The Polycystic Ovary Syndrome - a starting point, not a diagnosis.

Dr Warren Kidson MB BS, FRACP
Visiting Endocrinologist, the Prince of Wales and Sydney Childrens Hospitals, Sydney, Australia.
Dr James Mackenzie Talbot MB BS, FRANZCOG, FRCOG (Lond)
Gynaecologist, Monash IVF and Melbourne Assisted Conception Centre, Melbourne, Australia.

The polycystic ovary syndrome (PCOS) is a collection of symptoms and problems that affects at least 5% – 10% of women. The words "**polycystic ovary syndrome**" fill many women with fear and dread: "**Are my ovaries diseased?**", "**Can I ever have children?**", "**Can the cysts be cut out?**"

Over the past decade knowledge about the polycystic ovary syndrome (PCOS) has exploded, revealing a potential for a poor long term health outcome that can be greatly improved by simple therapies that also make infertility less likely for most women with this frustrating condition.

The Polycystic Ovary Syndrome! What is it? What is a Syndrome?

The word **syndrome** can mean a disease or disorder that can produce different collections of symptoms and physical signs. The word **syndrome** also can mean a collection of symptoms and physical signs that can be due to a variety of different diseases. The word **syndrome** in the polycystic ovary syndrome has both of these meanings.

In the polycystic ovary syndrome, women may suffer from a variety of symptoms and also have a variety of different physical signs, all of which can be due to a number of different causes. It is therefore important not to regard **the polycystic ovary syndrome** as a diagnosis or disease in itself but, instead, as the start of a search to find the underlying cause of the symptoms and problems. Treatment of the cause of a particular woman's PCOS will generally give her better results, both in the short term and in the longer term, than a **one-size-fits-all** treatment.

In the past the polycystic ovary syndrome has been diagnosed if a woman has two out of three sets of conditions:

- The first is increased levels of male hormone. It is usually first noticed by the effects of male hormones such as acne, excess body hair growth or accelerated loss of hair from the scalp.
- The second condition is called **anovulation**, the medical term for lack of regular ovulation. Lack of regular ovulation results in irregular and, usually, infrequent occurrence of menstrual periods. A few women who are not ovulating, however, will still have regular periods.
- The third condition is the finding of polycystic ovaries on an ultrasound examination of the ovaries or at laparoscopy, an operation where a gynaecologist inserts a laparoscope, a telescope and light, into the abdomen or tummy.

It is therefore possible for a woman to be diagnosed with the polycystic ovary syndrome without actually having cysts on her ovaries! The presence or absence of cysts on the ovaries usually does not make any difference to the best choice of treatment for the woman. Some leading doctors treating PCOS no longer routinely do ultrasound examination of the ovaries but simply investigate women with skin problems or with menstrual irregularity and fertility problems the same way.

Common misconceptions about the polycystic ovary syndrome:

In the past, some women with PCOS have been told

You will never have children

Take the "Pill" and come back when you want to have children

If you don't take the "Pill", you will get cancer!

Just go away and loose weight

You won't get pregnant without IVF

Many women with PCOS are unaware that their risk of developing diabetes over the next 20 years is 40-60% and that diabetes can be prevented by treatments that improve PCOS.

What causes the Polycystic Ovary Syndrome? (Table 1)

In order to understand the many possible causes of the polycystic ovary syndrome, it is important to understand a little about how a woman's reproductive cycle functions. Every woman knows that her eggs develop in her ovaries. Egg development is controlled by two hormones produced by the pituitary gland: follicle stimulating hormone, FSH, and luteinising hormone, LH.

The pituitary gland is the size of a peanut and is situated behind the eyes. It is connected to the base of the brain by a stalk. In the base of the brain just above the pituitary gland there is a centre than controls the production of FSH and LH in the pituitary gland. This is the brain's fertility centre. In men, this centre works in a continuous fashion but in women, this centre works in a cyclic fashion, usually in a monthly cycle and, hence, we will refer to it as the **fertility clock**.

If the fertility clock is exposed to higher than average levels of male hormones in a woman, the clock begins to work in a continuous fashion like a man rather than in a monthly cyclic fashion, making ovulation unlikely.

The ovulation cycle can be turned off by high levels of a pituitary hormone prolactin, sometimes caused by stress and sometimes made excessively by a tumour of the pituitary gland secreting prolactin. This is an uncommon cause of the polycystic ovary syndrome.

The Ovulation Cycle.

Early in a woman's cycle the fertility clock stimulates the pituitary gland to secrete a large amount of follicle stimulating hormone (FSH). FSH stimulates growth of the egg and the cells lining the follicle, the tiny bubble that holds the egg, so that the follicle enlarges and moves out towards the surface of the ovaries. At this stage, the follicle does not respond to stimulation by luteinising hormones (LH).

Around days 10, 11 or 12 of the cycle, the fertility clock stimulates the pituitary gland to make a very large amount of LH. By this time the follicle is 9.5 millimetres in diameter and has become sensitive to LH stimulation. The surge in LH from the pituitary gland always stimulates the **final** step of maturation of the follicle after which no further growth is possible. At this stage the follicle and egg are **ripe** or mature and the follicle will rupture or **ovulate**, releasing the egg.

Early in the cycle, the ovary and the developing follicle produce a female hormone called oestradiol or oestrogen. Oestrogen stimulates the lining of the womb to grow and thicken. After the follicle ruptures and releases the egg in the middle of the cycle, the ruptured follicle (or **egg shell**) changes its function and produces the second female hormone, progesterone. Progesterone changes the lining of the womb so that it no longer grows thicker but becomes receptive to the implantation of a fertilised egg. This change also allows the lining of the womb to separate from the womb promptly and evenly after blood oestrogen levels fall if fertilisation and implantation have not occurred that cycle. This will result in a normal menstrual period that lasts from four to six days.

The consequences of lack of ovulation.

If ovulation does not occur, the follicle continues to produce oestrogen for some time, causing the lining of the womb to grow thicker than usual. The situation is made worse because the ovary does not produce progesterone if ovulation has not occurred. The lining of the womb then breaks away in an erratic fashion. This causes the menstrual bleeding to be long, often with large quantities of blood and tissue, causing menstruation that can be heavy, painful and prolonged.

