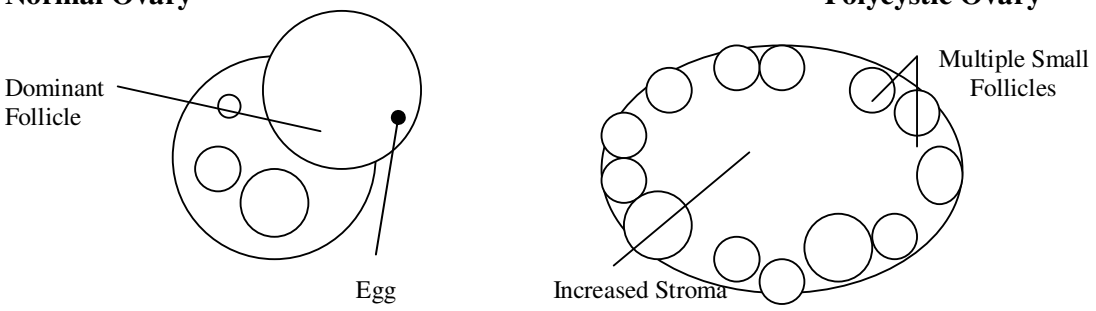
POLYCYSTIC OVARY SYNDROME (PCOS)

What is Polycystic Ovary Syndrome?

- Polycystic Ovary Syndrome is a condition characterised by:
    1. Characteristic ultrasound appearance of the ovaries
    2. Abnormal hormone levels
    3. Physical signs including irregular periods, acne, increased hair growth involving the face, upper lip and chin.

Normal Ovary **Polycystic Ovary**



What happens in the ovaries of a woman without PCOS?

- In a normal woman, each month, in response to the message hormone (FSH), sent from the pituitary gland, 10 – 20 small follicles begin to grow.
- One of these follicles is more efficient in trapping the FSH hormone coming from the pituitary gland. This follicle, called the dominant follicle, grows quite large and finally ruptures, releasing the egg inside. (ovulation)
- The other small follicles, deprived of the FSH hormone, stop growing whilst they are quite small, shrivel-up and die.

What happens in a woman with PCOS?

- In a woman with PCOS, 10 – 20 follicles begin to grow each month but for reasons that are not fully understood, none of the follicles becomes dominant.
- As a consequence, all the developing follicles continue to grow but none become large enough to ovulate.
- Instead of shrivelling-up and dying, they remain inside the ovary, usually just beneath the surface where they make male hormones
- These male hormones are then released into the bloodstream.

What is the effect of having higher levels of male hormone in the blood?

- The male hormones in the blood further upset the balance of message hormones coming from the pituitary so that the following month, when the next group of follicles begin to develop, they are unable to grow properly, resulting in the ovary having even more small follicles under the surface.
- As the number of small follicles in the ovary increases, more male hormones are released into the blood

What problems are caused by excess male hormones?

- Greasy skin with a tendency to acne
- Excess hair growth particularly on the cheeks, upper lip and chin.
- Tendency to weight gain

Are there any other hormone problems?

- As each follicle develops, it produces the female hormone, **oestrogen**.
- In PCOS, large numbers of small follicles develop each cycle resulting in oestrogen levels that are slightly higher than normal.
- Following ovulation, the follicle normally goes on to produce a second hormone, **progesterone**.
- Failure of the small follicles in women with PCOS to ovulate, results in very low or absent levels of the hormone, progesterone.

What problems are caused by excess oestrogen and insufficient progesterone?

- Irregular and/or infrequent periods
- Thickening of the womb lining (endometrial hyperplasia)
- Cancer of the womb lining (endometrial cancer)

Do women with PCOS experience any other problems?

- Subfertility - due to failure to ovulate regularly
- Increased risk of miscarriage – due to the hormone imbalance at the time of conception
- High blood pressure
- Diabetes

Is there anything that a woman with PCOS can do to reduce the risk of developing other problems?

