



POLYCYSTIC OVARIES / OVULATION DEFICIENCIES

Ovulation problems are a common cause of sub-fertility and gynaecological problems. To understand problems and difficulties with ovulation it is important to understand how normal ovulation works. Ovulation is defined as the production of an egg, preferably on a cyclical basis. This monthly production of an egg which allows pregnancy in the female is controlled by a number of factors. The steps involved are:

1. A higher thinking centre of the brain (**the hypothalamus**) sends a messenger chemical called a hormone to a gland in the centre of the brain (the pituitary gland). This messenger chemical is called GnRH and its role is to release a second set of messenger hormones from the pituitary gland which will travel to the ovary.

2. The **pituitary gland** is a small 1½ cm diameter gland situated in the centre of the brain. It releases hormone messengers that control many functions in the body such as the thyroid gland, the adrenal gland, and breast milk production. It releases two important hormones which control both egg production and release in the ovary:

to - **FSH (follicle stimulating hormone)**. This messenger hormone travels from the pituitary gland to the ovary and tells the ovary to grow an egg or eggs.

to - **LH (lutening hormone)**. For 2 days out of every 28 days this hormone is produced in large quantities and travels from the pituitary gland to the ovary and tells the ovary to ripen and then release the egg. LH levels only increase in the bloodstream 36-40 hours prior to egg release. The sudden spike of LH released by the pituitary gland is called a "surge". It's rather like a "sneeze" of hormone being released. Daily blood levels can be used in patients to predict this LH surge and therefore predict the time of egg release to within a couple of hours. This technique is widely used to help infertile patients become pregnant by telling them when to time their intercourse or artificial insemination.

3. All the eggs present in the **ovary** for a woman's lifetime are actually produced when she is still a foetus inside her mother. As she enters puberty she has approximately 400,000 eggs in her two ovaries. When all the eggs are used up and there are none left to proceed to maturity each cycle, the female goes into menopause. This happens at an average age of 52 years.

From puberty, at the start of each menstrual cycle 30 to 100 eggs are stimulated by the release of FSH from the pituitary gland. In the context of the normal 28 day cycle this usually occurs between Day 1 and Day 5 of the cycle, often the period is still occurring. Each of the eggs develops in a very small cyst called a follicle. These follicles all begin to grow under the influence of FSH. However, it would clearly be very undesirable for 30 to 50 eggs to be released every cycle. This would make the risks of multiple pregnancy far too high. The body and the ovary therefore have a mechanism of selecting only one (and sometimes two) follicles to become the selected egg which will grow onto maturity for that month. This process of egg selection and its subsequent growth to a mature egg occurs between Day 5 and Day 12 of the average 28 day cycle. As this dominant follicle and egg grow, the other numerous little follicles which started to grow fade away and the primitive eggs die off, never to be used.

During this phase of egg development and maturation, cells in the wall of the developing follicle/cyst start to produce a hormone called oestrogen. Oestrogen is the most important female hormone and it is possible to measure its daily rise in the bloodstream from Day 5 to Day 14 in parallel with the egg development. Typically a single follicle producing a single egg will have a peak oestrogen level about one day prior to ovulation of 400- to 1400 p.mols per litre.

4. **Ovulation** - the release of the now mature egg occurs usually between about Day 12 and 15 of the average 28 day cycle. The pituitary gland releases a rapid spike of LH messenger hormone which travels to the ovary and starts a complex series of chemical actions which ripen the egg, detach it from the wall of the cyst/follicle in which it is growing so that it is now floating free in the fluid in the follicle. Finally the follicle splits open to release the egg. The egg is hopefully picked up by the waiting fallopian tube and if intercourse or insemination occurs around this time, sperm and egg may meet together in the fallopian tube and a pregnancy may result.

5. After ovulation the follicle reforms and the cells in the lining of a follicle change their chemical structure and begin to produce a hormone called progesterone. The follicle which has just released the egg is now called a **corpus luteum**. Progesterone is a very important hormone which travels from the corpus luteum to the uterus and changes the lining of the uterus preparing it to receive a pregnancy. This second half of the menstrual cycle is therefore called the luteal phase of the menstrual cycle and would typically run from Day 14 to Day 28 of the normal cycle. If the female does not become pregnant in this particular cycle the corpus luteum cyst will degenerate around 14 days after ovulation (Day 28 of the cycle) and as the progesterone levels drop the lining of the uterus becomes unstable and the period will begin.