The other obvious consequence of lack of ovulation is reduced fertility.

Alterations in the ovulation cycle in PCOS.

Many different conditions can disrupt the ovulation cycle, resulting in the polycystic ovary syndrome. Severe stress can **"turn off"** the fertility clock. These women will often begin to menstruate and ovulate regularly after stress management and relaxation training known as **"cognitive behaviour therapy"**.

In a few women, the fertility centre or clock does not fully mature until after a woman's first pregnancy. In this situation, the periods usually start later than usual, between 14 and 18 years of age, and the menstrual cycle is usually irregular from the first period onwards. An immature fertility clock does not coordinate the pituitary gland's secretion of FSH and LH and, consequently, the development of the follicle and egg is incomplete.

Some women have a normally functioning fertility clock until they develop an eating disorder such as anorexia or bulimia or until they take part in extreme physical training in ballet or competitive sport. Severe weight loss will turn off the fertility clock to protect the woman from starting a pregnancy in a state of malnutrition. Ovulation no longer occurs and the periods disappear. When the woman recovers from her eating disorder and gains weight, the clock function appears to return to normal but often, some years after recovery, the periods become erratic, cysts develop in the ovaries and signs of excess male hormone such as increased body hair growth and acne appear. The period of eating disorder and weight loss therefore appears to have done some permanent damage to the clock in that it does not work in the same fashion as it did before the eating disorder and weight loss.

High levels of male hormone in a woman will change the functioning of the fertility centre from the cyclic pattern of a woman to the more continuous pattern of function of a man. This may occur in a rare condition known as **congenital adrenal hyperplasia** or **"CAH"**. In this condition, the adrenal glands make an excess amount of male hormone. The adrenal glands always make a certain amount of male hormone as a by-product of the production of cortisone, the main hormone produced by the adrenal glands. The severe form of congenital adrenal hyperplasia is diagnosed in infancy when masculinisation of both girl and boy babies is obvious. In women with a milder form, **late onset congenital adrenal hyperplasia**, the adrenal glands begin to make much more male hormone, the fertility control centre no longer functions cyclically and polycystic ovaries then develop.

A similar situation is seen in women who have a tumour secreting male hormone in an ovary or in an adrenal gland or in women who decide to have a sex change operation and who are subsequently given large amounts of testosterone, a male hormone, to give them male body characteristics. The male hormone changes the function of the fertility clock and these women develop polycystic ovaries.

Table 1:

Causes of the polycystic ovary syndrome		
Mechanism	**Cause**	**Investigations**
Interruption of fertility centre cycling by male hormones	Late onset CAH	Early cycle 17~hydroxyprogesterone
	Tumours of the adrenal glands, ovaries or the pituitary gland	History of rapid onset, 24 hour urinary cortisol, ultrasound of ovary, CT scan of adrenals, MRI of pituitary gland
	High blood levels of insulin	The most common cause of PCOS - see text
Inhibition of fertility centre	Anorexia, bulimia, stress, excessive exercise	History of weight loss, vomiting or extreme exercise , weight, BMI, low oestrogen, LH, FSH
Immature fertility centre	Unknown	No history of other problems, examination, normal levels of oestrogen, LH, FSH
Inhibition of secretion of LH and FSH from the pituitary gland	High blood levels of prolactin	History of stress, milk in breasts, prolactin, TSH, MRI scan of pituitary
Premature response of ovarian follicle to LH stimulation	High blood levels of insulin	The most common cause of PCOS - see text

Insulin resistance, high blood insulin levels in PCOS.

The most common cause of the polycystic ovary syndrome, affecting around 70-80% of sufferers, is a condition that we now call **insulin resistance**.

Insulin is a hormone made by the pancreas gland at the top of the back of the abdomen. It is produced in small amounts between meals (fasting levels) and in larger amounts during and after a meal (meal levels). One of the main functions of insulin is to control the storage of energy foods around the body after a meal. Food energy comes in two main forms: **fats** and **carbohydrates**. Carbohydrates come in two main forms: **starch** in bread, rice, pasta, cereals and potatoes and **sucrose**, the "double" sugar from cane found in soda drinks and candy. In our stomachs, starch and sucrose are both digested to the "single" sugar **glucose**, which is then absorbed into the blood stream. Fats are digested to smaller fats, which are then also absorbed into the blood.

After glucose is absorbed from the gut into the blood, the meal level of insulin stimulates muscles and the liver to suck up glucose and store it as a carbohydrate called **glycogen** for later energy use. Glycogen is the human and animal equivalent of starch, the storage form of carbohydrate in the plant world. Insulin also stimulates fat cells and the liver to make "triple fat" or "triglycerides" so that it can be stored for later energy use. More importantly, fat breakdown is turned off by insulin at quite low levels and only happens at fasting levels.