- High blood pressure, diabetes and the associated risk of having a heart attack at a relatively young age is due to increased insulin resistance, a problem that is thought to be due to the same group of genes that causes PCOS. Unfortunately, we do not have any control over the genes that we inherit from our parents. We do, however, have some control over whether or not the potential associated problems actually develop.
- Women with PCOS who become significantly overweight are at much greater risk of developing high blood pressure.
- High cholesterol levels in the blood increase the risk of having a heart attack. The cholesterol levels can be kept to a minimum by taking regular exercise, maintaining an ideal weight and taking a diet low in fat and avoiding excess alcohol.
- Finally, the risk of diabetes can be reduced by maintaining an ideal weight, avoiding sugar in the diet and taking a diet low in fat but with plenty of complex carbohydrate and fibre.
- To date, there is no evidence as to whether or not the use of the drug, Metformin, which reduces insulin resistance, will actually reduce the risk of developing the associated complications in later life.

MENSTRUAL PROBLEMS

Polycystic ovary syndrome is associated with a variety of menstrual disturbances:
- Typically periods are irregular and are often delayed by several weeks
- Periods may occur at intervals of three to six months - Oligomenorrhoea
- Occasionally periods may completely stop - amenorrhoea.

When periods occur after prolonged intervals, they may be excessively heavy and are often associated with the passage of clots and flooding. Sometimes they are so heavy that they are mistaken for a miscarriage.

The periods are heavy and irregular due to the imbalance of hormones.
- Excess oestrogen causes the womb lining (endometrium) to become very thick
- Deficiency of progesterone results in the absence of the normal changes that occur in the endometrium before a period, causing the bleeding to be both heavy and irregular.

Does it matter if my periods are very irregular?
- In women having normal, regular periods, the endometrium is shed efficiently each month.
- This means that there is very little risk of the womb lining remaining inside the womb for too long, giving it the opportunity to develop abnormalities that could ultimately become cancer.
- In women with PCOS, the womb lining may remain in the womb for many months or sometimes even years.
- The longer the womb lining remains inside the womb without being replaced by new, healthy womb lining, the greater is the risk that it could become abnormal
- In women with PCOS, the risk of developing mild abnormalities of the endometrium and consequently, endometrial cancer, is increased.

MANAGEMENT OF MENSTRUAL PROBLEMS

The most appropriate management will depend on the age of the woman and her desire for fertility.

Regular but heavy periods

Non hormonal drugs
- Cannot regulate irregular periods
- Only need to be taken during ‘heavy bleeding’
- Have very few side effects
- May be taken for as long as required
- Include antiprostaglandins and antifibrinolytics.

Antiprostaglandins
- Are non-hormonal drugs that reduce the amount of bleeding and clotting.
- Are taken only during the period bleeding
- Have the advantage that they are also very effective painkillers and would be particularly appropriate for women with regular, heavy and painful periods.
- Do not affect fertility in any way.

Antifibrinolytics
- Are non-hormonal drugs that reduce the amount of bleeding and clotting.
- Are taken only during period bleeding

- Do not have any specific effect on period pains.
- Do not affect fertility in any way.

Irregular Periods

- If your periods are irregular, you will require some form of hormone therapy.
- Non-hormonal therapy cannot help with regulation of irregular periods.

Hormonal Drugs

- They are only effective in the month that they are taken.
- If you stop your hormonal medicines, the periods will revert to how they were before you started the hormone treatment.
- They do not have any significant long-term side effects
- They are more likely to have side effects than non-hormonal treatment.
- The side effects are usually mild but may include nausea and mild depression.

Combined Oral Contraceptive Pill

- This is ideal for a woman with irregular periods who also requires safe and reliable contraception.
- Pills containing the newer progestogens (Marvelon, Mercilon, Femodene) tend to have a particularly beneficial effect on acne and to a lesser extent, on hirsutism.

Dianette

- This is a combined oral contraceptive pill that contains the anti-androgen, Cyproterone Acetate.
- It is specifically indicated for women with irregular, heavy periods and **hirsutism**.
- Cyproterone Acetate is teratogenic (may cause abnormalities in a developing male fetus)
- It is essential that pregnancy be avoided whilst taking Dianette.

Cyclical Progestogen Therapy

- This is suitable for women who do not require contraception of when the oral contraceptive pill is contraindicated e.g. obesity.
- Use of a progestogen in the second half of the cycle mimics the natural production of progesterone by the ovaries.
- It ensures that the womb lining undergoes the normal secretory changes in preparation for a period
- As a consequence, the bleeding pattern is regular and the amount of bleeding is reduced.
- It is a safe form of treatment with relatively few side effects
- Some women will experience premenstrual symptoms including breast discomfort and mood swings.