If however pregnancy has occurred the pregnancy itself begins to send special hormonal messengers to the corpus luteum telling it not to degenerate. The corpus luteum continues to produce progesterone past Day 28 of the cycle and no period occurs. The lack of the menstrual period therefore serves as a marker that the patient may be pregnant and several days later a pregnancy test can be performed.

DISORDERS OF OVULATION

Keeping in mind the preceding basic explanation of how the menstrual cycle and ovulation works it is now possible to understand how ovulation can fail or become unreliable. The following ovulation disorders can therefore occur:

1. The higher centres of the brain do not send GnRH messenger to the pituitary gland. This is probably a common form of ovulation failure and may be particularly precipitated by such things as stress, diet, and possibly excessive exercise.

2. The pituitary gland (a) Does not send messenger hormone FSH to the ovary to tell it to grow eggs. This often occurs in association with the higher brain centres failing to send down GnRH hormone which releases FSH. However there are different forms of pituitary failure e.g. tumours, radiation damage, damage due to excessive blood loss or trauma and absence of the pituitary gland as a baby. (b) The pituitary gland sends mixed messages to the ovary with the wrong amounts of FSH and LH acting as conflicting messengers. The ovary is therefore unable to grow a mature egg in a logical and organised fashion. This form of ovulation disorder is commonly called polycystic ovary disease and is very common. It is discussed later in this information sheet.

3. The ovary is absent or has no eggs. Some patients are born without ovaries. When the ovary runs out of eggs menopause occurs. This can sometimes occur in very young patients. If the patients are younger than 35 years they are described as having premature menopause. Sometimes the ovaries will have a small number of eggs left but be very resistant to the influence of FSH telling the eggs to grow. This condition is very difficult to pick from premature menopause and is called resistant ovary syndrome.

4. Other influences which can upset egg production include:

(a) Diseases of other glands e.g. the thyroid gland, adrenal gland, or diabetes or sugar intolerance.

(b) A special sort of pituitary tumour called a prolactinoma. Prolactin is the hormone which produces breast milk. Prolactinomas grow in the pituitary gland and the hormone they produce reduces the production of FSH and therefore prevents ovulation.

(c) Exercise. Excessive levels of exercise e.g. marathon training or excessive gym work increase the level of chemicals called endorphins in the spine and brain. These have the effect of dampening FSH output by the pituitary gland. The ovary therefore receives significantly reduced messages telling it to grow and release an egg.

(d) Drugs and medicines. A wide range of these can inhibit or change ovulation. If you are on a medication it is best to consult your doctor and ask if this medication could specifically affect ovulation.

(e) Ovarian conditions such as cysts and endometriosis can sometimes interfere with the ovaries response to the messages it receives from the brain and the pituitary gland thereby preventing orderly egg growth and ovulation.

MENSTRUAL CYCLE CHANGES AND DISORDERS OF OVULATION

The commonest feature of disordered ovulation is change in period frequency and timing. The following changes in the menstrual cycle are indicative of disordered ovulation:

Amenorrhoea:

This is the medical term for an absence of periods usually for six months or more. Occasionally there are uterine disorders that can cause a loss of periods but generally it implies that the ovary is not making an egg and therefore the uterus is receiving no hormonal messages from the ovary as the normal cycle of ovulation commences.

Oligomenorrhoea:

This means infrequent periods with an increased time span between them, often two to four months. It is possible that patients who only get three to six periods per year are occasionally ovulating but in many cases the irregular bleeding which occurs is anovulatory type bleeding where there is a small amount of oestrogen thickening the lining of the uterus but this is not associated with mature and complete egg development.

Short Cycle/Deficient Luteal Phase:

Some patients may have shortened menstrual cycles especially where the second part of the cycle after ovulation is shorter than it should be. This is termed deficient luteal phase and it implies that the uterus does not have enough time to prepare itself to receive a pregnancy. Luteal phase deficiency is often associated with lowered progesterone output in the second part of the cycle. It is more common in patients who have menstrual cycles of less than 25 days in length.

POLYCYSTIC OVARY DISEASE (PCOD)

Polycystic ovary disease is a poor term which often covers a spectrum of ovulation problems. Other terms for PCOD are Stein-Leventhal Syndrome (although this is now rarely used) and polycystic ovarian syndrome (PCOS) which is probably the best descriptor.