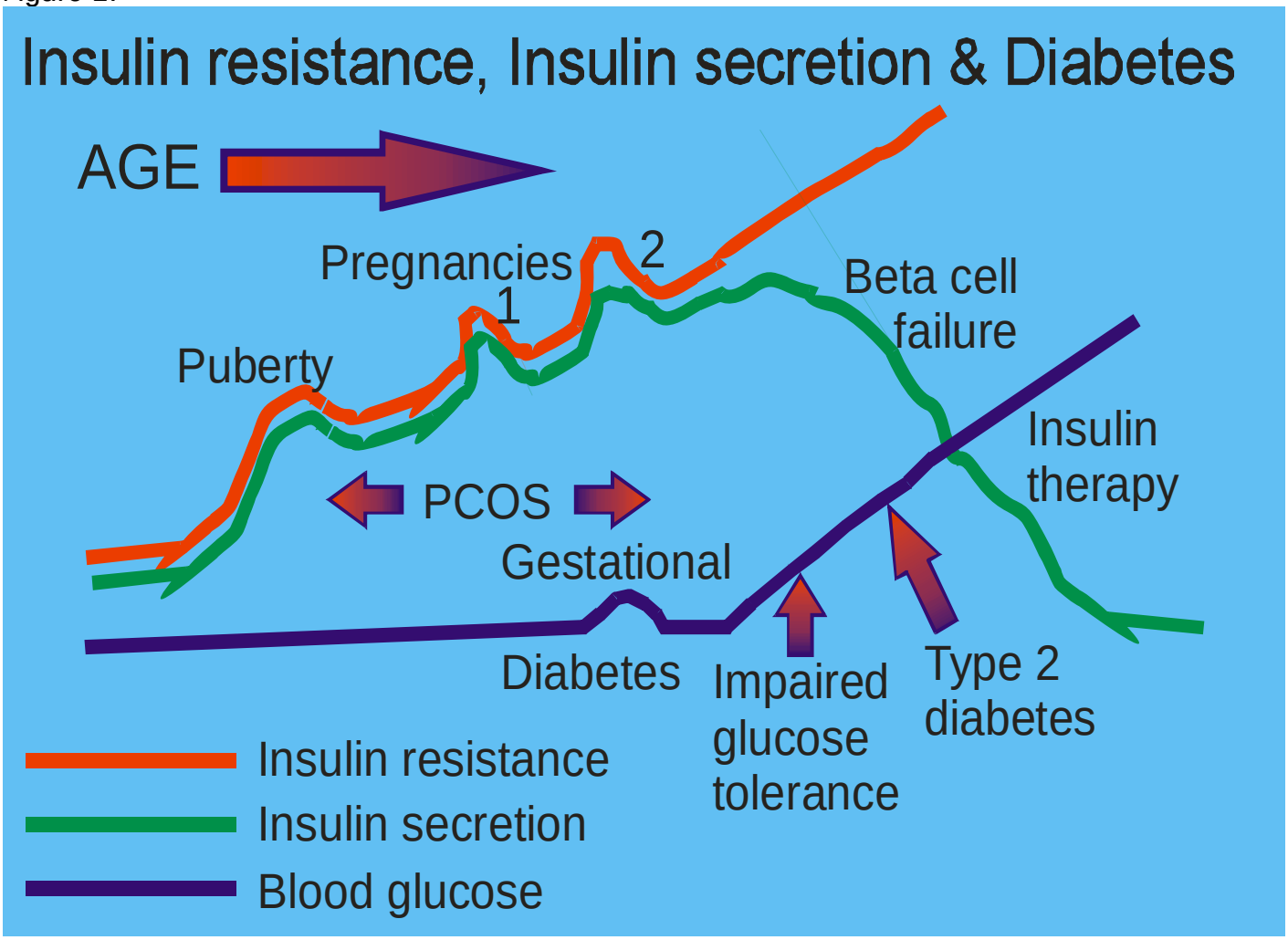
In people who suffer from **insulin resistance**, the liver and muscles do not take up glucose from the blood stream as efficiently as other people's livers and muscles at normal meal levels of insulin. In other words, their muscles and liver do not respond efficiently to insulin stimulation of glucose uptake.

One might think that this would lead to high levels of glucose (sugar) in the blood after a meal. However, this does not occur as the body controls the level of glucose in the blood by a **feedback control system**, just like a thermostat in a refrigerator or oven, so that the pancreas gland secretes much higher levels of insulin than usual. The high level of insulin in the blood stimulates the muscles and liver to withdraw the right amount of glucose from the blood stream to keep the blood glucose levels normal. These higher levels of insulin then have effects in the body that are not normally caused by insulin (Table 2). People with insulin resistance usually have high levels of insulin in their blood when

fasting and after a meal, although some will have high levels of insulin in the blood only when fasting while others will have high levels of insulin only after a meal.

After many years of working at 2, 3 or even 5 times the normal rate, the insulin-producing cells of the pancreas gland in insulin resistant people can "wear out" and die off. Insulin levels fall and blood glucose levels rise through a phase called "impaired glucose tolerance" to the development of type 2 diabetes, a condition that should be preventable (Figure 1).

Figure 1:



Why do some people gain weight easily and then cannot lose it?

In most people with insulin resistance, fat breakdown is still switched off at the usual low level of insulin. It is therefore harder to lower the blood insulin from the high meal peak level in insulin resistance to the low level below which the process of fat breakdown can switch on (Figure 3).

Enlarging fat cells secrete a variety of hormones including **TNF-alpha, Il6** and **resistin**. These hormones from enlarged fat cells act on the muscles to make the muscles more resistant to insulin. The pancreas gland therefore has to secrete even larger amounts of insulin in order to keep the blood glucose levels normal and these higher levels of insulin make fat breakdown even harder to achieve. The fat cells therefore enlarge further and make even more TNF-alpha, Il6 and resistin, starting the vicious outward spiral of weight gain that commonly affects women with the polycystic ovary syndrome. Many women with the polycystic ovary syndrome notice that weight gain occurs easily and that weight loss is difficult, despite diet and exercise.

How does insulin resistance cause PCOS? (Table 2)

The follicles in the ovary are lined by two types of cells, **theca cells** and **granulosa cells**. Theca cells take cholesterol out of the blood stream and, after a series of chemical steps, turn it into **androstenedione**, a weak male hormone. Theca cells pass the androstenedione on to the adjacent granulosa cells where it is converted into oestrone, a weak oestrogen or female hormone and then into oestradiol, a strong oestrogen or female hormone (Figure 2).

In women with a genetic susceptibility, high levels of insulin in the blood stimulate an enzyme called **cytochrome P450c 17-α** in both the ovaries and the adrenal glands to produce increased amounts of

male hormones (Figure 2). The excess of male hormones in the polycystic ovary syndrome therefore comes from both the ovaries and the adrenal glands. This is why removal of the ovaries does not solve the problem of excess body hair and acne and another reason why the name "**the polycystic ovary syndrome**" is stupid! The high levels of male hormones change the functioning of the fertility clock.

The high level of insulin in the blood stream also stimulates the pituitary gland to produce increased amounts of LH. It does not, however, stimulate a surge in LH secretion. The higher baseline levels of LH stimulate the same enzyme, cytochrome P450c 17-alpha to produce even more male hormones, but only in the ovaries not the adrenal glands.