Fertility Drugs

- These are only used in women actively wishing to conceive.
- By helping to ensure regular ovulation, they help to restore the normal balance of oestrogen and progesterone.
- Provided that they are successful in making the woman ovulate, the use of fertility medicines will result in a regular cycle.

PREVENTION OF ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA

- Women with PCOS are at increased risk of developing endometrial hyperplasia (thickening of the womb lining) and endometrial carcinoma (cancer of the womb lining).
- The more irregular and infrequent the periods, the greater the risk.
- The risk may be minimised by ensuring regular shedding of the endometrium.
- This may require the use of some form of hormonal medication (Contraceptive pill, progestogen therapy or a Mirena Coil) until the periods stop completely at the menopause.
- As PCOS may cause the periods to become absent for prolonged periods of time, it may be difficult for a woman to know whether or not she has reached the menopause.
- The only reliable way to determine if the menopause has been reached, is for the woman to be given a 7 – 10 day course of a progestogen. If she fails to have a bleed in response to courses of progestogen given for at least three consecutive months, it is reasonable to assume that she has reached the menopause.

Management of very heavy and prolonged bleeding

- If bleeding is very prolonged or heavy, it is wise to seek medical advice.
- The gynaecologist will undertake one or more of the following procedures, to ensure that the womb lining has not developed any abnormalities.
  1. Ultrasound scan to measure the endometrial thickness
  2. Pipelle endometrial biopsy – this is an outpatient procedure and involves the passage of a fine 'straw' through the cervix and into the womb. A small amount of womb lining is then 'sucked out'. This will be sent to the laboratory to be checked under a microscope.
  3. Hysteroscopy – this may be an outpatient or inpatient procedure. A small telescope is passed through the cervix into the womb. This allows direct visualisation of the endometrium.

Management of Endometrial Hyperplasia

- Endometrial hyperplasia may range in severity from a very mild form which is very unlikely to develop into cancer, to a much more abnormal form which must be regarded as pre-cancer.

- Mild Endometrial hyperplasia
  1. usually managed with a three month course of cyclical progestogen therapy
  2. would be expected to result in the endometrium reverting to normal
  3. on completion of the progestogen therapy, an endometrial biopsy will be performed to confirm that it has retuned to normal.

- Atypical or Severe Endometrial Hyperplasia
  1. Total Abdominal Hysterectomy and Bilateral Oophorectomy is the treatment that would usually advised.

2. Following hysterectomy, there is usually no contraindication to the use of Oestrogen Replacement Therapy to prevent the onset of menopausal side effects.
3. This is quite safe. If the womb has been removed, there will no longer be any womb lining at risk of becoming cancerous with the use of HRT.

ACNE AND HIRSUTISM

- Women with PCOS tend to have increased levels of male hormones.
- These hormones may cause troublesome acne and excess hair growth known as hirsutism.
- Excess hair growth tends to have a male pattern of distribution.
- Characteristically this occurs on:
  Cheeks and the side of the face - sideburns
  Upper lip - moustache area
  Chin and neck - beard area
- In addition, some women will experience hair growth on the chest and extending up from the pubic area towards the umbilicus.
- Other body hair on the back, arms and legs may be relatively thick and coarse.
- Rarely, the scalp hair becomes thinner with a receding hairline.

Treatment of Acne

- For minor degrees of hirsutism, the use of waxing, depilatory creams and electrolysis, may be effective.
- For women with dark hair, bleaching will render the hair on the upper lip much less conspicuous.
- Shaving is not advocated, as it tends to make the hair coarser.
- Laser Therapy is probably the most effective treatment. The effect is permanent but has the disadvantage of being both time consuming and expensive.

Oral Contraceptive Pill (OCP)

- Use of the OCP results in the ovaries being 'put to sleep'. This results in a reduction in the circulating male hormone levels in the blood.
- Oestrogen contained in the pill will cause a further reduction in male hormone level
- The OCP has the additional advantage of providing safe and effective contraception and regulating the periods.
- Progestogens in the newer OCPs (Marvelon, Mercilon, Femodene) have a particularly beneficial effect on acne and hirsutism.

Cyproterone Acetate

- This is an anti-male hormone
- It works by reducing the amount of male hormone produced by the ovaries and by interfering with the normal actions of the male hormones on the skin and hair follicles.
- It also increases the rate at which the male hormones are removed from the body by the liver.

