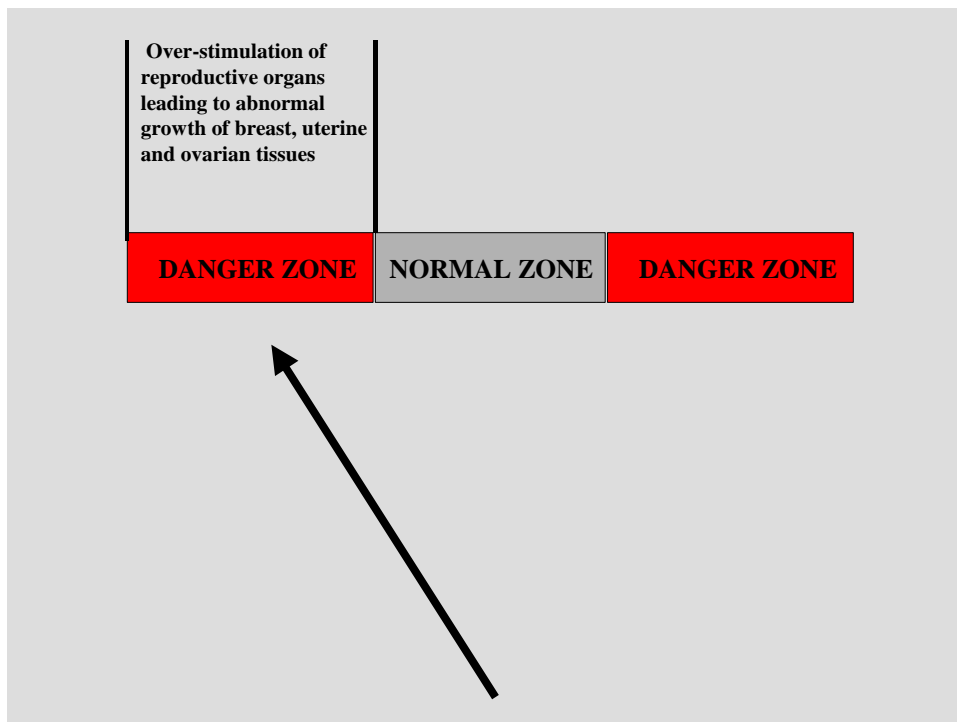


Problems of the pre-menopause - 'too much' estrogen



A detailed review of the problems of 'estrogen excess' affecting women before the menopause.

The breast

In the unromantic, literal sense, the breast is a gland and its glandular secretion is milk. The milk is made by cells known as glandular cells. The secretion from these cells drains via a complex system of milk ducts down to the nipple. Supporting this complex system of milk ducts is an underlying framework of fat and fibre. The entire breast structure exists to support these glandular cells.

In the breast of a woman who is neither pregnant nor breastfeeding, the glandular cells are few and far between, and fat and fibre account for the bulk of the tissue. The glandular cells that are present in the resting breast are not even capable of producing milk because they are immature cells. Their milk-producing capacity does not get switched on until they mature, and this maturation process is controlled by estrogen.

The rising estrogen level in the blood with each menstrual cycle causes the breast to spring into life for about 1 week each month. This comes about as a result of ovulation when the ovaries produce an estrogen surge in the middle of the menstrual cycle. This is meant to be the first signal to the breast of an impending pregnancy. Its purpose is to start the process of maturation and multiplication of the glandular cells - not a lot, but just the first stage of preparing the breast for the coming pregnancy. If pregnancy doesn't result, which is the usual situation in most modern women, then the cells stop multiplying and their numbers fall back over the next week or so to their resting level.

If pregnancy does proceed, then estrogen levels continue to rise and the glandular cells mature and multiply hundreds of times in order to provide the manufacturing capacity of the large amount of milk required. Other hormones aside from estrogen are responsible for instructing these cells to make milk, but estrogen is the key to their expansion to produce an enlarged breast capable of making milk.

✓ The normal breast experience

The normal cycle of the breast should be

- that the breast begins to grow from about the age of 10, finishing about the age of 17
- that between the ages of about 17 and 45, the breast then stands ready to fulfil its role of milk production. For about 7-10 days each month, it will 'switch on' the glandular cells in preparation for pregnancy, and then 'switch off' those same cells if pregnancy doesn't ensue. This switching mechanism is controlled by estrogen coming both from the ovaries and from the fat inside the breast. Under normal circumstances a woman should be quite unaware of this 'switching on/switching off' process. That is, the breast for all intents and purposes should feel and look unchanged throughout the menstrual cycle
- if pregnancy proceeds, then the glandular tissue in the breast will expand considerably to produce the milk to nurture the child. At the end of breast-feeding, the breast will return to its normal state
- on reaching menopause, the glandular cells and the milk collecting ducts will disappear, leaving a smaller breast composed largely of fat. In later life, even the fat will start to disappear.

This is the normal cycle and experience of the breast. Apart from growth leading up to puberty, the 'un-growth' following menopause, and enlargement during pregnancy, the breast should be unremarkable, experiencing little or no change in shape, size or feeling during a woman's

reproductive years. And being no more prone to cancer than the normal background rate to which all tissues are subjected.

✱ Abnormal breast experience

Unfortunately, the normal, uneventful cycle of the breast that we saw above is the exception rather than the rule in modern Western women. We have the extraordinary situation where the majority of women cannot go through their reproductive life without experiencing symptoms of pain, discomfort, swelling or life-threatening cancer associated with one of the following two conditions.

CYCLIC MASTALGIA

Cyclic, meaning it comes on regular monthly basis, and *mastalgia*, meaning breast ('mast') pain ('algia'). It also known by a variety of other names such as *cystic breast disease*, *benign breast disease* and by the aptly descriptive term, *lumpy breasts*. Strictly speaking it is one of the symptoms of the pre-menstrual syndrome (PMS), but it is such a common and distinctive problem that it really warrants special consideration as a stand-alone condition.

It is a very common condition, according to some surveys affecting about two-thirds of women to a greater or lesser extent. The symptoms result from an increase in the amount of water held within the breast. The water is contained within cysts, or fluid-filled sacs within the breast tissue. These usually are easily felt within the breast as hard lumps and are present in most affected women throughout the menstrual cycle. It is usually in the middle of the cycle when estrogen levels are reaching their peak that these cysts swell and become more prominent. Women who suffer this condition often also suffer water-logging in other parts of the body, resulting in swollen feet and legs, abdominal bloating, joint and muscle pain (due to swelling of ligaments) and weight gain.

The underlying cause of the problem is not well understood. One school of thought is that it is the result of the action of estrogen on kidney function. Estrogen can reduce the kidney's capacity to make urine, with the result that water levels build up in the body. We see the same water-retaining effect in menopausal women who are given HRT. Another school of thought believes that it is the result of the effect of estrogen on a group of substances made in the body called prostaglandins. Prostaglandins are chemicals involved in tissue inflammation - the swelling and tenderness that usually accompanies any tissue damage is due mainly to the irritating action of prostaglandins released by damaged cells. The prostaglandins cause blood vessels to dilate and to bring more blood and fluid into the tissue so that repair results. We know that estrogen stimulates the production of prostaglandins, and so it is thought that this might be occurring in the breasts of women suffering from mastalgia.