The developing follicle and egg do not become sensitive to stimulation by LH until the follicle has grown to a diameter of 9.5 mm. High levels of insulin, however, cause the developing follicle and egg to respond to stimulation by LH at an earlier stage of development, at 4mm. diameter rather than at 9.5 mm. As no further development of the follicle is possible after LH stimulation, the growth of the follicle is therefore stopped at a diameter of 8 mm and the follicle is left too immature to ovulate (Figure 2).

Figure 2: Insulin stimulation of ovarian and adrenal male hormone secretion

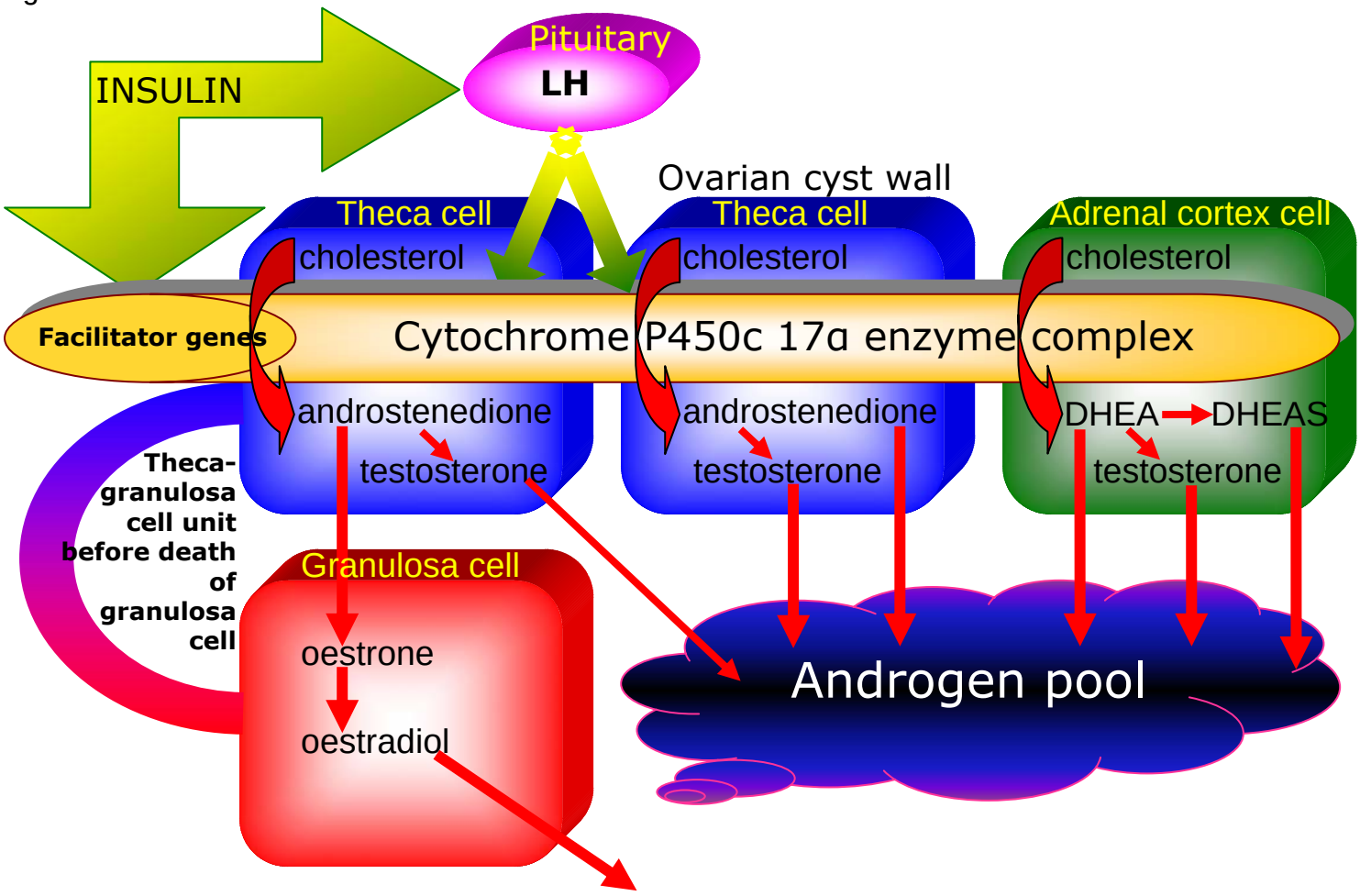


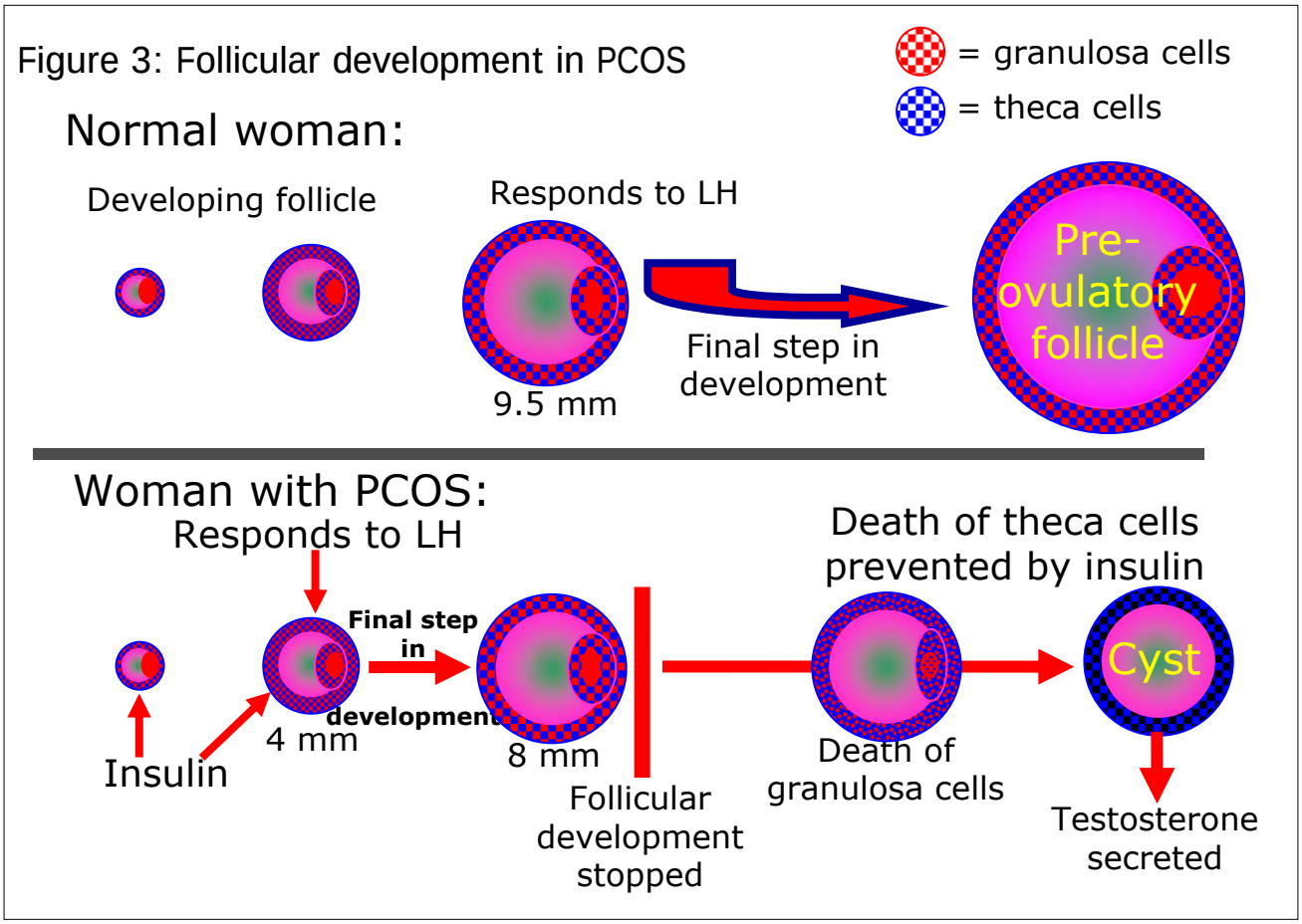
Table 2:

Effects of high blood insulin levels		
Area of action	**Effect** (stimulatory unless specified)	**Comments**
Energy storage	Glucose uptake in muscles	Defective in insulin resistance. Therefore high levels of insulin are necessary for glucose handling
	Glycogen formation in liver	
	Glucose uptake in fat cells	
	Inhibition of fat breakdown	Occurs at low insulin levels
"Hormonal" effects	Stimulation of adrenal male hormone production	Not universal, depends upon woman having other genes for this response.
	Stimulation of ovarian male hormone production	
	Sensitises follicle to respond to LH at 4 mm rather at 9.5 mm diameter	Follicular development stopped at 8 mm diameter
	Inhibition of programmed death of theca cells	Cysts lined by theca cells
	Stimulation of pituitary LH secretion	Cause of elevated LH
	Reduction of liver SHBG production	Increases active male hormone
	Stimulates the conversion of testosterone to dihydrotestosterone, increasing hair growth & acne	Probable explanation of excess hair growth in women with normal testosterone levels
Other liver effects	Suppresses HDL cholesterol levels	Increased artery blockage
