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## Endometriosis

### What Is Endometriosis?

Endometriosis is a disease process which affects women, mainly during their reproductive years. The same tissue which lines the inside of the uterus (womb) establishes itself in sites of the body other than the uterus. Mostly, this is within the pelvis. If a sample of the endometriosis tissue is taken and sent to a pathologist, then under the microscope it has exactly the same appearance as the internal lining (endometrium) of the uterus. This means that it functions in much the same way, growing through the cycle in response to the ovarian hormones and then shedding some of its tissue and also bleeding at the time of the period. Obviously, the amount of blood loss from any particular patch or spot of endometriosis will depend on how much tissue is present. Endometriosis can therefore occur in tiny spots no larger than a pinhead, but can vary in size from these to masses which are larger than a cricket ball. Fortunately, minor endometriosis, which involves very small amounts of abnormal tissue, is more common than very severe levels of disease where very large amounts of endometriosis tissue are present.

In the normal female menstrual cycle, the internal lining of the uterus (endometrium) is very hormone responsive. The appearance of the tissue on any particular day of the cycle is dependent upon which ovarian hormone, or combination of ovarian hormones, is affecting it. Therefore, in the first half of any one cycle the lining of the uterus grows rapidly; in the second half it begins to secrete mucous, compact and organise itself to receive a pregnancy, and during the menstrual phase of the cycle the tissue sheds off and bleeds quite freely. Endometriosis tissue, due to its abnormal site and blood supply, is sometimes a little less responsive than the normal endometrium, but it essentially undergoes the same changes.

The most damaging of these is the bleeding which occurs at the time of the period. Menstrual-type blood can therefore be released into sites in which it was never meant to occur, eg. inside the pelvis. This release of menstrual-type blood explains many of the side effects and symptoms that are associated with endometriosis. The hormone responsiveness of endometriosis also explains why we can use sometimes hormone therapy to treat the disease. By interrupting the constant ebb and flow of ovarian hormones to the endometriosis, we are able to disrupt the course of the disease and prevent it from growing or spreading and, in many cases, we are able to get rid of it entirely.

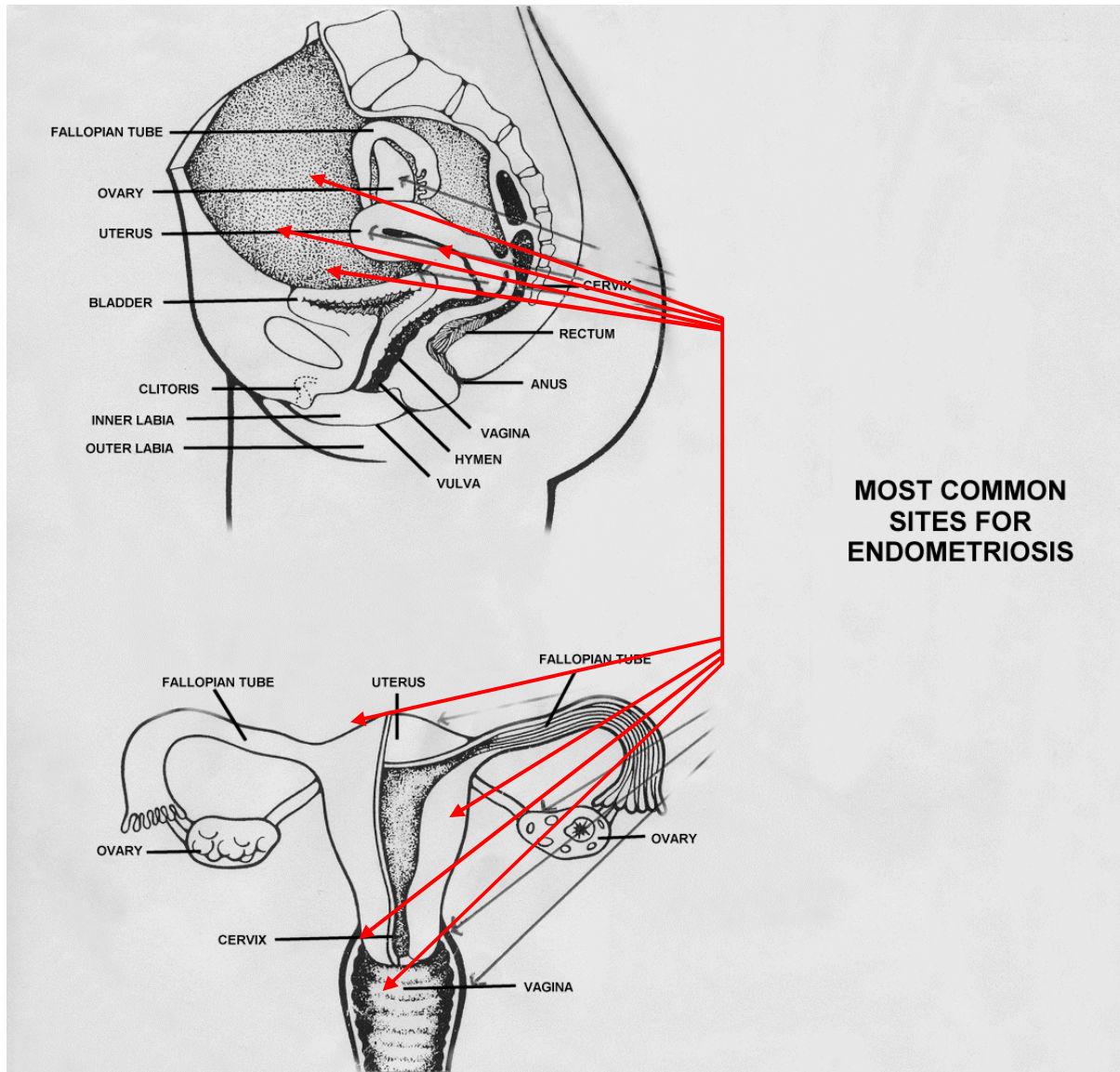
### Where Does Endometriosis Occur?