But whatever the mechanism, it is widely accepted that the condition is the result of abnormally high estrogen activity

Cyclic mastalgia is a benign condition and there is no evidence that women who suffer this problem are any more or less prone to breast cancer. However, one of its main concerns is that it can interfere with effective mammography screening for breast cancer by obscuring early cancer changes behind fibrous cysts.

The most effective treatment for this condition is menopause. The onset of menopause and the accompanying fall in blood estrogen levels normally brings about total alleviation of the symptoms. Unfortunately until that time, there is no particularly satisfactory therapy for this condition. A firm-fitting bra and reduced physical exercise during the worst of the condition are probably the best medical advice at the moment. Vitamin B1, evening primrose oil,

avoidance of caffeine (coffee, tea, chocolate etc) and mild diuretics (to increase fluid loss) are claimed to provide assistance in some women, although the effects are equivocal. Taking the oral contraceptive pill in order to regularize the menstrual cycle appears to help some women.

Caroline is a 38 year old high school teacher and mother of three. She had suffered cyclic mastalgia regularly every month since she was a teenager - regularly, that is, except for when she was pregnant and breast-feeding. She had always been aware of lumps in both breasts, and precautionary X-rays her doctor had ordered had shown they were just benign fluid-filled cysts and that there was no sign of cancer.

The lumps were not particularly tender at the start of each monthly cycle - she could press them without any great problem. But as the middle of her cycle approached, the lumps became swollen and very tender. The best way she could describe them was as 'feeling like boils'. Each breast swelled up by about one-quarter of its normal size, which she knew because she usually needed a larger bra size at this time. Both breasts were affected, but it wasn't unusual for one breast to be more affected than the other each month. The swelling would last for about 7-10 days and usually start to go down by the time her period started.

The worst problem for Caroline was if she bumped her breasts when they were swollen, making many simple every-day tasks more difficult. She was a keen weekend golfer and tried to play every week, but she found it just too painful to swing a golf club when her breast swelling was at its peak. She also could not bear to have her husband touch her breasts when they were in this state.

Her doctor had not been able to offer much in the way of treatment, suggesting that she try vitamin B and evening primrose oil supplements. She had tried these on and off over the years, but they had not provided any permanent relief.

BREAST CANCER

One in nine women living in Western countries up to the age of 85 will develop breast cancer. It is the leading cause of death among women between the ages 40-55. In Western communities, deaths from breast cancer rose steeply in the first half of the 20th century, but have remained fairly stable since 1950. The recent apparent rise in the incidence of breast cancer is thought to be more a matter of better detection procedures and increasing longevity, than a true increase in incidence. However, breast cancer is now occurring at alarming proportions and represents a major mid- and older-life threat to women.

Breast cancer starts from the milk collecting ducts - either the glandular epithelium or the cells that line the ducts. This results in two distinct types known as *lobular carcinomas* or *ductal carcinomas*. In either case, it starts with a few cells showing abnormal behaviour such as excessive multiplication. This cluster of abnormal cells is termed hyperplasia - it is not a cancer at this time, but a pre-cancer, which means that it has the potential to go on to form cancer. Hyperplasia probably is a normal part of human experience and is going on in all of our tissues every day of our lives - given the huge number of times our cells multiply, the opportunity for something to go wrong is immense. The critical thing is what happens next to that hyperplasia. Most cases don't progress any further. But those that do require something else to tip them over the edge, turning the hyperplasia into cancer.

The primary risk factors responsible for that progression from pre-malignancy into full-blown cancer in about 50% of cases have to do with estrogen exposure and are

- fewer children
- less time spent breast-feeding

- higher blood estrogen levels.

Genetic predisposition appears to account for only about 5% of breast cancers. Certainly having a mother, daughter or sister with breast cancer increases the risk, and having a mutated form of the BRCA1 or 2 genes increases the risk (as with ovarian cancer) by about 30-40%.

For the remaining 50% of cases, the risk factors are unknown, but the following lifestyle factors have been identified

- high fat diet
- obesity
- high alcohol intake
- tobacco smoking.

It perhaps is no coincidence that the first 3 of these lifestyle risk factors above are associated with increased estrogen production in the body.

Breast cancer normally is a very vigorous cancer. Once it starts in the wall of a milk duct, it breaks out and infiltrates the surrounding tissues, and if left unchecked will ultimately displace much of the normal tissue of the breast. Breast cancer cells also are liable to spread beyond the breast (a process known as *metastasis*), travelling to various parts of the body where they can establish secondary cancers.

The risk of breast cancer increases with age, which is something of an apparent paradox, because if estrogen is a prime factor in the development of most breast cancers, then we might have expected the onset of menopause to bring about a reduced risk of breast cancer. But it doesn't, and there are several reasons for this. First, breast cancer, like many forms of cancer, probably starts as much as 15-20 years before it makes itself obvious. In other words, most cases of breast cancer probably start in the pre-menopause, but only get diagnosed after menopause. Second, the breast goes on making estrogen well after menopause has started thanks to the fat tissue within the breast. The result of this is that estrogen levels within breast tissue are about 20x greater than estrogen levels in the blood. This 20x difference can be maintained in many women even after menopause, keeping the glandular cells within the breast multiplying long after menopause has set in.

Jennifer's story is fairly typical for a large number of women. She is 45, married and with two children. She is average body size and an otherwise healthy and active mother of teenage children.

Jennifer had had a fairly uneventful reproductive history. She had always suffered mild mastalgia during her cycles, but not to the extent that she would say that she was bothered by it. Her two pregnancies had gone well, although she had found it difficult to breast-feed and so had not persevered with that.

She was aware that an elderly aunt had died from breast cancer, but her mother and her elder sister had not had any history of breast cancer, so it was not something that was large in her mind. She had never bothered to have a mammogram screen although she knew that women were being advised to do so once they reached 40. Occasionally, when she thought of it, she would self-examine her breasts, but apart from the cystic lumps as part of her mastalgia, she never felt anything abnormal. Her breasts were firm and large and she took some pride in their shape.

Twelve months ago she had first become aware of a hard lump - in fact it was her husband who first noticed it, just below the nipple. It was hard but not painful. She had gone immediately to her doctor who ordered a biopsy and a mammogram. The mammogram confirmed that the lump was infiltrating into the surrounding tissue and the biopsy showed that the cancer was a vigorous one and of the type that responds to estrogen.