	Increases plasminogen activator inhibitor type 1	Increased risk of clots
Miscellaneous	Acanthosis nigricans: dark skin on neck & arm pits	Severe insulin resistance
	Skin tags arm pits, thighs, belt and bra lines	Moderate insulin resistance

How and why do cysts develop in the ovaries?

When ovulation does not occur for some reason, both the theca cells and the granulosa cells lining the follicle should self-destruct by a process of "programmed cell death", known medically as **apoptosis**. This causes the follicle to collapse and disappear. In the polycystic ovary syndrome the granulosa cells self-destruct normally after failure of ovulation but the theca cells do not die because they are kept alive by high levels of insulin, preventing the follicle from collapsing, resulting in a cyst (Figure 3).

After failure of ovulation and after death of the granulosa cells, the theca cells that should have died continue to produce androstenedione. As there are no longer any adjacent granulosa cells to convert the androstenedione into estrogens, the theca cells convert the androstenedione into testosterone (Figure 2). In other words, for whatever reason a woman may have an ovarian cyst, the lining of the cyst will produce testosterone in most cases.



Treatment of the Polycystic Ovary Syndrome

The aims of treatment in PCOS are to improve the skin and to restore regular ovulation and, in the case of insulin resistant women, also to prevent diabetes, heart disease, strokes, clots in the legs and cancer of the womb. For the vast majority of women with PCOS, these aims can be achieved by lowering the insulin levels (Figure 4). Insulin levels can be lowered by exercise, diet, weight loss and the diabetic medication metformin. Insulin levels are increased by stress, lack of exercise, weight gain and hormonal contraceptives.

