomised controlled comparisons of these treatments have not been made.

If these tablet treatments are not successful then two options follow: injectable hormone treatments and ovarian diathermy.

- **Hormone fertility treatments**

The hormone FSH and LH can be given by daily intramuscular injection. Various preparations are available and all are equally effective in women with PCOS when used for ovulation induction. Low doses are used at the beginning of a cycle and then increased depending on the results of monitoring with hormone tests, or more usually, ovarian ultrasound. Close monitoring will show how many follicles are developing on each occasion. If too many follicles grow then the risk of twins or *hyperstimulation* might be considered too great and treatment will be abandoned and the couple advised not to have intercourse. If, as intended, up to three follicles develop then the eggs can be released with an injection of hCG (*Profasi*) when they are sufficiently mature.

One side effect of this type of treatment is over stimulation of the ovaries - *ovarian hyperstimulation syndrome*. This occurs when too many follicles develop and the ovaries become quite markedly enlarged. The symptoms include abdominal discomfort, nausea and vomiting. In severe cases specialist hospital treatment may be required.

An alternative to FSH and LH injections, is the GnRH pump - also known as the LHRH pump. The hormone, gonadotrophin releasing hormone, is given by a syringe pump through a needle inserted under the skin. The syringe driver or pump, is worn for

several weeks and delivers a pulse of GnRH every 90 minutes. This pump treatment is usually available in specialist fertility units.

- **Ovarian diathermy**

It has been known for many years that damage to the ovary in women with PCOS is often followed by more regular ovulation. This effect was first noticed after an obsolete operation, *'ovarian wedge resection'*, when part of the ovary was removed. This procedure has been refined and now replaced by applying four small burns to each ovary at laparoscopy. In this way an open operation is avoided.

Ovulation can occurs within a few weeks of diathermy and can continue for many months. Often the effect of diathermy gradually wears off over time. Results vary from each specialist centre depending on the experience of the surgeon. This treatment is popular because it can prevent the need for fertility drugs. It is only possible to use this treatment in women who are not over weight as laparoscopy is technically difficult if overweight. Particularly good results are recorded in women who have raised LH concentrations.

- **In vitro fertilisation**

When all other treatments have failed then IVF may be the only option. In women who have blocked fallopian tubes then IFV is in fact the only answer.

Metabolism

- **Diet and exercise**

Reducing insulin by diet, weight loss or drugs results in a lowering of testosterone and improved symptoms of PCOS. All women with PCOS who are over weight would benefit from a regime of diet reform and exercise. Diet should be at least three light meals per day, which are low in sugar and fat and high in fruit, pulses, fresh vegetables and salad. Light sustained exercise such as walking, cycling or swimming for at least an hour at a time several times per week.
The only drug currently available in the UK which reduces insulin is Metformin - newer alternatives such as Troglitazone are available in other countries.

- **Metformin**

Metformin has been used for over 30 years to treat maturity onset diabetes mellitus. It acts by making the body more sensitive to insulin.

Several studies have recorded the use of Metformin in women with PCOS. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. While Metformin starts to improve the prospects for fertility in few weeks, a reduction in unwanted hair growth would be expected to take some months. Women can find weight loss easier when taking Metformin even though it is not a traditional weight reducing agent. One placebo-controlled trail has shown that Metformin is better than placebo in inducing ovulation in women with PCOS. The effectiveness of Metformin has been demonstrated best in obese women and it is likely that women of normal weight would only benefit little from this drug.

Side effects to Metformin treatment are rare. In particular, Metformin does not cause hypoglycaemia. In the first week of taking Metformin, an upset stomach or diarrhoea is common and this side effect can be reduced by taking it after food and by starting with a very low dose (250 mg) and to increase slowly by 250 mg per week until the full dose of 1700 mg is achieved (850 mg twice per day). Women who have reduced kidney function are at an increased risk of a very rare side effect of Metformin therapy called lactic acidosis. The drug should be given cautiously, if at all, in this instance. While safety during pregnancy has not yet been established many women over the years have inadvertently taken Metformin when pregnant and no adverse effects have been reported. Indeed, one group has reported the intentional use of Metformin to treat diabetes throughout pregnancy.

Dr Gerard Conway
Department of Endocrinology
The Middlesex Hospital
Mortimer Street
London W1N 8AA

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