Mostly, endometriosis occurs in the pelvis. The female pelvis is a space continuous with the abdominal cavity. It contains the bladder, the rectum and other bowel, and, most importantly, the female reproductive organs, including the vagina, uterus, tubes and ovaries. Internally, the pelvis is lined with a glistening, membrane-like material called pelvic peritoneum. This is continuous with the peritoneum of the abdomen, which lines the abdominal cavity all the way from the bottom of the pelvis up to the diaphragm. This smooth, glistening membrane allows bowel and other organs to slide around inside the abdominal cavity without sticking and, also, it protects the abdominal cavity from such things as infection.

Endometriosis can occur at almost any site in the pelvis. The accompanying diagram shows the most likely sites that it will occur. Endometriosis is most commonly found to be sitting on the peritoneum of the pelvis behind the vagina and uterus, underneath the ovaries and sometimes on the ovaries. It can also occur on the peritoneum in front of the uterus, between the uterus and the bladder. It less commonly grows on the fallopian tubes and, therefore, disrupts their function. More severe forms of endometriosis can grow inside the ovary, rather than just on the ovarian surface. This sort of endometriosis often forms cysts, which we think may grow in from the pelvic wall, which slowly take over a lot of the ovarian substance. As these cysts have a small period every month, they soon fill with a thick, menstrual-type blood which, as the water is absorbed out of it, starts to look like melted chocolate. This is how the "chocolate cysts", which are part of the more severe forms of endometriosis, occur. Fortunately, they do not occur in the majority of patients as they are quite damaging to both the ovarian structure and its function. Rarely, endometriosis occurs in body sites away from the pelvis. It can occur in other parts of the abdominal cavity, eg. on the surface of the liver, and has rarely been found in such places as abdominal wounds, or even in lung tissue.

This makes endometriosis sound as though it may spread like a cancer but, in fact, endometriosis is not malignant and is hardly ever life threatening. Patients' lives are only really put at risk from endometriosis by the pressure symptoms that it can cause if it becomes very large, or if they develop obstructions due to the severity of the adhesions it may cause. Again, these are rare circumstances.

**Figure 1.** The site at which endometriosis occurs is important in explaining its side effects.



Nodules or plaques of endometriosis which occur behind the vagina and behind the cervix on the womb are commonly associated with pelvic pain and, particularly, deep pain on intercourse. This is because the sites of the endometriosis are directly hit during intercourse by the penis. Similarly, endometriosis which occurs underneath the ovaries, and perhaps tethers the ovaries down to the vaginal area, can also cause pain during intercourse. Extensive endometriosis in and around the ovaries can also disrupt menstrual function, causing period abnormalities. Endometriosis is classically associated with period pain because it releases a small amount of thick, menstrual-type blood, rich in various chemicals which cause period pain. The major problem is that this blood, instead of flowing out of the vagina as nature intended, is caught inside the abdominal cavity. Due to the thickness of the blood and its chemical nature, it can cause quite intense period pain, particularly in ladies who in the past have never been particularly troubled by this problem.