Oral contraceptives in PCOS

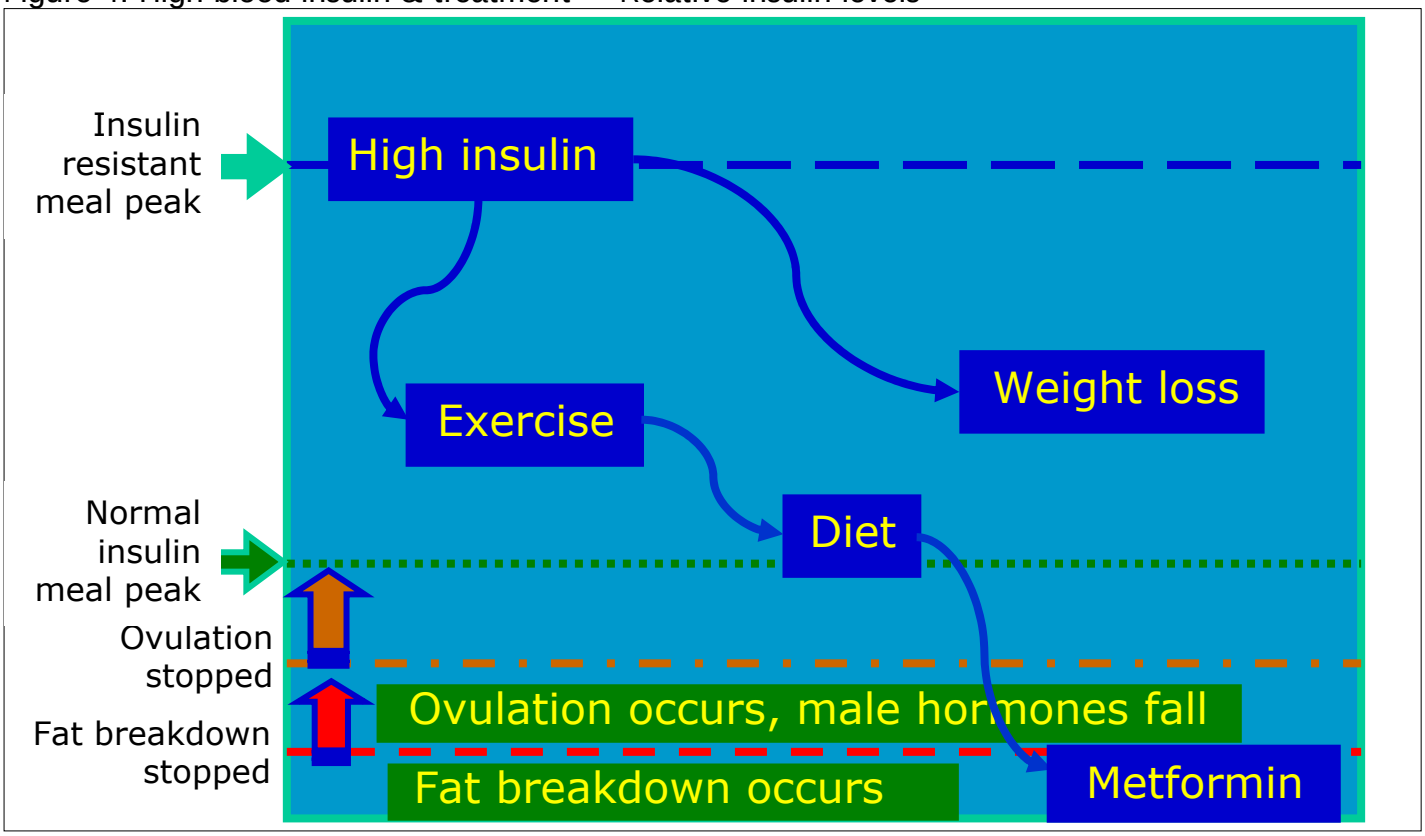
Oral contraceptives (OCPs) have been widely used in the treatment of PCOS. OCPs generally give predictable and consistent withdrawal bleeding, removing an important source of frustration. They reduce ovarian male hormone secretion, usually improving acne and excess hair, although they do not reduce adrenal gland male hormone secretion. Above all, they provide reliable contraception. There is no strong evidence that any one OCP is more effective on the skin. OCPs also protect against the build up of excess lining of the womb which can cause erratic and prolonged bleeding. However, the link between PCOS and cancer of the lining of the womb has not been proven.

Recently, leading doctors in PCOS have expressed concern about the short and long term safety of OCP treatment of PCOS[1]. OCPs make insulin resistance worse and further increase the tendency for clots in PCOS. The OCP **Yasmin** elevates blood glucose levels by 19%[2]. Type 2 diabetes (T2D) was 60% more

prevalent in women currently taking OCPs than in women who had never taken OCPs in a study of 98,500 US nurses

Women with PCOS must therefore be warned of the risks of deteriorating glucose tolerance and diabetes with OCP use. Before a woman with PCOS starts an OCP, a glucose tolerance test (GTT) should be performed and then repeated after six months of treatment. If a woman has impaired glucose tolerance or diabetes, OCPs should not be used. If glucose tolerance deteriorates on an OCP, it should be stopped.

Figure 4. High blood insulin & treatment — Relative insulin levels



Diet, exercise and weight reduction in PCOS.

Exercise is probably the most effective method of lowering insulin levels. Diet and weight reduction are also effective in lowering insulin levels and, hence, improving ovulation and conception in PCOS. Often only 3 to 5 Kg weight loss will restore regular menstruation, ovulation and fertility[3,4]. All women with insulin resistant PCOS should exercise regularly as one of the most important parts of treatment.

The best diet for PCOS is debated. If a woman with PCOS is overweight, a reduction in food energy intake is important. Slowly digested or **low glycaemic index** (low GI) carbohydrate foods stimulate less insulin production than high GI carbohydrate foods, helping partially with the problem of high insulin levels. However, some women will not lose weight until total carbohydrate intake is reduced and the **CSIRO Total Wellbeing Diet** is a safe method of reducing carbohydrate intake.

Metformin in PCOS.

Metformin is a drug that has been used for the treatment of diabetes for 50 years. It is found in a common European weed! It makes the insulin response in muscles and the liver last longer so that less insulin is needed to stimulate glucose storage in the muscles and liver. The body therefore automatically lowers the insulin level.

Metformin was first found to be effective in restoring normal menstrual cycles and fertility in 1994. Metformin will usually establish regular menstruation and ovulation within 4 to 6 months in both overweight and normal weight women with PCOS. A British study showed metformin to be at least as effective as an OCP in the improvement of increased hair growth in PCOS[5]. Metformin lowers insulin levels, reducing insulin-stimulated adrenal and ovarian male hormone production, reducing insulin interference with maturation of ovarian follicles and eggs and allowing fat breakdown to occur.

However, metformin should not be used in PCOS without a diet and exercise programme in order to maximise the fall in insulin levels (Figure 3).