EXPLANATION OF PCOS/PCOD:

PCOS is essentially a disorganisation of ovarian function. Normal regulation of orderly egg growth and release in the ovary is disrupted by a number of influences from within the ovary and from outside it. Messenger hormone from the pituitary gland to the ovary is often unbalanced and insufficient to maintain egg growth in a single cycle. 70% to 80% of patients will have high LH levels. LH is the messenger hormone which releases the egg. It is therefore possible that patients with PCOS may prematurely activate their egg release resulting in eggs that are prematurely aged. The higher levels of this LH hormone may also prematurely change the lining of the follicles where the eggs are growing thereby unbalancing hormone production from the follicles and contributing to infertility which is often seen with this condition.

In many patients with PCOS there are increased levels of male-type steroid hormones circulating in the blood. These are produced mainly by the ovaries which are acting in an abnormal way but are also produced in the fat tissue of the body. Many patients with PCOS have obesity as a central problem and the excessive fat tissue contributes to the abnormally high levels of male hormone production. These male hormones contribute to some of the symptoms and signs of PCOS including acne, abnormal hair growth and occasional voice deepening.

If the abnormalities that occur in PCOS are to be understood it is very helpful to have a good understanding of the normal mechanisms of egg growth as described in the first part of this information paper. In the PCOS patient the ovary receives a series of very mixed messages from the pituitary gland. In the normal menstrual cycle each month a large number of very primitive egg cysts begin their development as follicles. Under normal circumstances only one of these will be selected to be "the egg of the month". In the patient with PCOS due to the disorganised communication between the pituitary gland and the ovary and within the ovary itself this process of

appropriate egg selection does not occur. This means that at any one time there may be many small, developing follicles within the polycystic ovary but it will only be on rare occasions that one of these will develop into quite a large follicle which will produce and release a mature egg. Patients with PCOS have disorganised egg development with fluctuating female and male hormone levels. Periods are therefore often irregular and when bleeding occurs it is often irregular amounts of poorly controlled loss which is not a true period which follows the orderly release of an egg. This very disorganised ovary also produces inappropriate amounts of male hormone which contribute further to the problem. Lack of organised egg production means that the messages going back to the pituitary gland are inappropriate. As the pituitary gland is receiving very confusing communications from the ovary this worsens the problem as the pituitary gland sends down more confused messages to an already confused ovary.

As many patients with PCOS have excessive body weight, obesity can be an important factor. The fat tissue has the ability to produce both male and female hormones. Very fat patients can actually produce very large quantities of female hormone. The female hormone (mainly oestrogen) will return to the ovary and have an effect on the ovary like taking the oral contraceptive pill. The oestrogen also has an effect on the pituitary gland and interferes with the pituitary gland's ability to understand how the ovary is functioning. Excessive amounts of fat therefore worsen the problem of uncoordinated ovulation and often contribute to infertility. The female hormones produced in fat may affect the uterus and fat patients are much more likely to have irregular bleeding. Obesity is therefore also a risk factor for cancer of the lining of the womb due to the effect of these female hormones.

There is also a relationship between PCO and sugar intolerance. Patients who have PCO have a higher incidence of adult onset diabetes in later life and a higher chance of diabetes in pregnancy. There is an increasing trend to test PCO patients for sugar intolerance and sometimes treatment with anti-diabetic drugs.

SYMPTOMS AND SIGNS

1. MENSTRUAL PROBLEMS:

(a) Amenorrhoea/Oligomenorrhoea:

As the ovary is not reliably producing an egg, female hormone levels produced by the ovary are often low. The uterus therefore receives very few messages to thicken its lining. As there is no orderly ovulation there is no drop in progesterone levels to trigger a period so bleeding does not occur. Patients with PCOS therefore often have absent or sparse periods.

(b) Heavy periods or irregular frequent bleeding:

This is more common in patients who are obese with PCOS. Sometimes the small and primitive follicles produce enough oestrogen to thicken the lining of the uterus but the compacting and balancing hormone, progesterone, is absent. This can lead to the lining of the uterus becoming thicker and thicker and eventually undergoing a form of pre-cancerous change. This may be associated with quite heavy bleeding or irregular, frequent and even constant bleeding. Patients with this form of bleeding need investigation of the lining of the uterus by hysteroscopy and biopsy to make sure that they are not developing cancerous or pre-cancerous changes.

2. OBESITY:

Obesity will be present in many patients with PCOS. However many patients whose ovaries function in a PCOS way can be quite thin. Obesity can become self-perpetuating with PCOS in that the abnormal hormone levels being produced by the ovary can predispose to obesity. As explained above, once the fat tissue is laid down it then starts to produce female hormone which increases the level of disorganisation in the body's environment which can lead to further obesity. Good weight control and dieting is an effective method of treating PCOS.