As endometriosis becomes more severe, the inflammation it causes by growth and its release of blood can cause adhesions to form. Adhesions are bands of scar tissue which form between two surfaces within the body. In the pelvis, the uterus, tubes and ovaries, whilst connected to each other anatomically, are supposed to be able to move reasonably freely. This means that the tubes can move over the ovaries to pick up an egg in order to enhance the chances of pregnancy. Endometriosis can cause quite extensive scarring in the pelvis which immobilises the movement of the uterus and thus can cause pain on intercourse and pelvic examination. Similarly, these adhesions can tether the ovaries down to the pelvic wall, which can cause pain and sub-fertility. The fallopian tubes can sometimes be caught in these adhesions,

which can limit their mobility across the surface of the ovary and prevent them from being in the right spot on the ovary each month to catch the egg as it is released. Bowel which is normally sitting down in the pelvis can also get caught up in these adhesions and it can cover the uterus, tubes and ovaries. This can make the pelvis very difficult to see at laparoscopy, as well as causing significant pain by the disruption of the normal pelvic anatomy. It can also contribute significantly to infertility. Fortunately, these very severe cases of endometriosis where extensive pelvic adhesions occur are, again, relatively rare.

### **What Causes Endometriosis?**

The most truthful answer is that nobody is really sure. As fast as one theory attempts to explain the occurrence of endometriosis, a special set of circumstances is demonstrated in a particular group of patients which negates that particular theory. The most widely accepted theories include:

#### **1. Retrograde Menstruation and Implantation**

This is the most classic theory. It suggests that blood and fragments of endometrial tissue travel up the fallopian tubes at menstruation instead of flowing down into the vagina. These tissue fragments then are able to implant within the pelvis and become endometriosis. This theory is attractive in that it has been shown to be true in animal models by injecting samples of menstrual blood into the abdominal cavity and looking for evidence of seeding later. However, like all the theories associated with endometriosis, it does not hold true for all patients. Endometriosis has been demonstrated in patients who have had tubal ligations many years before. In this circumstance, it is impossible for retrograde menstruation to occur. Also, this theory fails to explain the diverse sites in which endometriosis can occur. Retrograde menstruation cannot explain endometriosis occurring in an abdominal wound or in the umbilicus, for example. It therefore may provide some of the answer as to why endometriosis occurs, but it is clearly not the whole reason.

#### **2. Spread of Endometrial Tissue by the Blood or Lymphatic Channels**

It has been suggested by some authors that fragments of endometrial tissue are carried by the veins or lymphatics (channels in the body which parallel the bloodstream and are responsible for carrying the clear serous fluid which makes up most of our body tissue). This theory may have some part to play in the transmission and spread of endometriosis and may explain the very rare sites, such as lung, which are far from the pelvis, where endometriosis can occur. However, most workers in the field feel that this explanation is insufficient to explain how endometriosis really occurs.

#### **3. Metaplasia**

The ability of cells to undergo metaplasia provides the basis of the most plausible theory as to why endometriosis occurs. Metaplasia is a process in the body whereby one adult cell type can undergo transformation to become another adult cell type. For example, a cell may change its shape and specialised function from being a long, thin cell which produces mucous to being a round, flat cell which protects the surface of the body upon which it sits. This sort of metaplasia occurs every day in the cervix. Most of the specialised types of cells and tissue which occur in the pelvis are derived from the same primitive cell line when a baby is forming in utero. Therefore, the ability exists right throughout your life for one specialised cell type to change into another specialised cell type, provided it comes from the same primitive tissue cell line and it is given the appropriate set of stimuli. This forms the basis of how endometriosis is thought to occur.