Compared to clomiphene citrate in normal-weight women with PCOS, metformin had a similar ovulation rate (63 vs 67%) but superior pregnancy rates (69 vs 34%) and miscarriage rates (10 vs 38%)[6]. As metformin was ceased at diagnosis of pregnancy, it would appear that the reduction in prevalence of miscarriage results when metformin is taken prior to rather than after conception. In a carefully controlled trial over 6 months comparing laparoscopic ovarian diathermy ("**golf-balling**") with metformin in PCOS women who had not responded to clomiphene, metformin had an identical ovulation rate (55%) but superior pregnancy rates (19 vs 13%) and miscarriage rates (15 vs 29%)[7].

Metformin, with exercise and diet, will restore fertility in most women whose PCOS is due to insulin resistance, reducing the need for more costly, invasive and emotionally stressful assisted reproductive interventions.

In two studies, metformin taken before and during pregnancy dramatically reduced the high miscarriage rate seen in PCOS from 42% to 9%[8,9]. Metformin has now been used extensively during pregnancy for four years without apparent ill-effects but with reduced rates of gestational diabetes[10] and severe hypertension in the 3rd trimester. Metformin occasionally reduces absorption of vitamin B12 and B12 levels should be checked in pregnancy.

Metformin commonly causes nausea and diarrhoea, with occasional vomiting. It should be introduced slowly over 4 to 6 weeks to a dose of 1500 mg/day. Gut side-effects are more commonly associated with the lunch dose or with poor dietary compliance as metformin partially blocks glucose absorption from the gut. Gut side-effects often do not recur after a 2 month break from therapy. At long last, slow-release metformin is available and causes 80% fewer gut side-effects.

Pioglitazone and rosiglitazone are other insulin-lowering drugs which are effective in PCOS but they are expensive, cause weight gain and cause reduced litter sizes in animals. They probably should not be used in PCOS until further clinical trials have been completed.

Table 3. Anti-male hormone drugs (anti-androgens) in PCOS

Anti-androgen	Dosage	Advantages	Disadvantages
Spironolactone (Aldactone, Spiractin)	25–100 mg twice daily	Inexpensive, preserves bone density, does not aggravate insulin resistance	Frequent vaginal bleeding in 25-30% — may need an OCP. Periods occasionally stop. High blood potassium, particularly in older women or with NSAIDs (some pain killers)
Cyproterone acetate (Cyprostat, Androcur)	25–100 mg daily		Aggravates insulin resistance Weight gain, depression Lowers oestrogen level — **must use** an OCP
Flutamide – blocks androgen uptake & receptor (Eulexin, Flutamin, Fugerel)	62.5-250 mg daily	Improves fertility clock function, lipids, insulin resistance	Expensive, toxic to pregnancy — **must use** an OCP
Finasteride - 5α-reducyase inhibitor (Propecia, Proscar)	1-5 mg daily	Equal to or slightly less effective than flutamide	Expensive, ? toxic to pregnancy — **must use** an OCP

Anti-male hormone drugs (anti-androgens) in PCOS

Whilst acne will clear in 8-10 weeks and excess hair will greatly improve over 12-18 months in many women with PCOS taking metformin or an OCP, some will have an insufficient response and will need the addition of an anti-androgen or anti-male hormone drug. Anti-androgens either block the effect of testosterone or stop the conversion of testosterone to dihydrotestosterone, the male hormone that has the most effect on the skin. They are helpful in the improvement of acne, excess hair and scalp hair loss in PCOS. They are generally of equal efficacy but have individual problems (Table 3). Scalp hair loss should be treated early and intensively as it is the most difficult male hormone effect to reverse.

Infertility in PCOS

Infertility in PCOS caused by fertility clock problems

Most women in this category will have an immature hypothalamic fertility centre, an eating or exercise disorder and/or extreme stress. Regular ovulation will usually return after reduction in excessive exercise and resumption of normal nutrition. Relief of stress and/or cognitive behaviour therapy can slowly restore ovulation but removal from a stressful working environment can rapidly restore fertility. Clomiphene citrate will be effective if oestradiol levels are normal but ineffective if low.

If a woman is underweight, ovulation induction and/or IVF will be effective but pregnancy should not be induced in a malnourished woman as the baby's brain and physical development may be reduced.

Infertility in insulin resistant PCOS

If conception has not occurred with exercise, weight loss and metformin, other causes of infertility should be excluded and the following treatments implemented in a stepwise fashion.

Clomiphene citrate (CC) (Clomid, Serephene)

Clomiphene citrate should be added to metformin for six cycles as these drugs work together. CC has an anti-oestrogen effect on the fertility clock, increasing LH and FSH levels, with an increase in ovarian follicles reaching ovulation[11]. In PCOS, CC has an ovulation rate of 60-85% and pregnancy rate of30-40%[12]. CC is low cost, simple to administer and has limited, dose-related side effects[13].

Ovulation induction in PCOS

Ovulation induction uses synthetic forms of LH and FSH (known as gonadotrophins) and has a high success rate in PCOS[14] but carries an increased risk of multiple pregnancies. Women with PCOS are particularly susceptible to the ovarian hyperstimulation syndrome (OHSS) by gonadotrophins. Hence gonadotrophins should only be used by an expert, monitoring treatment carefully with ultrasound and blood tests. The risk of the ovarian hyperstimulation syndrome can be reduced by treatment with metformin.

Laparoscopic ovarian diathermy (LOD) in PCOS

Laparoscopic ovarian diathermy ("**golf-balling**") is indicated only after failure of conception with the above treatments and has ovulation and pregnancy rates of 70% and 55%[15,16]. LOD is also indicated in the uncommon problem of bilateral ovarian pain in PCOS. LOD releases male hormones stored in the cysts and reduces the number of male hormone-producing theca cells. Each ovary is punctured 6-10 times. Excessive punctures can destroy too many eggs and cause of ovarian failure. Adhesions are fortunately uncommon but can block access of the egg to the fallopian tube.

IVF in PCOS

IVF is now reserved as a last resort in the treatment of infertility in PCOS, particularly in those insulin resistant women with high oestrogen levels because of the risk of ovarian hyperstimulation.