Jennifer went for surgery within days, having her left breast removed and the draining lymph nodes in her armpit removed as well. Biopsies of the lymph nodes had revealed the presence of cancer cells

in them, indicating that the cancer had spread beyond the breast. Whether or not they had spread beyond the lymph nodes was the big question that only time would tell. But her surgeon had been totally frank with her, explaining that the odds were not good. The advanced size of the tumour in the breast, the fact that it was a vigorous cancer, plus the presence of cancer cells outside of the breast made it quite likely that the cancer had spread to other parts of her body such as the liver and bones. The next steps for Jennifer were radiotherapy and chemotherapy.

The uterus

The uterus (or womb) has one function only, and that is to support pregnancy. It has a blood-rich lining whose job it is to provide nutrition to the embryo and young foetus, and a muscular wall designed to stretch and to hold the heavy weight of another growing body within a woman's abdomen.

The inner lining is known as the endometrium (from the Greek word *endon* meaning 'within' and *metra* meaning 'womb'). The role of the endometrium is to provide a supportive environment for the sperm on their passage up to meet the ovum, and then to receive and nourish the young embryo until the body establishes a direct blood supply to the growing child (the *placenta*).

The endometrium does this each month by multiplying and thickening (about 3x) into a deep, lush, blood-rich environment in the week leading up to ovulation in expectation of the arrival of a fertilized egg. If that egg doesn't arrive, then the endometrium falls away to produce a bloody fluid that drains away through the cervix and vagina in what is recognized as a woman's period (or menstruation). The remaining endothelium is just a thin layer that responds about a week later to the next surge of estrogen coming from the ovary to start the menstrual cycle all over again.

The menstrual cycle (the time between the end of one period and the start of the next) has an average length of 28 days, but varies normally between 25-36 days.

When a woman enters menopause and her estrogen levels fall, then the driving force behind the monthly growth of the endometrium falls away. The endometrium stops its monthly cycle of growth and remains in a resting state, ultimately wasting away after a year or two to nothing. The muscle in the wall of the uterus also depends on estrogen for its strength, and so after menopause it also starts to retract. The result of menopause therefore is a shrinking uterus that ultimately collapses to just a small mass of fibrous tissue.

✓ The normal uterine experience

The normal uterine experience for a woman should be as follows:

- the uterus begins responding to rising estrogen levels during adolescence, generally starting menstruation at the age of about 12-14. The early monthly periods may be irregular for about a year or so until the ovarian cycle is fully synchronised
- once the ovaries and uterus are working in harmony, a woman should have regular monthly cycles from the ages of about 15 to about 45
- the amount of thickening of the endometrium each month should be fairly uniform, and the amount of bleeding (the period) each month should be uniform
- the stripping away of the endometrium each month should occur uneventfully and without pain or muscular cramps
- the endometrium should undergo this regular monthly growth/regression cycle without misadventure, finally at the time of menopause wasting away to nothing
- the uterine wall should remain in a healthy and constant state throughout a woman's reproductive life, collapsing at menopause into a small mass of inert tissue
- during pregnancy, the uterus will expand and grow to support and nourish the growing fetus, expelling the child after 9 months before returning to its resting state.

✘ **Abnormal uterine experience**

As with breast function, a large proportion of Western women do not experience 'normal' uterine function. For many, menstruation can be a difficult, hated time filled with heavy bleeding, cramps and pain. For these women, what should be a natural, uneventful monthly cycle of tissue replenishment can turn into a week of pain or discomfort or physical restriction due to excessive growth of the endometrium. For others, their problems may extend into long-term physical changes, resulting in abnormal growths.

All of these changes represent an imbalance in the normal hormonal harmony between ovaries and uterus. The uterus (or womb) is a slave to the ovaries. Its shape, size and function are dependent entirely upon the female sex hormones coming from the ovaries and any disturbance to that relationship will result in disharmony within the uterus.

Disharmony within the uterus can affect either of its two main parts – the muscular wall or the thin internal lining (the endometrium). The only significant problem affecting the wall is the condition uterine fibroids. The endometrium, on the other hand, is involved in a variety of problems including endometriosis, endometrial hyperplasia, menorrhagia, and cancer.

UTERINE FIBROIDS

This is a very common condition, with somewhere between 20-40% of women developing fibroids by the age of 45. They are the major cause of hysterectomies in countries like the US.

Fibroids are a form of tumour (meaning an abnormal overgrowth of tissue) and are known medically as *leiomyomas*, meaning they are a benign, non-malignant growth of muscle and connective tissue. If you were to look at a cross-section of the fibroid, you would see whorls (or circular layers) of muscle cells, with the entire mass held within a capsule.



They arise in the muscle in the wall of the uterus and can grow to a large size - in most women they vary in size between that of a pea and an egg, but in some cases they can grow to the size of a softball. Women can have a single fibroid or multiple fibroids. The problems that they can cause are a function of their size and the general direction in which they grow.

Many women can have small fibroids and be quite unaware of them. But for others, they can produce a variety of discomforts. Typically they show up in women in their 40s. They probably start much earlier than this, but their slow-growing nature means that

they usually don't become obvious until they have been there for 10 years or so. Most women are unaware that they even have fibroids and they are often only picked up when the woman has an ultrasound examination for some other reason.

If the fibroids grow inwards towards the internal lining of the uterus, then it is possible for them to burst through the endometrium and to erode, resulting in bleeding. This tends to make the periods

heavier and less regular and can result in painful menstrual cramping and pelvic pain. But others can grow to considerable sizes (up to the size of a soccer ball) within the wall of the uterus or on its outer surface without causing any bleeding. The main problems that these outward-growing fibroids cause are related to the pressure that they exert on surrounding structures. If they press on the bladder, then they increase the need to urinate. If they press on the bowel, then they can cause a change in bowel habits.

Fibroids are dependent upon estrogens for their growth. They rarely occur before a woman reaches puberty and they usually disappear after menopause. They also have a tendency to cyclically shrink and then grow again in response to rising and falling estrogen levels throughout the menstrual cycle. Obesity is associated with an increased risk of fibroids, presumably because of the increased estrogen levels in the body as a result of estrogen production by fatty tissue. Women suffering other conditions associated with excessive estrogen activity such as endometriosis are at greater risk of developing fibroids. Interestingly, pregnancy reduces the risk - the more pregnancies a woman has, the lower the risk of developing fibroids. Women who have had five children have only one-quarter the risk of getting fibroids as women who have had none.

The most common method of managing fibroids is to 'watch and wait'. Unless they causing considerable blood loss or pain or inconvenience (from pressure on surrounding structures), many women in their 40s prefer to ride out the situation, secure in the knowledge that menopause invariably brings an end to the problem.

For others, however, doing nothing is not an option because the symptoms are so severe. One option is to switch off estrogen production by the ovaries. This is usually done with drugs known as GnRH agonists that block the messages coming from the brain to the ovaries and which tell the ovaries how much estrogen to make. These drugs are very effective, but they have the serious disadvantage that they immediately induce menopause, often with severe hot flashing and severe osteoporosis.

The other option is to use surgery. If a woman has a single fibroid, it may be possible to preserve the uterus and to cut out the offending fibroid (an operation called *myomectomy*). But for most women opting for surgery, complete removal of the uterus (known as *hysterectomy*) is the norm.