Specialised adult types of cells which line the pelvis, eg. the pelvic peritoneum, can therefore change into endometriosis type cells, provided the correct set of stimuli occur. We are unsure as to what these stimuli are. Current theories suggest that patients who develop endometriosis may have an imbalance of hormones and chemicals released into the pelvic cavity by the ovaries. These hormones and chemicals, eg. oestrogen, progesterone and prostaglandins, may provide the stimuli to change pelvic cells into endometriosis cells. Conditions where there is a very low output of hormone from the ovary, such as pregnancy, lactation or anti-endometriosis drug therapy, can therefore decrease the stimuli to the pelvic cells and decrease the rate of change to endometriosis type cells. Other factors associated with regular monthly ovulation may modify this response. There are clearly a group of susceptible patients who develop endometriosis, even though their ovulation may not be much different from other patients who do not develop endometriosis. We do not, again, understand why some patients do and some patients don't respond to these stimuli. The immune system may have an important part to play in preventing the development of endometriosis or allowing it to occur. It has been well demonstrated that patients with endometriosis have altered immune function. It is likely that the immune system alternately allows endometriosis to grow and then perhaps contributes to its dying off so causing small areas of scar tissue in the body. Immunology is still a relatively poorly understood area of medicine and the protective role it may play in the development of endometriosis is still poorly understood. Further research is clearly required into the aetiology of endometriosis and this is currently being performed in a number of centres around the world.

### **Who Gets Endometriosis?**

The answer is that almost any female between puberty and menopause is susceptible to the onset of endometriosis. As younger girls in their mid-teens are being laparoscoped to investigate their period pain, we are finding an increased incidence of endometriosis in this group. Similarly, endometriosis has also been found in peri and post-menopausal women. However, endometriosis is relatively rare in this group. It would seem that endometriosis is more likely to occur in females through their twenties and into their thirties. Women who delay their childbearing would seem to be more

susceptible, although young women can still develop quite severe forms of endometriosis. Stress factors may play a part and contraceptive history may be important. Pregnancy may disrupt the course of endometriosis, although not cure it in all patients. However, women who have had children are somewhat less likely to have endometriosis, although it is by no means rare in patients who have had perhaps one or two children.

Patients who are particularly likely to have endometriosis are those with the onset of increasing period pain where this has not been a particular problem in the past. Patients who are developing new pain on intercourse or vague, unexplained abdominal pain, which may be unrelated to either intercourse or periods, may also have endometriosis. Endometriosis can sometimes be associated with period dysfunction and irregularity. Sometimes patients may present with symptoms of pain or pressure due to endometriotic cysts in the ovaries. The classic association with endometriosis is, of course, infertility. Most patients with infertility are now laparoscoped, specifically to look for evidence of tubal damage and to check for endometriosis.

Gynaecologists need to be aware that the incidence of endometriosis is increasing as more patients defer their childbearing. Therefore, young women under the age of 40 who present with infertility or abnormal gynaecological symptoms, such as pain, bleeding, dyspareunia (pain on intercourse), or dysmenorrhoea, need active investigation to exclude the possibility of developing endometriosis.

### **How Is Endometriosis Diagnosed?**

The clues to diagnosis in endometriosis are the symptoms and signs that we have already discussed. Endometriosis can sometimes be diagnosed on pelvic examination. The gynaecologist may feel nodules of endometriosis at the top of the vagina and around the uterus or may suspect the presence of endometriosis by the fact that the uterus is tethered, rather than quite mobile, or that the ovaries are similarly tethered and perhaps tender to touch. Rarely, we may see overt endometriosis in the vagina when we do a speculum examination, or sometimes nodules of endometriosis on the skin, eg. in an old surgical wound.

However, most endometriosis needs to be accurately and directly diagnosed by seeing it. This means that the patients need to have at least a minor form of surgery called a **laparoscopy**. In this operation, a short anaesthetic (perhaps about 10 minutes) ensures that the patient feels no pain. A small incision is made in the umbilicus and then a telescope is inserted into the abdominal cavity to look carefully at all the pelvic organs and surfaces. In this way, endometriosis can be correctly identified and its severity assessed. Various grading systems exist for endometriosis to assess its severity. These are perhaps more important in methods in research and drug trials. Mild endometriosis generally just means a few spots scattered around the pelvis. Severe endometriosis usually implies significant adhesions and perhaps endometriosis with large cysts occurring in the ovary with subsequent damage. In between the two, we have moderate levels of endometriosis where the disease is extensive and has caused some pelvic scarring, but not to the level that we would define severe endometriosis. Paradoxically, the severity of the endometriosis that we diagnose visually may not correlate well with the severity of the symptoms the patient is experiencing. Quite mild forms of endometriosis can cause quite severe pelvic pain, whilst some patients with very severe levels of endometriosis and extensive pelvic damage have had the endometriosis found by accident and have never really complained of the symptoms of endometriosis before.