3. ACNE AND ABNORMAL HAIR GROWTH (hirsutism):

As described in the preceding section, increased levels of male hormone are produced by the ovary and to a lesser extent by any excess body fat. These increased levels of male hormone travel to receptors in the skin and may trigger an outbreak of acne or spots. Different patients will have different sensitivities to these changes in male hormone so measuring the levels of these male hormones in blood tests is not always predictive of how severe the skin changes will be. Patients also have different abilities to convert the male hormone which is present in blood into more active forms of male hormone which affect the skin and hair follicles of the skin.

Some patients will have their hair follicles activated by these increased male hormone levels and begin to develop excessive hair growth which is called hirsutism. This may occur particularly on the upper lip, chest, stomach and legs and arms. It may also be accompanied by a more coarse hair growth rather than the normal fine female hairs.

4. INFERTILITY AND PCOS:

One of the most common presentations of patients with PCOS is difficulty becoming pregnant. Reading the information above it is easy to understand why. The most common problem associated with PCOS is disordered ovarian function and poor ovulation. This predisposes to infertility. However it must be stressed that there are many patients who have a mild form of PCOS who can become pregnant. Not all patients with PCOS fail to ovulate. Some may ovulate less regularly than a normal 28 day menstrual cycle but on each occasion that ovulation does occur an opportunity to become pregnant exists. Some patients may ovulate only a couple of times a year with PCOS but become pregnant during this time. Other patients who have very mild PCOS may even have a regular 28 day cycle and have only mild difficulty becoming pregnant. They will appear to be ovulating normally and the doctor will only discover that they have very mild PCOS when the ovary is stressed by challenging it with some ovulation inducing drugs.

There may also be an association between endometriosis and PCOS. The theories as to why endometriosis occurs are many but endometriosis would seem to be more common when there is a disordered hormonal environment and inadequate ovulation. There may be an indication to investigate patients with PCOS and infertility for associated endometriosis. Sometimes endometriosis may be increased when higher oestrogen levels occur in association with induced ovulation.

5. PCOS AND DIABETES:

Recent research has shown that there is a link between PCOD and insulin resistance. Insulin is the hormone produced by the pancreas in the body. It is responsible for helping sugar to be metabolised into energy in the body. Patients who have PCOD are therefore more likely to have trouble handling a sugar load. When this occurs the condition is called diabetes. There is now a case for testing some patients with PCOS for early stages of diabetes. Patients with PCOS are more likely to develop diabetes later in life. They are also more likely to develop diabetes during the course of a pregnancy. This is called gestational diabetes. Testing for diabetes should be done on PCOS patients at about 26 - 30 weeks of pregnancy. There is some research to suggest that drugs which help control blood sugar levels can

sometimes improve ovulation in patients with PCOS but these need to be used with caution.

INVESTIGATION OF PCOS:

(a) Hormonal investigations:

Blood tests can be used to measure the levels of FSH, LH and circulating male hormones. The circulating male hormones which can be measured include testosterone, but more importantly is the amount of free testosterone which is not bound to the protein that carries it around in the bloodstream. A male hormone precursor is often raised in PCOS. This is called dihydroepiandrosterone sulphate (DHEAS) and is one of the most commonly elevated male hormones in PCOS.

A significant number of patients with PCOS will have a reversal of the ratio of the FSH and LH levels present in their blood. Normally FSH levels are somewhat higher than LH. In patients with PCOS the LH levels are often higher than the FSH levels. The importance of this is explained in the preceding section *Explanation of PCOS*.

(b) Ultrasound scans:

Patients with PCOS have characteristic findings when a scan (often transvaginal) is performed of their ovaries. The little developing follicles usually sit under the surface of the ovary but do not invade the centre of the ovary. These follicles (which can look like black holes on ultrasound) are usually about 6 to 10 mm in diameter and form a ring around the surface of the ovary. A solid white centre can be seen to the ovary. This sign is called *the pearl string sign* because it looks like a string of black pearls around a white neck. Polycystic ovaries may also seem increased in size on ultrasound scan.

(c) Laparoscopy and hysteroscopy:

Many patients with PCOS, particularly those who are having trouble becoming pregnant will have a laparoscopy. A laparoscopy is an operation whereby the patient is given a short general anaesthetic, a small cut is made in the umbilicus, and a telescope is inserted to look at the pelvic contents including the uterus, tubes and ovaries. At laparoscopy PCOS ovaries look rather like ping pong balls. The white capsule of the ovary is thickened and the ovary is often very rounded. At the laparoscopy, checks will also be made to assess the health of the fallopian tubes and to look for any associated endometriosis.