Even though fibroids are a form of cancer, they are a benign cancer. It is very rare for a fibroid to progress into a dangerous cancer, and there is no evidence that women who have fibroids are any more at risk of developing the more dangerous endometrial cancer.

Allison is a 42 year-old accountant. She is in a relationship, but is unmarried and has not had any children although she has not totally ruled out that possibility.

She first became aware of her fibroids five years earlier when her previously normal periods had started to become abnormal. They became heavier and she started to get some cramping and after 12 months of this she went to her doctor who performed an ultrasound and diagnosed a fibroid growing into the cavity of the uterus. The fibroid was about 5 cm (2 inches) in diameter, which meant that it was taking up virtually all of her uterine cavity. Her doctor recommended surgery to remove it and this was done. For three years her periods had been normal but then had started to change again. A follow-up ultrasound revealed a much larger fibroid that this time was growing within the wall of the uterus.

Her symptoms this time were more severe. Her periods were now very heavy, producing 2-3 times the amount of blood as normal. And while this caused certain practical problems for the working woman that she was, the worse outcome was the pain and cramps. These often were so bad that she had no alternative but to stay home in bed. Recently she had noticed the development of frequency, having to urinate every hour or so, and her doctor thought that this was a sign that the fibroid probably was growing and had started to press on the bladder which sits next to the uterus.

Allison had been faced with three choices:

do nothing and wait for menopause to bring about shrinkage. She had rejected this since that could have been another 10 years away and being an accountant she quickly had computed that that meant the possibility of another 120 periods of pain and discomfort.

take a GnRH agonist drug therapy. She also had rejected this because of the down-side of instant menopause and the need to take HRT. Her mother had died from breast cancer, so she had no interest in pursuing this line of treatment.

have a hysterectomy. She had decided to take this option. Initially she had been reluctant because of a vague notion of having a child in the next few years, but her doctor had explained that the likelihood of her falling pregnant with her uterus in its current state was pretty remote. So the decision ultimately had been fairly easy, if not emotional.

ENDOMETRIOSIS

Endometriosis is a condition where the endometrium grows outside of the uterus, producing growths in the abdomen.

The major significance of endometriosis is that it has the capacity to be quite debilitating and even life threatening. The incidence of this condition is unclear. A figure of 5% is often quoted, but recent studies suggest that it might be a lot higher than this if it is looked for pro-actively. The only effective way to diagnose endometriosis is by surgery, such as laparoscopy, where the abdominal cavity can be viewed directly. Some recent reports of women having laparoscopy for tubal ligation have indicated an incidence of endometriosis as high as 22%.

The endometrium is a glandular tissue that sits as a thin internal lining of the largely muscular uterus. The purpose of the endometrium is to provide a moist environment for sperm to travel through on their way up to meet the ovum in the Fallopian tube, and then to receive and nourish the embryo once conception has occurred.

The endometrium thickens each month in response to rising estrogen levels associated with ovulation, producing a lush environment for sperm and embryo. In the absence of a pregnancy, falling estrogen and rising progesterone levels in the blood cause the thickened endometrium to break away and flush out down through the cervix and out through the vagina. However, this flow is not entirely one way, and it is quite usual in normal menstruating women to find a small amount of menstrual blood in the abdomen, indicating that at least some of the broken-down endometrium does find its way under normal circumstances into the abdomen. The menstrual blood is just like normal blood in that it contains living cells - in this case living endometrial cells. This suggests that there is nothing abnormal or potentially dangerous about endometrial cells finding their way into the abdomen. What clearly is abnormal is that those cells should survive and re-establish themselves outside of the uterus.



This is what happens in endometriosis - the endometrial cells attach themselves to various structures in the pelvic cavity. Most cases involve the ovaries or the outside of the uterus. Less commonly it involves other structures within the pelvic cavity such as the large bowel and the bladder. In rare cases it can spread outside of the pelvis to involve the lining of the abdomen and even the lungs. These bits of endometrium respond to estrogen in the blood in exactly the same way, as does the endometrium back in the uterus.

The cells multiply under the influence of estrogen each month to produce reddish-blue 'raspberry-like' nodules over the surface of the organs. And just like the normal endometrium in the uterus, this abnormal endometrial 'menstruates' in response to the menstrual cycle. They often form little cysts that become full of dark blood and which can burst each month (as per the photo above). Long-standing cases of endometriosis usually are associated with the formation of scar tissue as a result of repeated bursting of cysts, and this scar tissue once it contracts can lead to problems if it involves the bowel or bladder.

Some women are unaware that they have endometriosis and it is only discovered accidentally at the time of surgery for some other matter. But most suffer some symptoms. Pain is a common symptom, usually due to the presence of menstrual blood in the pelvic cavity coming from a burst cyst. Usually the pain is worse at ovulation, in the middle of the monthly cycle when estrogen levels are at their peak and the endometrial nodules are swelling. If the nodules are close to a nerve, then this swelling can result in severe pelvic pain. The endometrial nodules themselves are tender and if they occur on the back of the uterus, they can be bumped during intercourse, producing pain at that time. Endometriosis normally is associated with irregular menstruation and premenstrual spotting is a classic symptom of endometriosis. Endometriosis involving the ovaries invariably is associated with infertility.

The usual treatment consists of using drugs to combat the effects of estrogen in combination with strong painkillers. Alternatively, women can have surgery to remove the bits of offending endometrium and to cut the scar tissue adhesions that build up. The risk of recurrence is high, with about half of all women undergoing surgery re-developing the endometriosis within five years. The most effective cure is to remove the uterus and ovaries.

The risk factors in endometriosis are unclear. Factors that have been suggested are (a) a family history of endometriosis, (b) later age of starting a family, (c) the use of an IUD contraceptive device (d) an early onset of menstruation and more menstrual cycle per year, (e) heavy periods, and (f) having sexual intercourse during menstruation.

The big question is why the majority of normally menstruating women can have small amounts of menstrual blood in their abdomen and yet not develop endometriosis. We just don't know if women who develop endometriosis do so because more menstrual blood goes up into the abdomen than it does in other women, or whether the normal mechanisms in place to clear the migrating endometrial cells from the abdomen fail. The risk factors noted earlier point towards interruption of normal menstrual flow and/or increased estrogen load in the body as important factors.

Nadine is a 37 year-old, Afro-American, television presenter, divorced with a 14 year-old daughter.

Nadine was diagnosed as having endometriosis when she was 33. She had always suffered from PMS, virtually ever since her periods had started, with symptoms of mastalgia and headaches for about a week each month. She mostly also suffered some pain and cramps when she was menstruating, but nothing so severe that regular painkillers couldn't handle and it didn't interfere with her social or professional lives. After her divorce 10 years ago, she had stayed on the contraceptive pill because she remained sexually active, plus she felt that it was helping her PMS symptoms.