Endometriosis can also be diagnosed at laparotomy. This is a far more significant operation than laparoscopy as a full-sized incision is made in the abdominal wall so the anaesthetic time is longer, the discomfort is greater and the recovery time is also longer.

There is no substitute for an accurate diagnosis of endometriosis. It is a prerequisite to prescribe many of the drugs that we use to treat endometriosis. It is also worthwhile doing a "second look" laparoscopy at the end of the course of treatment to ensure that the endometriosis is adequately treated prior to ceasing therapy. It seems illogical to place a patient on up to six months of drug therapy to cure a symptomatic and damaging condition and yet not check that the condition is cured prior to ceasing therapy. The other advantage of "second look" laparoscopy is that it is an ideal time, with most of the disease gone, for any residual disease to be treated surgically, eg. by excising it with diathermy, or scissors.

### **What Are The Symptoms of Endometriosis?**

These have been extensively discussed, so they are listed for convenience and reference.

The major symptoms of endometriosis are:

1. Dyspareunia (pain on intercourse)
2. Dysmenorrhoea (pain with periods)
3. Pelvic and abdominal pain
4. Abnormal bleeding
5. Pelvic pain
6. Infertility
7. Feelings of pressure and discomfort in the pelvis
8. Occasional bowel disturbance or bowel motion pain, especially with periods.

Again, it is worth stressing that a wide variety of symptoms can occur in patients and the severity of these symptoms is also very diverse. Often patients with quite severe forms of endometriosis can have the most subtle of symptoms.

### **Treatment of Endometriosis**

The principles of treating endometriosis are:

1. At the end of treatment the patient should optimally be **disease** and **symptom** free.
2. Treatment should be **individualised** to take account of the severity of each patient's endometriosis and to minimise the side effects of treatment.
3. Laparoscopic surgery with excision and removal of all the endometriosis has become the best treatment for most levels of endometriosis.
4. Minor surgery in the form of laparoscopy/laser treatment in some cases maybe as effective as drug treatment in relieving symptoms and producing pregnancies. It has a definitive role to play in the management of mild or moderate endometriosis.
5. Hormonal (drug) therapy in general can be used as a primary method of treating minor endometriosis. It is less invasive than surgery.
6. **All** forms of hormone therapy have potential side effects. These are usually minor in nature, are tolerated and it is uncommon to have to change a drug once it is started by a patient. However, doctors must be flexible if the patient is experiencing problems.
7. Before drug treatment is ceased, or soon after, a "second look" laparoscopy should be performed to ensure it has worked and the endometriosis is gone.
8. Sometimes it is better to attempt to achieve a pregnancy to improve the endometriosis rather than use hormonal or surgical treatment. This decision will depend on the individual patients fertility needs.
9. Laparotomy (ie major open, large cut surgery) should be used only in severe endometriosis or where all other therapy has failed and then hardly ever.

### **Surgical Treatment of Endometriosis**

Various levels of surgical treatment are available for endometriosis. The simplest type of surgery is laparoscopy and various types of procedures may be done down the laparoscope to get rid of the endometriosis or its effects. A more significant form of surgery is laparotomy, where a large incision is made in the abdominal wall to actually perform a definitive surgical procedure. Obviously, this takes longer, is more painful and the patient is in hospital for longer.

The risks and side effects are also greater than for laparoscopy. It is therefore better to keep laparotomy as a last resort treatment for endometriosis, to be used only when other methods of treatment have failed or when the endometriosis is very severe and then only very rarely. Burning endometriosis by diathermy or laser may be used to treat mild endometriosis or may be used in the context of a second look laparoscopy at the end of the period of hormonal therapy.