Hysteroscopy is an operation whereby a fine telescope is used to look inside the cavity of the womb (uterus). This is particularly important where the patient has had significant abnormal bleeding. Abnormal areas in the uterus can be seen and specific biopsies taken to assess for cancerous or pre-cancerous changes.

TREATMENT OF PATIENTS WITH PCOS AND OTHER OVULATION PROBLEMS

Treatment of patients with ovulation problems which are causing menstrual problems will depend mainly on whether the patient wishes to become pregnant or not.

Prior to beginning treatment it is important that the patient is adequately investigated to define the exact cause of the ovulation problem and menstrual disturbance.

In the great majority of cases it should be possible to tell patients why their ovaries are not working properly and why they have some menstrual disturbance.

(a) Treatment for patients who do not wish to achieve pregnancy:

1. No treatment:

If the patient has been thoroughly investigated and understands the cause of her ovulation problem and her absent or deficient periods then no treatment is one option. This means if the patient can continue to have no periods or infrequent periods. There are however two problems with this option.

If no treatment is given the patient will not have any contraception. Patients who do not wish to become pregnant but are sexually active can therefore become pregnant even though their periods may be infrequent or absent. Patients in this situation often have periods of great anxiety when they have been sexually active but are not having any periods. They may be constantly concerned about whether they are pregnant or not.

In patients with no periods, it must be remembered that the ovary is not working properly and is not providing the full quota of the female hormone, oestrogen. Therefore many patients with ovulation disorders and infrequent or absent periods are hormonally deficient for much of the time. This hormonal deficiency is like that of a menopausal lady. This means that patients may be prone to increasing demineralisation and weakening of their bones as well as exposing themselves to an increased risk of heart attack and stroke. There is therefore an argument for hormone replacement therapy in women where their ovaries are working poorly. If hormone replacement is given the hormone deficiency status is reversed. They may feel and function better, have better intercourse and avoid the risks as discussed.

2. Oral contraceptive pill:

Patients who are not having any or many periods and who have been adequately investigated but do not wish to become pregnant may be put on the oral contraceptive pill. The advantages of this treatment are:

- (a) contraception is provided
- (b) regular bleeds occur (although these are not true periods but hormone withdrawal bleeds)
- (c) hormone replacement therapy is achieved
- (d) anxiety about unwanted pregnancies is reduced
- (e) the pill provides a cheap and convenient form of packaging for such therapy
- (f) the lining of the uterus is controlled and the development of serious abnormalities in the lining of the uterus are often avoided.

Almost any of the commercially available oral contraceptive agents can be used. The usual side effects and risks of the oral contraceptives may occur.

For patients with PCOS the oral contraceptive of choice is called Diane-35. This is a relatively new oral contraceptive agent on the Australian market but has been one of the most popular pills in Europe for many years. It contains an oestrogen (ethinyloestradiol) which is the most common oestrogen used in nearly all the oral contraceptive pills. It contains 35 mg of ethinyloestradiol. This is slightly more than some of the ultra low-dose pills on the market which may contain only 30 micrograms of oestrogen. However it is still a lower dose pill when many other commercially available oral contraceptives which may contain up to 50 micrograms of oestrogen. What makes Diane-35 special is the progesterone agent.

Nearly all oral contraceptive pills contain two components. These *combined* oral contraceptives contain oestrogen and a progesterone agent. The progesterone agent used in Diane-35 is cyproterone acetate. This has rather special properties in that it is an anti-male hormone. Cyproterone acetate reduces the conversion of testosterone to its more active forms in areas of the body such as the skin. Diane-35 therefore has the ability to reverse the action of excessive or too active male hormone and reduce problems such as acne and abnormal hair growth. Diane-35 is the oral contraceptive pill of choice for patients with PCOS or patients who have evidence of excessive male hormone activity such as acne or excessive hair growth. It comes in a packet with 21 active pills and 7 sugar pills. It has the usual risks and side effects of any oral contraceptive pill. In Australia it is not available on the NHS and is therefore slightly more expensive than the ordinary pill. Patients with PCOS can sometimes claim the costs from their health funds in view of their medical condition.