Investigations in PCOS

Doctors perform a variety of tests on women with PCOS and most of these are briefly described in Table 4. Many doctors no longer perform ultrasound examination of the ovaries for diagnosis or monitoring treatment of PCOS. Ultrasound results rarely alter the diagnosis or treatment.

Every woman with PCOS ***must*** have a glucose tolerance test (GTT) at the time of diagnosis to check that she does not have impaired glucose tolerance or diabetes. Insulin measurements during a GTT will usually determine if the woman has insulin resistance as the cause of her PCOS.

Table 4: Investigations in PCOS

Investigation	Results	Comments
Pelvic ultrasound — vaginal better than transabdominal	Polycystic ovaries Thickened lining of womb	Not necessary for diagnosis Useful in prolonged or heavy bleeding
Sonohysterogram (ultrasound with water in the womb)	Thickened endometrium, polyps	Useful in prolonged or heavy bleeding
s. oestradiol	Often low in disorders of the fertility clock or at time of menstruation	Low level raises possibility of an eating or excess exercise disorder
s. progesterone	Elevated after ovulation	Must be measured in 2nd half of cycle
s. 17~hydroxyprogesterone	Elevated in congenital adrenal hyperplasia	Must be measured in 1st half of cycle
s. LH, s. FSH	Low to normal in disorders of fertility clock	LH/FSH ratio of no diagnostic value
s. total testosterone	Often elevated in PCOS	
s. free testosterone	Often elevated in PCOS	Assay unreliable, SHBG not measured
Sex hormone binding globulin (SHBG)	Often depressed, < 35nmol/L = insulin resistance. Elevated by OCPs. Used in calculation of Free Androgen Index.	Mandatory — most reliable measure of insulin resistance, less affected by exercise than s. insulin but useless if on oral contraceptives.
f. glucose	> 5.9 mmol/L = deteriorating glucose tolerance	Misses 80% of PCOS women with impaired glucose tolerance and diabetes
Glucose tolerance test (GTT)	Use international standards for interpretation	Mandatory — detects all PCOS women with impaired glucose tolerance and diabetes
GTT with insulin levels	Detects 80% of PCOS women with insulin resistance	Insulin assays difficult, unreliable. Results not standardised. Useful in progress assessment.
Fasting blood fats	Frequently abnormal	Predicts heart attack and stroke.

Contraception in PCOS

Many women with PCOS, because of infrequent periods and their misperceptions, believe that they are severely infertile and do not need contraception. Many do not believe that they may ovulate within 4-6 weeks of commencing metformin. They need to be fully informed about their risk of pregnancy and their difficult choices in contraception.

The ideal contraceptive for women with PCOS should be safe, simple, convenient and without complications or aggravation of insulin resistance. **It does not exist!**

Condoms and other barrier methods are seen as an anti-infective agent and, hence, a necessity by some women but meddlesome and messy by others.

Oral contraceptives are convenient but have the significant disadvantages described earlier. Sequential OCPs do not arrest follicle development until the oestrogen dose rises and, hence, lead to the development of small ovarian cysts in many women. Progestogen-only OCPs lead to diabetes more quickly than combined preparations in women who have had gestational diabetes and are likely to have a similar effect in women with PCOS. OCPs aggravate blood clotting problems. If a woman has a problem with the fertility clock, switching the clock "off" with an OCP may simply delay restoration of normal cyclic ovulation. The era of prescribing an OCP to "**regulate your cycle**" has finished!

The Implanon implant also disrupts the fertility clock. It aggravates insulin resistance and can cause weight gain. Injectable medroxyprogesterone acetate (Depo-Provera) is worse, often causing considerable weight gain.

The Mirena intrauterine device is the ideal choice for a woman after her first pregnancy but some gynaecologists prefer not to insert anything into the cavity of the uterus in a woman who has never given birth.

Prolonged or heavy bleeding in PCOS

Prolonged or heavy bleeding in women with PCOS is usually due to a build up of the lining of the womb that has not been controlled by progesterone which is only secreted if ovulation has occurred. Although OCPs have traditionally been used to control this problem, establishment of regular ovulatory menstrual cycles with exercise, weight loss and metformin is generally as effective as progesterone secretion will occur after each ovulation.

A very thin lining of the womb can also cause bleeding. This occurs in oestrogen-deficient states such as fertility clock problems. If the blood oestradiol is low, replacement may be necessary to protect the bones from osteoporosis.

A pelvic ultrasound ± a sonohysterogram will detect generalised or localised thickening of the lining of the womb. If a woman has localised thickening, she should have a hysteroscopy, a view into the womb with a flexible light, and possibly a "D and C" (scraping out of the lining of the womb) to exclude cancer of the lining of the womb and to clear away any polyps.

Prolonged lack of menstrual bleeding in PCOS

Prolonged lack of menstrual bleeding is often due to oestrogen deficient states such as fertility clock problems, prompting the difficult decision as to whether a woman should have oestrogen replacement or simply wait in order to allow recovery from weight loss. A pregnancy test should be performed and spironolactone stopped.

In women with prolonged lack of menstrual bleeding but with normal oestradiol levels and who wish to avoid OCPs, the endometrium should be shed every 3 months by the administration of an effective progestogen such as norethisterone acetate (Primolut N) 2.5 mg for 14 days.

Support for women with PCOS

There are several US-based web sites providing emotional support and information for women with PCOS. Australia has its own patient-orientated organisation — the **Polycystic Ovarian Syndrome Association of Australia** (www.posaa.asn.au).

Conclusion:

Every woman with PCOS should have the cause of her problem determined. If the PCOS is due to insulin resistance, she should understand her risks of diabetes, heart attack, stroke and blood clots and be tested for those risks. She should understand her treatment options, including the risks of treatment. Her diabetes and vascular risk factors should be assessed regularly.

Treatment of your particular cause of PCOS will result in better cosmetic, menstrual, reproductive and long term outcomes. There is no longer any place for the "**one-size-fits-all**" approach to the treatment of women with PCOS.

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