### **Laparoscopy, with Laser or Diathermy**

Laparoscopy is initially used to diagnose endometriosis. When we visualise areas of endometriosis it is possible to destroy them under the control of the laparoscope by burning or excising it. This can be done simply with the diathermy or in a more elegant way using the laser. We have the technology to direct a laser beam down the laparoscope and use it to excise both adhesions and areas of endometriosis. Simple burning treatment is not always the answer for endometriosis as it is rather like trying to treat a case of measles by burning the spots away. The basic disease process probably still remains or returns quite quickly. It is sometimes better to combine a hormonal (drug) regime with local destructive therapy for extensive mild endometriosis. Laser destruction of endometriosis (or diathermy) is probably best used in the context of a second look laparoscopy at the end of the period of drug therapy. The endometriosis and its causes have therefore been definitively treated and laparoscopic surgery is used to get rid of any residual disease so that the major aim of therapy is achieved, ie. the patient becomes disease free of the endometriosis.

Laser therapy can also be used down the laparoscope to divide the adhesions caused by endometriosis. The beauty of laser surgery is that it is cleaner than ordinary diathermy as it vaporises endometriosis and the adhesions with less subsequent formation of adhesions after the surgery. Laser surgery, however, is not entirely without its risks. Due to the intensity of the laser beam, it is possible to burn vital structures within the abdomen whilst treating the endometriosis. In rare circumstances this can mean more major surgery for the patient to fix up the damage caused by laser surgery. Laser surgery should be approached with caution and should only be performed by people competent in the technique.

### **Advanced Laparoscopy with Excision of Endometriosis**

There is now a worldwide trend to more advanced laparoscopic surgery for endometriosis. In the past few years some gynaecologists have become cleverer in operating telescopically. This has meant that very major surgery, previously performed through a large incision, can now be done laparoscopically. This means short (often one night) hospital stays and quicker return to work with much less post-operative pain. This is very skilled surgery and often requires extra training. It often can take 1 - 3 hours and involve a lot of dissection of the pelvic structures when the endometriosis has caused severe damage which must be repaired. The bowel often needs to be freed from the ovaries and uterus. Lumps

of endometriosis are removed with great precision due to the improved visibility of the laparoscope.

At these laparoscopies all the scarring and endometriosis (old and new) is excised and removed. The aim is to leave the pelvis completely free of all scarring and endometriosis. Long-term pain relief may be obtained from this level of surgery.

Patients often need prior to surgery a bowel clean out (bowel prep), as often at this level of severity, the endometriosis involves bowel adhesions. Data suggests excellent long term results from this surgery.

### Laparotomy

This is now very rarely used in the presence of persisting very severe endometriosis after other forms of therapy are not possible. It is particularly used where large lumps of endometriosis (endometriomas) form in the ovaries and are difficult to treat with drug therapy or laparoscopic surgery. A large incision is made in the abdominal wall and the aim of the surgery is to remove as much endometriosis as possible to leave the patient disease-free. Any adhesions which may be present are divided in the most careful way possible. This type of endometriosis surgery is often done to improve an otherwise badly damaged pelvis and enhance a patient's fertility or at the time of a hysterectomy.

There are significant risks to all surgery; the most important of which is subsequent adhesion formation. Once the patient has surgery for endometriosis she runs a significant risk of having tethering of the ovaries and the tubes to each other, with a subsequent decrease in fertility. The results of surgery can therefore be somewhat variable and can have, in fact, a deleterious effect on the patient's fertility status. Surgery should therefore be approached with caution, but has a place to play in the definitive management of endometriosis. Advanced laparoscopy has taken the place of laparotomy.

The final alternative is hysterectomy with removal of the womb, all the endometriosis and sometimes the ovaries. This is curative in 90% of cases, but only can be used when childbearing is complete. It must be stressed that hysterectomy is not a cure for endometriosis unless all the endometriosis is removed at the same time. Laparoscopic Hysterectomy with excision of all the disease is the final best treatment for advanced endometriosis.

### Risks of Surgery

Due to the difficult nature of Endometriosis it is important to understand that surgery does carry risks. These include:

1. The risk of putting a laparoscope in the abdomen. Bowel or a major blood vessel can be damaged at laparoscopic entry. The risk of this is 1-3 cases/1000.
2. Other organs in the pelvis and abdomen can be damaged as the endometriosis is removed. This includes the bowel, the bladder, nerves and blood vessels and the ureter (a tube which connects the kidney to the bladder). If such damage does occur prompt repair will usually solve the problem. Rarely, damaged bowel may need resection or very rarely, a colostomy and bag. A catheter or tubes may need to stay in the bladder or ureter if these organs are damaged. The risk of inadvertent organ damage is less than 1:100 cases.
3. Adhesions can form as the result of surgery, especially with the inflammation of endometriosis. Every attempt is made to minimize this but scarring can still occur.
4. Infection is a risk of surgery. Major cases will usually have antibiotic cover. Infective complications are uncommon.
5. Bleeding can occur during or after surgery. Major cases of endometriosis almost never need blood transfusions but these may occur.
6. Clots can form in veins of the legs or pelvis and travel to the lungs causing a pulmonary embolism. The risk of this is about 1:400 cases.