3. Other hormonal treatments:

It is not necessary to only use the oral contraceptive pill. Patients can have hormone therapy protocols made for them using either oestrogen and progesterone or progesterone alone. Various commercially available progestones can be used such as Norethisterone (Primolut-N), Medroxyprogesterone (Provera) and the mini-pill preparations. These can be used to regulate cycles and produce more regular and controlled periods. Their place however is quite limited and they are not often used.

A special sort of ovulation disturbance caused by pituitary tumour called a prolactinoma has been previously discussed. The treatment of choice for this condition is a drug called Bromocryptine or a newer one called Dostinix. Its actions can be explained to patients with this relatively rare condition.

(b) Treatment for patients who wish to become pregnant:

Patients with disordered ovulation who wish to become pregnant can have treatment with a number of hormones which will induce ovulation. The success rates with these treatments are very high. Ovulation defects are the most successfully treated area of infertility.

Agents used to induce ovulation:

1. GnRH

As previously explained GnRH is the messenger hormone which travels from the higher centres of the brain to the pituitary gland. It is possible to administer GnRH in small continuous doses via a syringe pump. This pump is normally attached to the patient's arm, leg or abdomen and connected to a needle which is permanently left in place. In this way small continuous doses of GnRH are pumped into the blood stream. These can then go to the pituitary gland and encourage it in turn to send messenger hormone (FSH and LH) to the ovary.

In practice GnRH is very rarely used. The reasons for this are:

- (a) it is expensive
- (b) the doses are complex
- (c) the patient needs a permanently inserted needle attached to a syringe pump for 7 to 14 days
- (d) it is often easier to use other agents such as clomiphene or give injections of FSH and LH which will go directly to the ovary

than indirectly attempt to influence the ovary through the pituitary.

2. Clomiphene citrate (Serophene or Clomid)

This is one of the oldest ovulation induction agents available. It is a steroid-like substance which binds to oestrogen receptors. Oestrogen receptors are protein sites in the body which bind the female hormone oestrogen and then trigger the response to oestrogen in the individual cells and tissues of the body. It is only through these receptor sites that the hormones can exert their influences throughout the body.

When clomiphene binds to oestrogen receptor sites in the pituitary gland in the brain it prevents the pituitary gland receiving any oestrogen messages from the ovary. The pituitary gland is then dummied into believing that the ovary is not working and therefore proceeds to pump out more FSH to tell the ovary to work harder. This FSH travels to the ovary and induces egg growth and development.

Serophene/Clomid comes as 50 mg tablets. The normal dose is a half to one tablet per day for five days but up to three tablets per day for five days can be given. If a patient is having disturbed ovulation with roughly 28-day cycles it would normally be given from Day 4 to Day 8 or Day 5 to Day 9 of the cycle. In patients who do not have periods (or only have them infrequently) it can be given for five days. Ovulation usually occurs five to eight days after the last tablet.

It is often sensible to combine treatment with some monitoring of the cycle to assess how well the Clomid has worked and to define the time of egg release. Patients can have daily blood tests which begin usually about five days after the last tablet. These blood tests can predict the time of egg release to optimally time intercourse or artificial insemination.

Side effects of Serophene/Clomid relate mainly to the fact that it blocks the action of the female hormone oestrogen. The patient may get a dry vagina, mood changes, hot flushes, headaches and breast discomfort. These side effects are often minor and will disappear near ovulation. The multiple pregnancy risk has been quoted at 4 to 8% of all pregnancies. Clomid is a relatively weak fertility agent and is rarely associated with high-order multiple pregnancies. Quadruplets and triplets have been reported after treatment but the majority of multiple pregnancies are twins.

Serophene/Clomid works best in patients who have minor disorders of ovulation. In these patients it will induce ovulation 60 to 70% of cases with pregnancy rates of up to 50%. In patients who have more severe ovulatory disturbance e.g. absent or very infrequent periods the response will be much less. Ovulation will only be induced in 30 to 40% of patients and pregnancy rates are usually in the order of 25 to 30%. Many of these patients will need more sophisticated treatment than Serophene/Clomid provides.

The advantages of Serophene/Clomid therapy are:

- (a) it is cheap
- (b) it is simple to take 5 or 10 tablets over 5 days
- (c) it is convenient
- (d) it has a low incidence of side effects
- (e) it has a low incidence of multiple pregnancies
- (f) it does not require complex or sophisticated monitoring.

3. FSH

FSH is the hormone which travels from the pituitary gland to the ovary, telling the ovary to grow and mature eggs each month. FSH is available in ampoules. It can be given by daily injection. Each ampoule has a dose of 75 or 150 units.