- Cyproterone acetate is given in combination with the female hormone, oestrogen. This both potentiates the effect of the cyproterone and also ensures a regular menstrual cycle.
- The commonest form of cyproterone acetate and oestrogen is marketed as the oral contraceptive pill, Dianette.
- The use of cyproterone acetate results in a reduction in the number of hairs, the rate of growth and the coarseness of the hairs with the result that the hairs become fewer, finer and fairer.
- Cyproterone acetate also has a beneficial effect on acne.
- It will take a minimum of three months to have any effect on hair growth and may take up to twelve months to achieve maximum benefit.
- Most women experience regrowth of unwanted hair on discontinuing therapy.
- Side effects of treatment with cyproterone acetate and oestrogen are rare but may occasionally include nausea and headache.

Vaniqua Cream

- This is a cream that contains an anti-androgen
- It is used in the management of excess hair growth on the face and neck only.
- Like cyproterone, it is absorbed into the skin and results in hair growth becoming fairer and finer.
- It takes a minimum of three months to have any effect and may take up to twelve months to achieve maximum benefit.

Spironolactone

- This is also an anti-androgen (anti male hormone).
- It works by reducing the amount of male hormone made by the ovaries, converting some of the male hormone into female hormone, oestrogen and blocking the action of the male hormones both on the skin and hair follicles.
- The use of spironolactone alone tends to cause totally irregular bleeding. For this reason it is usually used in combination with the OCP.
- Dosages vary from 50 –200mg daily.

Cimetidine

- This drug, developed for the treatment of peptic ulcers also has anti-male hormone properties.
- It blocks the action of male hormones in the hair follicles, resulting in a reduction in the rate of hair growth.

Dexamethasone

- This drug acts to reduce the amount of male hormone produced by the adrenal gland.
- It is used in women who have been shown to have excess male hormones of adrenal origin.
- Side effects include high blood pressure, an increased risk of developing diabetes and thinning of the bones (osteoporosis).
- In view if the side effects, only very low doses of dexamethasone are recommended for the treatment of patients who have failed to respond to all other medications.

Surgery

- Women who have completed their family and who are troubled by excessively heavy and irregular periods may wish to consider hysterectomy (removal of the uterus) together with bilateral salpingo-oophorectomy (removal of both tubes and ovaries).
- This will result in a very significant reduction in both the male and female hormones in the body.
- Oestrogen replacement therapy would be advised post-operatively to prevent the onset of menopausal side effects and should be continued until the natural age of the menopause.
- Hysterectomy and bilateral oophorectomy has the added advantage that it eliminates the possibility of developing either cancer of the endometrium or ovary at some later date.

SUBFERTILITY

Although women with PCOS may experience subfertility problems, **the majority of women will conceive without difficulty.**

When women with PCOS experience difficulty in conceiving, this is usually due to a problem with ovulation. These problems tend to become progressively worse with increasing age. Having conceived the first pregnancy without any difficulty, a woman with PCOS may find that she subsequently experiences difficulty in achieving a second pregnancy.

Diagnosis

- If cycles are regular, ovulation may be confirmed by measuring the level of the hormone, Progesterone **seven days before the onset of the next menstrual period**.
- If the cycle is irregular or prolonged, ovulation may be confirmed or refutes by serial measurements of progesterone every 6 – 7 days, from the 21st day of the cycle until the onset of the next menstrual period.
- If periods are very irregular (more than 35 days apart) or have stopped altogether, **anovulation may be assumed.**

Treatment

- In women with PCOS problems with ovulation are common.
- This does not however mean, that there may not also be tubal problems or male factor problems.
- It is therefore important, to confirm that the tubes are not blocked and that the seminal fluid analysis is adequate, **before starting fertility drugs.**