### Hormonal (Drug) Therapy

Hormonal therapy works on the principle that endometriosis is lessened during pregnancy or by menopause. Therefore, the aim of drug therapy is to put patients into a hormonal state of pseudo-pregnancy or pseudo-menopause. Side effects that patients may sometimes experience relate to these conditions. The hormones which can be used are:

#### GnRH Agonists

This is a new class of drugs which have already been used extensively in most IVF programs. GnRH is the hormone which travels from the brain to the pituitary gland in the brain to release most of the hormones which control ovarian function.

The GnRH agonists are very powerful drugs which mimic this hormone and therefore travel to the brain, but they are up to 2,000 times more powerful than the natural hormone. They therefore cause exhaustion of the pituitary gland in the brain and this means that there is no longer any stimulating factors controlling the ovary. The ovary goes into a pseudo-menopausal state and refuses to work. This is the basis of treating the endometriosis. Patients on GnRH agonists may have significant menopausal side effects, eg. hot flushes, dry vagina and mood changes. However these are often well tolerated by patients. Currently there are three GnRH Agonists available on the Australian market.

The first is **Zoladex**. This is given as a once a month injection. The drug comes prepared and preloaded in a syringe. A small amount of local anaesthetic is given into the injection site. The hormone is then injected into the layer of fat under the skin. It is then slowly absorbed over the next 28 days. Each injection needs to be repeated very reliably every 28 days. A course of treatment is usually six months.

**Lucrin** (Leuprorelin) has been used for some time on IVF programs. It is given daily by little subcutaneous injection similar to a diabetic receiving daily insulin. Each bottle contains enough doses for one month and sells for approximately \$200.00. At the moment Lucrin is not available on the pharmaceutical benefits and therefore a six month course of treatment will cost approximately \$1,200.00. A further disadvantage is the idea of a daily injection. However the injection is not very painful and can be self-administered. Lucrin is available in the depot form in the United States whereby an injection only needs to be given once a month. It is currently not available in Australia in this form.

The third agonist currently available is **Synarel**. This is a metered nasal spray which again is used daily or twice daily. The spray is inserted into a nostril and the metered dose given by depressing the spray mechanism and simultaneously sniffing. This gives a reasonably reliable dose of hormone. It does have the advantage of a very non-invasive form of administration. However absorption can be somewhat variable and some patients with sensitive nasal passages may be irritated by the spray. Also during the 6 month course of treatment if patients get colds or the flu the absorption of the dose may be also be affected. The current cost of Synarel is approximately \$100.00 a month. The cost of a full course of treatment will be approximately \$600.00. From October 1994 Synarel has been on the PBS Scheme and costs approximately \$20 per month for patients with proven endometriosis.

### **Progestogenic Agents**

Several synthetic progesterone agents are used in the treatment of endometriosis. In general, progestogenic agents are designed to produce a "pseudo-pregnancy" effect, rather than a pseudo-menopause effect. Progestogenic agents have been used for many years in the treatment of endometriosis, but are probably significantly less effective than Danazol for the same treatment time. The major progestogenic agents used are Duphaston (Dydrogesterone), Provera (Medroxyprogesterone) and Primolut-N (Norethisterone). Of these, my own preference is for Duphaston, in that it is a relatively gentle treatment with fewer side effects than the other two. It also has a proven anti-endometriosis effect in good clinical trials.

The side effects of progestogenic agents include weight gain, loss of libido, depression, breast changes, irregular vaginal bleeding and significant breakthrough bleeding. Occasionally, one can also get nausea, ankle and foot swelling, tiredness, acne, increased facial hair and breast tenderness. Primolut-N, in particular, can cause mild masculinising changes of acne and hair growth. The major problem with Provera and Primolut-N is that they cause significant amounts of breakthrough bleeding, which patients find exceptionally annoying. Sometimes patients can have spotting for as long as three to four months whilst they are on a treatment protocol that involves either Provera or Primolut-N. In these circumstances, it is better to stop the treatment for a short time or add in some oestrogen therapy to balance the progesterone. Duphaston is used in a dose of one to two tablets twice a day. Provera and Primolut-N can be used either two or three times a day in a manner similar to Danazol. In general terms, the progestogenic agents are second line rather than front line drugs for the treatment of endometriosis. Whilst the side effects are generally a little less than Danazol, their effect on the endometriosis is also poorer.