Treatment with FSH is the most powerful and reliable treatment for patients with ovulation disorders. Pregnancy rates of up to 15 to 20% per treatment cycle can be expected. The overall pregnancy rate for patients who need and use this treatment is in the order of 70% per patient. Unlike Clomid, the more serious the ovulation disturbance the more likely FSH is to work.

The aim of giving FSH treatment is to mimic the normal egg development during the menstrual cycle. FSH injections are therefore given each morning as an intramuscular injection. It is best to start with the lowest dose of FSH per day (using 75 units per day). These doses are used for 4 to 6 days at a time. The ovarian response is determined by measuring oestrogen levels in the blood. When the oestrogen begins to rise the FSH successfully growing an egg or eggs. If there is no response to a dose of FSH in 5-6 days of injections the dose will be increased. The normal dose increments are 75 units, 112 units, 150 units and 225 units per day. Most patients respond with 75 to 150 units per day. However it is very important that increments are only made cautiously. The ovary is very sensitive to FSH dosage and too much FSH rapidly grows multiple eggs. It is important that patients receiving FSH therapy start with the lowest possible dose and the increments in the dose are only made gradually after a trial of a particular dose for at least five to seven days.

When the blood levels of oestrogen rise to a point consistent with the mature egg an ultrasound scan will be done. The size and number of follicles (egg containing cysts) growing on the ovary can be measured. Follicle sizes of 14 to 20 mm usually indicate a mature egg. It is important to know the number of follicles present to minimise the risk of a multiple pregnancy.

If conditions are favourable, release of the egg is then initiated. The egg is released by giving an injection of hormone called Human Chorionic Gonadotrophin (HCG). HCG is a natural pregnancy hormone. It has a structure almost identical to LH and can therefore be used to trigger egg maturation and release. A dose of 2,000-5,000 units of HCG is given as an intramuscular injection. Egg release will occur 36 to 44 hours later. The HCG injection is therefore given 1½ to 2 days prior to intercourse or insemination.

HCG is also used to provide support to the ovary in the second half of the cycle after ovulation has occurred. As the first half of the cycle has been artificially created with FSH injections it is important to support the second half of the cycle. If this is not done there will be insufficient progesterone production and the pregnancy will find it very hard to implant as the corpus luteum undergoes premature degeneration. HCG injections 3 days and 7 days after ovulation will prevent this and provide appropriate early pregnancy support.

Side effects of FSH treatment are few. FSH is a natural hormone and apart from the inconvenience of daily injection has little side effects. The major risks of FSH therapy are those of multiple pregnancy and overstimulation. Multiple pregnancy rates are up to 20% of all pregnancies produced by this treatment. If FSH treatment is not strictly controlled it is treatment with this ovulation drug which causes high order multiple pregnancies such as quins and sextuplets. The combination of oestrogen levels and ultrasound scan should be used to assess the likely number of eggs being released by the HCG injection. If more than two or three eggs are likely to be released, cancellation should be discussed with the patient.

It is very difficult in some patients, especially those with PCOS to choose the correct dose of FSH. If too little FSH dosage is used then no eggs grow. If the dose is increased only a very small amount sometimes many eggs grow on the ovary, often as many as 15 or 20. In some patients with PCOS there is no correct dose. Some patients with PCOS therefore have a very high risk of multiple pregnancy when FSH is used. A version of the IVF programme called GIFT is sometimes used to reduce this. After the HCG injection is given all the maturing eggs are sucked out of the ovary whilst the patient is asleep and having a laparoscopy. Two or three of the best eggs are then selected, mixed with the husband's sperm and put straight back into the fallopian tube while the patient is still asleep. In this way the patient has a very high chance of becoming pregnant (35% per attempt) but the risk of multiple pregnancy is controlled by only replacing two or three eggs and removing the rest.

If too much FSH is given the patient may develop over-stimulation syndrome. This is characterised by sore ovaries and a very swollen abdomen. It occurs about 7 to 10 days after ovulation and mostly in patients who are pregnant. It is actually very rare in patients who are having ovulation induction with FSH and then intercourse. Usually these patients do not have enough eggs growing to make overstimulation syndrome common. It is however much more common in patients who grow large numbers of eggs with FSH, usually on the IVF or GIFT programmes.

The advantages of FSH treatment therefore include:

- (a) high pregnancy rates
- (b) powerful management of serious ovulation disorders
- (c) conversion to versions of the IVF and GIFT programme can occur.