Weight Reduction

- Women with PCOS are commonly overweight.
- Excess male hormones, produced both by the ovaries and the adrenal glands, are converted by the fat tissues, into the female hormone, oestrogen.
- These additional female hormones add to the already high level of oestrogen coming from the ovaries, making the level of oestrogen in the blood even higher.
- The pituitary gland in the brain, which monitors the level of oestrogen in the blood, recognises the higher oestrogen level and is fooled into thinking that either there is

already a very large follicle (egg) developing in the ovary or that the woman is already pregnant.
- In response to this, the pituitary gland stops further release of the hormone FSH, which is required to stimulate follicular growth in the ovary and the follicles fail to develop any further.
- **It has been shown that the single most effective treatment of ovulation failure in women with PCOS is weight loss.**
- Women who are significantly overweight respond poorly to fertility drug therapy. Women with a Body Mass Index (BMI) greater than 35 (very obese) generally fail to respond to fertility drugs.
- **All women with PCOS, who wish to conceive, should ensure that they have a BMI of 19 – 25.**

Clomiphene Citrate
- This drug acts on the pituitary to block the oestrogen receptors.
- This fools the pituitary into thinking that the level of oestrogen in the blood is lower than it really is. The pituitary responds by releasing increased amounts of the hormone FSH. Hopefully the higher level of FSH will be able to stimulate the ovary to grow and release an egg (eggs).
- Clomiphene is a table, taken in varying doses, from the second to the sixth day of the cycle.
- The efficacy of clomiphene treatment is assessed by the induction of a regular cycle and monitored with estimation of serum progesterone levels and serial ultrasound follicle tracking
- The use of clomiphene is associated with an increase in the incidence of twins.

Metformin Therapy
- PCOS is associated with increased insulin resistance and an associated risk of developing diabetes, high blood pressure and cardiovascular disease later in life.
- Metformin is a drug used to treat Diabetes.
- In women with PCOS who are obese, the use of Metformin, either alone or in combination with clomiphene, has been shown to improve ovulation.
- It is a table, taken in varying doses, two or three times daily.
- It may cause side effects including nausea and diarrhoea.

Ovarian Diathermy
- This is a surgical treatment used in the management of women with PCOS who have failed to respond to simple fertility treatment.
- Polycystic ovaries tend to be larger than normal and to release increased amounts of male hormone into the bloodstream
- These male hormones interfere with normal follicular development and ovulation.
- Ovarian diathermy is a simple technique to reduce the size of the ovaries.
- By reducing the size of the ovaries, the amount of male hormone released will be reduced.
- Hopefully by reducing the amount of male hormone in the blood, it will be possible for the ovaries to produce follicles and ovulate normally.
- Unfortunately the beneficial effects of ovarian diathermy are relatively short-lived. After six to twelve months, the ovaries once again increase in size, the periods become irregular and ovulation may become irregular or stop.

- Risks of surgery to the ovary are small but there is a very small chance that by destroying part of the ovary, the woman may go through the menopause.

Gonadotrophin Therapy

- Gonadotrophin therapy is used in the treatment of women who have failed to respond the Clomiphene +/- Metformin and ovarian diathermy.
- It is an injection treatment given daily.
- It contains manmade hormones, FSH and LH
- It acts directly on the ovaries to stimulate the growth of the follicles.
- Serious side effects include large multiple pregnancies and Ovarian Hyperstimulation syndrome (OHSS).
- In order to minimise the risk of complications, all women having gonadotrophin therapy will be monitored closely with regular scans of their ovaries to how many follicles are developing.
- When the scan shows at least one and not more than three good-sized follicles, an injection of HCG is given to ensure that the eggs are released from the ovaries.
- If there are too many follicles, the injection of HCG will be withheld and the couple will be advised to abstain from sexual intercourse.

GnRH Analogues

- In some women with PCOS, the use of gonadotrophin therapy may be complicated by premature ovulation (the release of eggs from the ovaries before they are fully ripe).
- GnRH analogue may be used in an attempt to over come this problem.
- It prevents the release of the hormone LH (which triggers ovulation) from the pituitary gland and thereby prevents the risk of premature ovulation.
- When the follicles are large enough, an injection of HCG will be given to stimulate ovulation.
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The place of IVF in the management of PCOS

IVF is usually recommended to women:

- who have failed to conceive in response to all other simpler treatments
- who have had twelve confirmed ovulations in response to fertility medicines but who have failed to conceive
- who grow too many follicles in response to gonadotrophin therapy and who therefore have a very large risk of developing a large multiple pregnancy or OHSS.
- With IVF, all the ripe eggs are surgically removed from the ovaries, fertilisation occurs in a dish and only two pregnancies are returned to the womb. This both improves the chance of pregnancy and reduces the chance of a large multiple pregnancy.