Things had changed for the worse about the age of 30. Her periods had started to become heavier and the menstrual pain and cramps were worse. She had spoken to her doctor and he had put her onto a heavier dose contraceptive pill to see what would happen. But that had no effect, and 6 months later she noticed that she was getting pain about the middle of her cycle. The pain at the time of her period was usually a sharp, cramp-like pain, but this new pain in the middle of her cycle was more of a dull, heavy pain in her lower abdomen that lasted about 5-7 days. She also started to get backaches and a stiff neck. She noticed that the pain often got worse when she was having sex and when she had a bowel movement.

She went back to her gynaecologist who performed a pelvic examination, a procedure that caused Nadine excruciating pain. He then performed an ultrasound examination, finding ovarian cysts on one of her ovaries. Suspecting endometriosis, he then admitted her to hospital for a laparoscopic examination of her abdomen. He found evidence of moderately severe endometriosis. The presence of so much menstrual blood in the pelvic cavity had acted as an irritant, causing extensive scarring and adhesions throughout the pelvis and involving the ovaries, uterus and bowel.

Nadine had accepted her doctor's recommendation and had her uterus and both ovaries removed. The surgeon also had attempted to remove as much of the adhesions as possible from the bowel and surrounding structures. It was now 9 months since the surgery and she was feeling a lot better. The menstrual pain and cramps had gone as result of her hysterectomy, and she was able to enjoy sex without pain. The constant, heavy, dull pelvic pain was still there, but much reduced in intensity.

The biggest problem Nadine then had faced was the surgically induced menopause - she was having a rough time of it with multiple hot flashes and night sweats and it hadn't shown any sign of easing up after 6 months. Her doctor had been reluctant to give her any HRT treatment up to now for fear of re-activating any residual endometriosis.

ENDOMETRIAL HYPERPLASIA

The term 'hyperplasia' is from the Greek word *hyper* meaning more than usual, and the Latin word *plasia* meaning the growth of tissue. So *hyperplasia* means an abnormal and excessive growth of tissue, in this case, the endometrium. The endometrium as we have already seen normally grows rapidly in response to rising estrogen levels in the blood towards the middle of a woman's menstrual cycle and then strips away when progesterone levels in the blood fall. In endometrial hyperplasia, a small part of the endometrium defies the estrogen/progesterone cycle and continues to grow unchecked. The surrounding endometrium continues to behave normally and to produce menstruation each month, but this pocket of abnormal cells remains attached to the uterus and does not join in the menstrual flow.

The outcome of this condition in pre-menopausal women is erratic periods - often heavy periods and bleeding between periods. It can also occur in older, post-menopausal woman (usually in response to HRT therapy) where it is associated with frequent bleeding. Diagnosis normally is made by biopsy and treatment includes a D & C (dilute and curette) to scrape away the affected endometrium, followed by several months of progesterone therapy to induce the endometrium to strip away more efficiently. Often a normal pattern of ovulation and menstruation is restored by such therapy and the endometrial hyperplasia settles down. Older women usually are treated by having a hysterectomy (total removal of the uterus).

While endometrial hyperplasia is reasonably well controlled, it has a far more sinister significance. And that is, that it really can be considered the forerunner to cancer. The hormonal process that is initiating the excessive multiplication within the endometrium is the same process that is likely to lead to cancer of the endometrium. Not all cases of endometrial hyperplasia go on to form cancer, but about 20% do.

ENDOMETRIAL CANCER

The terms 'uterine cancer' and endometrial cancer' essentially are interchangeable because cancer of the uterus almost always starts in the endometrium and not in the muscle wall. The endometrium is naturally prone to cancer development simply because of the high rate of cell multiplication that goes on in that tissue, with the risk of a cell becoming cancerous increasing proportionally with the number of times that it multiplies. A cell is in its most vulnerable state to become cancerous when it is dividing into two daughter cells. In a young woman, the endometrium is the most rapidly dividing tissue in her body for one week each month. So by definition it is going to be at high risk of developing cancer. But nature provides the ideal antidote to this risk in the form of menstruation. The monthly flushing of the endometrium when pregnancy doesn't eventuate is an effective means of removing any cancer cells before they get established. And of course if pregnancy does develop, then the endometrium is eventually shed along with the placenta ('after-birth') once the baby is delivered.

In the menopausal woman, the lack of any ovarian function means that the endometrium becomes dormant. It simply shrinks to a thin lining with little or no cell multiplication occurring. So, even though the menopausal woman is not menstruating and therefore lacks the protective flushing mechanism, the likelihood of a cancer developing under normal circumstances in the dormant endometrium is remote.

The lifetime risk (that is, for women living to the average age of 85) for endometrial cancer is about 3%, or about 3x less than that of breast cancer. For women who take ERT (*estrogen replacement therapy*), also known as 'unopposed' HRT (*steroidal* estrogen without progesterone), the risk is doubled to 6%. The largest study carried out to date looked at women who had taken ERT at some point in their life and concluded that treatment for 1 year or less produced an increased risk of endometrial cancer of 1.4x, treatment for more than 10 years produced an increased risk of 10x, and treatment for over 20 years produced an increased risk of 20x.

Those women who develop endometrial cancer and who have not been taking ERT tend to develop the cancer before the age of 50. Those women, who get the cancer as the result of taking ERT preparations, obviously are developing the cancer after the age of 50, usually in their 60s.

The reason that estrogen therapy after menopause increases the risk of endometrial cancer is that the endometrium is now being stimulated unnaturally. Instead of lying dormant as it is meant to be, the endometrium is now responding to the extra estrogen in the blood as it did when it was an active uterus in a younger body. The only difference now is that without the benefit of an estrogen/progesterone cycle, there is no menstruation. Without that natural protective flushing mechanism, any cancer cells that develop are allowed to establish and flourish in the lining of the uterus.

Most people tend to associate endometrial cancer with estrogen therapy, but the incidence of this form of cancer in women not taking ERT or HRT is still unacceptably high at about 3%. This is an incidence hundreds of times greater than what would be regarded as a normal, background risk of developing cancer of any tissue. The endometrium of Western women clearly is at an unacceptably high risk of becoming cancerous even without HRT therapy. Taking ERT or HRT can simply increase that risk.

Endometrial cancer is a fairly vigorous cancer, growing into surrounding tissues in the early stages, before spreading to other parts of the body via the bloodstream, usually much later in the process. Fortunately most cases of endometrial cancer are detectable early in the process because of their tendency to cause unusual bleeding patterns - bleeding between periods in pre-menopausal women

and any bleeding at all in post-menopausal women. If detected early, then surgery to remove the uterus usually is sufficient to nip this cancer in the bud.

Jocelyn's story is fairly typical. She is 48, a doctor, married to another doctor, and a mother of two children.

Jocelyn had always been prone to irregular periods - sometimes heavy and sometimes just some spotting between periods. She had been checked out in her early 20s and found to be basically OK. There was some suspicion of endometrial hyperplasia but she opted to not have any treatment. She decided just to keep an eye on things by having fairly regular PAP smears and ultrasounds. She subsequently had two children in quick succession and returned to her busy general practice. She also had a tubal ligation when the last child turned 7.