The disadvantages are:

- a) It carries a higher community expense although patients receiving this treatment have substantial government subsidies to make it quite affordable.
- b) More sophisticated monitoring in the form of blood tests and ultrasound scans are required.
- c) Multiple pregnancy rates are higher unless great care is taken.
- d) It is a more inconvenient form of therapy as daily injections must be given.

New forms of FSH will be coming onto the Australian market in the very near future. These will have the advantage of being able to be given by a smaller less painful subcutaneous injection. This is a small injection using a fine needle which just goes under the surface of the skin into the fat rather the deeper bigger injection into the muscle. This will be also be a purer form of FSH which may have more controlled effects on the ovary.

GnRH AGONISTS AND PCOS:

Some patients with ovulation disorders have very little hormone coming from the pituitary gland to the ovary. FSH treatment therefore works very well in this group. However as previously discussed patients with PCOS have very mixed and disorganised messages of FSH and LH coming from the pituitary gland to the ovary. When external FSH is administered by injection and eggs begin to grow in the PCOS ovary the pituitary gland still has the ability to interfere with orderly egg development, maturation and release.

It is therefore sometimes helpful to block the effect of the pituitary gland using a special class of hormones called GnRH agonists. These hormones have a structure very similar to GnRH but are up to 1,000-2,000 times more powerful. When administered they go to the pituitary gland and rapidly exhaust all remaining stocks of FSH and LH hormone. The pituitary gland temporarily therefore stops releasing these hormones. The ovary is then able to be stimulated using FSH injections without any interference from the now blocked pituitary gland.

GnRH AGONISTS AVAILABLE IN AUSTRALIA INCLUDE:

(a) **Lucrin (Leuprorelin Acetate)**

This is administered each day by a small subcutaneous injection.

(b) **Synarel (Nafarelin)**

This is given as a nasal spray. The spray is administered twice a day, once in the morning and once in the evening. Each bottle of nasal spray lasts 28 days.

(c) **Zoladex:**

This is a depot-injection. A small pellet of GnRH agonist is injected under the skin. The pellet dissolves over 28 days. Zoladex is useful for treating endometriosis but is less helpful in infertility patients as GnRH agonists are better not used in early pregnancy. A depot-injection like Zoladex would often continue to have its effect in early pregnancy whereas Lucrin and Synarel can be ceased soon after ovulation occurs.

GnRH agonists can cause headache, nausea, hot flushes, and mood disturbance. However many of these side effects occur when the GnRH agonist is used for a significant length of time e.g. several months for treating endometriosis. When used over a short time period with FSH the side effects are minimal as the effects of the GnRH agonist are rapidly reversed by oestrogen build up associated with egg development.

SURGERY FOR PCOS

A limited number of patients may benefit from surgery on their polycystic ovaries. Historically PCOS has been treated by an open operation done through a large incision called wedge resection. A segment of the ovaries (a little bit like a segment of an orange) is cut out and the ovary repaired. This was quite successful in starting ovulation and creating some pregnancies. However there was a high risk of adhesions and patients were in hospital for quite a long time with the big cut that was made on their abdomens. Wedge resections slowly fell into disrepute through the 1960's and 1970's.

A more modern way of operating on polycystic ovaries is to use the laparoscope as previously described. A laser or burning tool called a cautery is used to drill little holes in the surface of the thick capsule of the ovary. At the end of the procedure the ovary looks rather like a golf ball that has been dimpled. This procedure in fact is called laparoscopic golf balling of the ovary. It too can cause adhesions although because the operation is done laparoscopically. Without a big cut it can be done as day surgery and patients recover much more quickly. There will also be fewer adhesions as there are no surgeons hands inside the abdomen, only a laparoscope. The success rate of this operation is quite high in inducing ovulation and enhancing pregnancy chances.

In general terms surgery is not usually used as a first option but is used with patients who are having longer term difficulty in becoming pregnant.

Each patient who has an ovulation and menstrual problem is different. The causes of ovulation problems are many and there are a wide variety of treatments depending on whether the patient wishes to become pregnant or not. It is therefore very important for your doctor to **INDIVIDUALISE** your treatments.

Do not hesitate to discuss your treatment with your doctor, particularly if problems are occurring. The majority of patients with ovulation problems will get pregnant. However 6 to 10 cycles of treatment may be required before pregnancy occurs. About 30% of patients with ovulation problems will not become pregnant with the above treatment and versions of the IVF and GIFT programme will be required. Separate information kits are available for these programmes.

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