Her periods had continued to be irregular into her early 40s, but her strategy was to see it out until she reached menopause in another seven years or so. But from about the age of 45, the occasional spotting between periods that she used to get started to become heavier and more regular. Doctors often are the worst patients, overlooking the obvious because of their busy workload. This was the case with Jocelyn. It wasn't until about a year later that she went to a gynecologist colleague for a check-up. An ultrasound and a biopsy revealed her gynecologist's worst fears - endometrial cancer. Fortunately it was a fairly low grade cancer, and the resulting surgery that Jocelyn had to remove her uterus and ovaries appears to have left her with a clean bill of health, even though it had the effect putting her into a fairly dramatic menopause with loads of hot flashes each day.

MENORRHAGIA

Menorrhagia is not any particular disease. It simply refers to heavy periods where there is no obvious explanation for the excessive bleeding, such as a structural abnormality (eg. endometrial hyperplasia and fibroids) or infection.

Most women can expect to experience an occasional heavy period - personal stress, travel, viral infections and so on are all capable from time-to-time of upsetting the normal ovarian/uterus balance and cause an unusually heavy period. That's just part of life. It only becomes a concern when the heavy periods are frequent and persistent, indicating a more serious and longer-term upset in the ovarian/uterus balance.

The definition of a 'heavy period' is a grey area because every woman can be different. But generally speaking, doctors regard a heavy period as one that produces more than 80 mL (about half a cup) of blood per day as measured by the need to use two or more tampons or pads per day, and/or lasts for more than one week, which is about 3 days more than average

The incidence of menorrhagia is not known because most women do not report the condition, not recognizing anything odd about their heavy periods - why would you be concerned if you have never known any better? But the experience of most gynecologists is that it is common, probably affecting about 5-10% of women.

Under normal conditions of menstruation, the endometrium that has thickened in preparation for pregnancy, falls away to leave a clean surface on the uterus with a new layer of fresh, young endometrium ready to respond to the next ovarian cycle. The blood vessels that were supplying the old layer of endometrium close over and new blood vessels are created to supply the next layer coming through. This is so the freshly exposed surface of the uterus doesn't bleed once the old layer falls away. The menstrual blood represents just the stripped layer of endometrium that has dissolved and which contains a special compound to prevent it clotting. The actual process of stripping away

occurs over about 24 hours and the menstrual blood then takes between 1 and 7 days to escape from the uterus.

No one is certain about the causes of heavy periods in the absence of any obvious causes such as fibroids, endometriosis, endometrial hyperplasia and ovarian disease. One theory is that it is due to a failure in the blood clotting mechanism, allowing the exposed surface of the uterus to continue to bleed after the old endometrium has fallen away.

The other more popular theory is that it is due to excessive inflammation of the endometrium. As we noted with the breast, estrogen can cause a build up of inflammatory compounds known as prostaglandins in tissues. A small build up won't cause any problems and in fact is probably quite normal. What we are talking about with cyclic mastalgia or menorrhagia is an unbalanced and uncontrolled excessive build up of prostaglandins resulting in increased blood flow, oedema (excessive fluid collecting in the tissue), and reduced blood clotting. When this happens in the breast it can cause the tenderness, inflammation and fluid accumulation that are the hallmark of cyclic mastalgia; when it happens in the endometrium, it causes an inflamed endometrium resulting in increased menstrual bleeding. The fact that many women with menorrhagia respond to anti-inflammatory drugs points to the likely importance of this prostaglandin mechanism in this condition.

Treatment for menorrhagia varies from

- using anti-inflammatory drugs to reduce inflammation within the endometrium
- suppressing ovulation for an extended period of time
- long-term use of progesterone to stop menstruation
- hysterectomy.

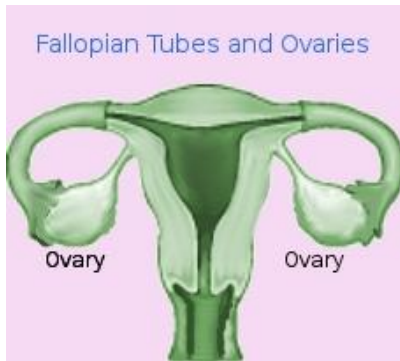
Kate was diagnosed with menorrhagia at the age of 25. She is a registered nurse working in a large hospital.

Kate had not always had heavy periods. At school her menstrual cycle was fairly unremarkable - her periods were regular as clockwork every 28 days or so, they lasted about 3-4 days and one tampon per day was always more than adequate. She had noticed a change about the time she started college - the periods were still regular, but she found herself bleeding for about 7-8 days and needed to change tampons at least 3 times a day. At the time she had put this down to the new level of stress that she was living under - the strain of her studies, the need to work a part-time job to fund those studies, and the stress of living away from home. However it had all come to a head once she graduated and started working in the emergency ward of a busy hospital. She collapsed at work one day and investigations showed that she was severely anaemic. The heavy periods, the long work-days, and an inadequate diet had finally taken its toll.

Once her doctor had eliminated other possible causes of the heavy periods, he diagnosed menorrhagia. She had a D & C to remove a thickened endometrium and then was put onto progesterone which totally stopped her periods. The progesterone caused bloating and made her breasts swollen and tender, but at least she wasn't suffering the heavy periods. Also, she had more energy as a result of a blood transfusion and an iron supplement that had reversed her anemia.

The ovary

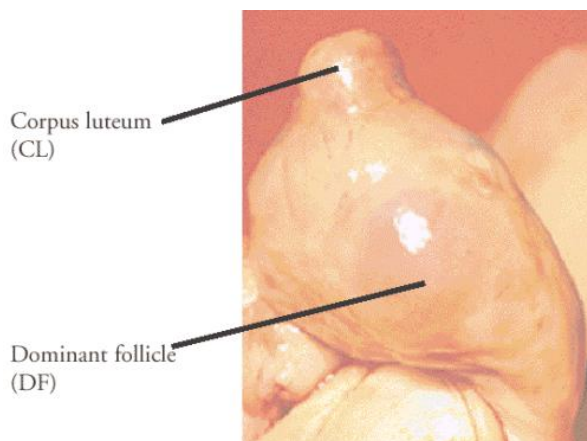
A woman has two ovaries, each about the size and shape of an almond, sitting in her pelvis and attached to the uterus by the Fallopian tubes.



The ovaries, like the breasts are glands. The secretions from these two glands (the sex hormones) are what drives the development of the female reproductive tract in the first place and then maintains it in a state of preparedness for pregnancy. The ovaries start this function in earnest about the age of 10, and then largely switch it off about the age of 50 when the body enters menopause.

The sex hormone output by the ovaries is tied to their other main function, which is to produce at least one egg each month. The two ovaries share this responsibility each month,

generally taking it in turns to produce the next egg. Each ovary contains hundreds of thousands of immature eggs known as follicles. Each follicle has the capacity to develop into a mature egg, but the vast majority never do. Out of the 2 million or so follicles that a woman is born with, only about 8 - 400 follicles (depending on the number of pregnancies) will actually make it to a mature egg stage. That's not to say that the millions of other follicles are wasted. They serve a vital support role by producing small amounts of estrogen that contribute to the overall estrogen output of the ovary. The great majority of follicles sacrifice themselves to ensure that a limited few of their number have the opportunity to mature into eggs.



At the beginning of each menstrual cycle, a small number of follicles (usually 4-6) are selected at random to start growing and to enlarge. This select few start producing more estrogen as they enlarge and this ensures that the endometrium starts to thicken in preparation for when one of them eventually makes it to a mature egg stage. After about a week of growth, one of the follicles races ahead and develops into mature egg, and the others don't progress any further. The maturing follicle moves gradually towards the edge of the ovary. Finally at about 14 days after this process began, when the follicle is sitting hard up against the surface of

the ovary, the fluid in the follicle has reached such a high pressure that it bursts, releasing the egg outside of the ovary. The egg then is directed down the Fallopian tube that surrounds the ovary, to hopefully meet the waiting sperm that have travelled up to there from the vagina.

The remaining casing of the follicle left behind in the ovary after bursting collapses into a ball of tissue known as the 'corpus luteum' (translates into the 'yellow body'). This corpus luteum remains active for about another week producing the other main female sex hormone, progesterone. Then it stops functioning and fades away.

✓ **Normal ovarian experience**

The normal life cycle of ovarian function is

- before puberty and after menopause the ovaries function purely as endocrine (or *hormone-producing*) glands, producing modest amounts of female and male sex hormones on a continual basis
- between puberty and menopause the ovaries maintain a monthly cycle of egg production plus glandular activity. Each month, one or two follicles will develop over 14 days to produce a mature egg. The estrogen output from those maturing follicles rises significantly
- the follicle(s) rupture on about day 14 of the cycle to release an egg and then will collapse to form a corpus luteum that produces progesterone for another 7 days or so
- the corpus luteum collapses and becomes replaced with scar tissue.

A woman should have little awareness of this cycle of ovarian activity. The ovaries are programmed to produce 1-2 eggs each month, and other than a slight change in body temperature at the time of ovulation, and occasionally a small amount of spotting at the time of ovulation, there should be no other sensation of this regular monthly function. If you were to look at the ovary of a woman of reproductive age, you would see either a developing follicle or a regressing corpus luteum, depending on the stage of the menstrual cycle, and areas of scarring on the surface where previous follicles have ruptured.

✘ **Abnormal ovarian experience**

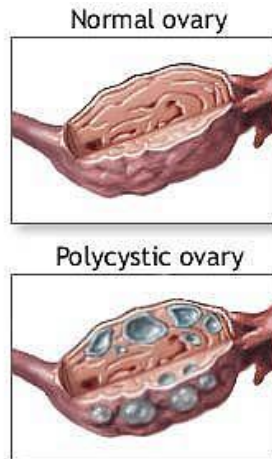
Unlike the breast and uterus where the majority of women do not enjoy normal function, the majority of women fortunately appear to enjoy normal ovarian function. Perhaps this is because unlike the breast and the uterus which are targets of estrogen function and therefore particularly sensitive to any imbalance in estrogen levels, the ovaries are less of a target and more a primary source of these hormones.

However, the ovaries still are the subject of two main types of abnormality, and while they might affect only a minority of women, they both occur at unacceptably high levels and are an important cause of disability, infertility and death.

POLYCYSTIC OVARY SYNDROME

About 10% of Western women are thought to have this condition. The ovaries are enlarged and have a lumpy appearance referred to as a 'pearl necklace' look. Originally it was thought that the lumps represented a collection of 'cysts' or fluid-filled sacs within the ovary, hence the name 'polycystic'. But it is now realised that what originally were thought to be cysts are in fact immature follicles.

PCOS reflects a failure of the normal process of development of follicles. It seems to be a failure in the final process needed to give one follicle a growth spurt each month to lead it to develop into a mature egg. The lumpy appearance is due to a progressive accumulation of follicles that have failed to develop fully.



Most women with PCOS have only a mild case and do not realise that they have it. Their periods usually are relatively normal and they will ovulate frequently enough to be fertile. It is usually only when they gain weight that it can tip over into symptoms and lead to a diagnosis of PCOS.

The extra body weight is thought to lead to increased estrogen production (from the fat) and this appears to be enough to worsen the condition, suggesting an estrogen excess might be associated with the problem in the first place.

These women usually experience irregular periods (from twice a month to no periods) and have trouble conceiving.

However, there is a group of women with PCOS where the condition progresses to a far more serious state. This state is known as polycystic ovarian disease (or PCOD for short) and upwards of 5% of Western women are thought to have this condition. In this disease, the accumulated follicles produce abnormally large amounts of male sex hormone leading to complications elsewhere in the body. The main consequences of this condition are

- erratic ovulation or failure to ovulate and to menstruate (PCOD is the most common cause of ovarian failure)
- infertility (most women with PCOD are infertile)
- hirsutism (or excessive hair production in a male pattern present in about two-thirds of women with PCOD)
- evidence of masculine characteristics including severe acne, a deeper voice, smaller breasts, and less feminine body shape
- a higher risk of cancer of the endometrium.

The usual treatment for PCOD involves

- losing body weight
- the use of drugs to block the production of male sex hormones to clear up acne and excessive hair growth
- the use of the oral contraceptive pill to regularize the menstrual cycle and to reduce the risk of endometrial cancer.

Janine comes from a family where her mother and one of her three elder sisters suffered PCOD. She is 27, married and wanting desperately to start a family.

She was diagnosed with PCOD at the age of 25. An ultrasound examination revealed the presence of multiple cysts in both ovaries and a blood test confirmed an abnormal sex hormone pattern. But even without those tests, her doctor had been pretty sure about the diagnosis, just because of Janine's symptoms. Janine had never had a normal menstrual cycle pattern. While most of her friends seemed to have regular monthly periods, Janine's periods were irregular, sometimes months apart. She also developed excessive hair growth, particularly around her nipples and on her face and this usually got worse just before her periods started. She had always been overweight, and despite her best efforts

to lose weight through diet and exercise, she just found it very difficult. Her doctor explained to her that she most likely had problems with her insulin hormone function, a common problem in women with PCOD that predisposes them to obesity.

In Janine's mind, her biggest problem was that she couldn't fall pregnant. Janine and her husband had been trying to have a baby ever since she got married at the age of 19, but so far with success. It was that problem that took Janine to her doctor in the first place that led to the diagnosis of PCOD.

Janine also was told that her problem could not be cured. That the best that could be hoped for was to minimize her symptoms. She started taking a drug to reduce the effect of the excess male hormones that her ovarian cysts were making on her body. She also was attending a diabetic clinic to help stabilize her insulin and weight problems. Of greater importance to her, however, was that her doctor had promised that as soon as those symptoms were stabilized, she could start taking treatment to induce ovulation, and that, she hoped, would allow her to become pregnant.

OVARIAN CANCER

Ovarian cancer is the fifth leading cause of death from cancer in women in the Western world. It is an aggressive cancer that is difficult to detect in the early stages and poorly responsive to treatment once established. Ovarian cancer can occur at any age, but like breast cancer, it is more common in older women. The average age for diagnosis of ovarian cancer is 59.

The lifetime risk for this cancer is about 1.6%, meaning that about 1 in 80 women in Western countries will develop this cancer. In women with a mother or daughter or sister who have developed the disease, the lifetime risk rises to 5%. In women with the mutated form of the BRCA1 or 2 genes, the risk rises to between 25-60%.

Much less is known about the causes of ovarian cancer than about breast or endometrial cancer, although as with those other two cancer types, increased exposure to estrogen is thought to be the prime risk factor since

- HRT therapy using estrogen alone is reported to lead to an increased death rate from ovarian cancer
- obesity is associated with an increased risk (presumably associated with higher estrogen production from body fat)
- more periods in a lifetime (due to earlier onset of puberty and/or later menopause) is associated with increased risk (presumably related to more estrogen surges over a woman's lifetime)
- the oral contraceptive pill is associated with a 60% lower risk of ovarian cancer (probably because fewer ovulations means fewer estrogen surges)
- an earlier age of pregnancy and a later age of final pregnancy and more pregnancies have a protective effect.

Pre-Menstrual Syndrome

So far in this section we have looked at the things that commonly go wrong with a woman's reproductive organs as a result of an imbalanced estrogen hormone system. But the consequences that a woman can suffer as a result of that imbalance go well beyond that of her reproductive tissues. The brain and skin and gut are just some of the different parts of the body that come under the influence of estrogen and so these body parts also can be adversely impacted by excessive estrogen function.

One of the most common general consequences of an imbalanced estrogen system in women during their reproductive years is the condition known as *pre-menstrual syndrome* (PMS). This condition is called a 'syndrome' because it covers a wide collection of symptoms and each woman can suffer a different set of symptoms. Despite being very common and affecting up to three out of every four pre-menopausal women in Western countries (depending on how strict you are in determining symptoms), very little is known about its cause. About the only thing that most doctors agree on is that it is associated with an imbalance of female sex hormones, in most cases estrogen.

The symptoms usually strike each month between ovulation and the start of the period. They usually last about a week and decline about the time the period starts. Curiously, PMS often is worse in a woman's mid-30s.

The range of PMS symptoms is large but tends to fall into about six categories. The distinction between these categories is blurred, and a woman can experience symptoms from different categories. But in most cases, a woman with PMS tends to suffer symptoms predominantly from one of the following six categories.

- Type 1. Symptoms associated with irritation of brain function - *irritability, anxiety, nervousness, agitation, mood swings, sudden anger.*
- Type 2. Symptoms associated with depression of brain function - *depression, confusion, weeping, memory loss, lowered libido, low self-esteem, feelings of uselessness, alcohol abuse.*
- Type 3. Symptoms associated with the digestive system - *sugar cravings, food binges, constipation, flatulence, poor digestion, diarrhoea.*
- Type 4. Symptoms associated with water retention - *cyclic mastalgia, swollen feet and hands, abdominal bloating, weight gain, joint pain.*
- Type 5. Symptoms associated with the skin - *pimples, severe acne, oily skin and hair.*
- Type 6. Symptoms associated with musculo-skeletal and cardiovascular systems - *backache, muscle pain, headaches, migraine, palpitations.*

Type 1 and 2 symptoms involving brain function are similar to those seen at other times of a woman's life when her body is responding to changing female sex hormone levels. Such as during puberty when female sex hormone levels are rising, and during menopause when levels of those same hormones are falling, and then when estrogens and progesterone are given as HRT therapy to menopausal women. The PMS type 4 symptoms involving fluid retention are thought to be associated with excessive production of prostaglandins (the substances we noted earlier that lead to inflammation of tissues) or the hormone aldosterone (the hormone that instructs the kidney to make less urine). The production of both prostaglandins and aldosterone is influenced by estrogen. PMS type 5 symptoms are those associated with excess production of male sex hormones. PMS type 6 symptoms are often seen in women entering the menopause when their bodies are faltering in their estrogen production.

The fact that we see such a wide range of symptoms under the title of PMS, probably simply reflects the individualistic response of women to an estrogen imbalance. The interaction between estrogen and progesterone (and even testosterone) is so intricate, that tilting the scales towards an 'estrogen excess' has the capacity to disturb the body's production of all of other sex hormones. PMS probably is the collective result of an imbalance in all sex hormones, triggered in the first place by an imbalance in the estrogen levels. Which particular collection of symptoms a woman might experience as a result of that imbalance probably just reflects her individual hormone status.

But irrespective of the precise causes of PMS, the underlying problem is a malfunctioning female sex hormone system. Just as any woman is entitled to the expectation that her reproductive tissues should behave normally in response to her female sex hormone changes, so the rest of the body should similarly be able to cope with the normal cyclical changes taking place in her body as part of her menstrual cycle. Clearly this is not happening. Up to 3 out of four women are experiencing some adverse physical or emotional changes in their bodies to the point where their lifestyles and well-beings are adversely affected.

Allyson and Belinda are twins, 20 years-old and college students.

Allyson and Belinda like many twins enjoy a close relationship and share the same likes and dislikes. Their similarity even extends to them both suffering PMS. But that's where the similarity ends, for while Allyson's PMS has never been particularly bad, Belinda suffers considerably and her symptoms are quite different to those of Allyson.

Allyson is very much a PMS type 4 person. In the week immediately before her period was due, she will get slightly swollen and tender breasts, her normally slim body develops a 'bit of a tummy', and she just feels heavy and sluggish. Occasionally she gets bad headaches, but mostly the symptoms didn't bother her too much. And they usually settle down once her period starts.

Belinda is a totally different case, which puzzles them both since they are so similar physically and emotionally in all other respects. Belinda is a type 1 person. Her symptoms are not only more severe, but they usually last longer, starting about the middle of her cycle and lasting for about 2 weeks. She gets irritable and agitated at everyone and everything, even down to her beloved pet dog. Minor things set her off, and the rest of the family, including the dog, have learnt to avoid her when she is in this 'short fuse' state as they called it.

She also has started having panic attacks. Things like having to complete college assignments will send her into a state of enormous anxiety, even though in her heart she knows that she can meet deadlines OK. Her heart races and she gets short of breath and dizzy just thinking about a deadline. There are even times when she won't go out with friends because of some unclear anxiety about going out in the car or being in public. At these times, she just feels as though she has lost control. The onset of her period invariably brings about a change in her personality, and she usually then has about 2 weeks of her normal confident, relaxed, outgoing self.