### **Danazol (Danocrine)**

This is a very mild anabolic steroid which is an effective treatment for endometriosis. Patients generally go on Danazol for four to eight months (average of six months). This drug works on the "pseudo-menopause" theory and, as such, the patients will usually lose their periods for the time they are on Danazol. Output of ovarian hormones is suppressed. Therefore, the stimuli which encourage endometriosis to grow and expand are removed. It is also possible that Danazol has an effect directly on the endometriosis. Endometriosis, in the majority of patients, will respond well to Danazol. In fact, quite spectacular cures have been achieved despite quite severe levels of endometriosis.

The side effects of Danazol relate to the fact it is a mild, male type hormone which induces pseudo-menopause. Most patients gain some weight, usually about 3 to 4 kilograms. This always engenders some panic initially, but this weight gain is reversible. It can also be prevented by careful dieting and it is often muscle rather than fat which causes the weight gain. Other "male" type side effects are mild acne, an increase in body hair, tender muscles, a noticeable increase in strength (particularly if you workout in a gym) and, very rarely, voice deepening. All of these previous side effects occur in fewer than 10% of patients. The only significant and irreversible one is the voice deepening, which hardly ever occurs but if any mild changes in voice are noted then the drug should be ceased immediately. Side effects of Danazol which relate to the pseudo-menopause effect include a dry vagina; a decrease in libido; hot flushes which begin soon after starting Danazol and usually resolve within several weeks; mood changes and irritability; and a decrease in breast tissue. Very rarely, a patient can be genuinely allergic to Danazol and develop a skin rash. Danazol should not be taken in pregnancy as it could masculinise a female foetus. Danazol is generally tolerated by patients and it is rare to have to cease the drug or change to another form of therapy. Many side effects will resolve as the patient becomes more used to Danazol. Side effects can also be dose-related, so we tend to start patients on lower to medium level doses of Danazol, eg. 2 to 3 tablets per day, rather than the higher doses of 4 to 5 tablets per day. Danazol is now rarely prescribed as the GnRH Agonists are equally effective and have fewer side effects.

### **Gestrinone**

Gestrinone is a drug which has been tested in Australia recently and has now been released for general use. It works by the pseudo-menopause effect and has side effects similar to Danazol in terms of causing hot flushes, a dry vagina, etc.

It may have the advantage of being able to be used on a two or three times a week dosage. Early trials using Gestrinone suggest it is as effective as Danazol for treating endometriosis but may not necessarily be more effective than Danazol for treating endometriosis. It could have fewer masculinising type side effects than Danazol.

### **Conclusion**

The message to be gained from treatment is that it is important to **INDIVIDUALISE EACH PATIENT'S TREATMENT DEPENDING UPON THE SEVERITY OF THE ENDOMETRIOSIS AND THE SYMPTOMS THAT SHE IS HAVING**. It is also important to assess the patient's level of symptoms, her demands for future children, as well as her social and occupational requirements. Good discussion with each patient, as well as the adequate provision of information is essential in this process. Endometriosis is often a chronic disease and a good level of patient understanding is essential. Some patients with endometriosis will have increasing fertility problems. Fortunately, the results of assisted reproduction (such as IVF) after treatment for endometriosis are very good. Most patients with endometriosis, even if they have an initial problem with their fertility, end up becoming pregnant after adequate and carefully monitored treatment. Some will require a higher level of technology to achieve a pregnancy, such as IVF or GIFT. Whilst pregnancy is not a complete and definitive cure for endometriosis, the combination of pregnancy plus breastfeeding significantly slows down the course of the disease and, in fact, may get rid of it entirely.

These notes have been designed to provide information for patients who have recently had endometriosis diagnosed and are seeking more information. Please do not hesitate to discuss any aspect of your problem and ask for further information. Any comments on these notes which you think may be of assistance would also be welcome. These notes were prepared by Dr. David Molloy, Clinical Director, Queensland Fertility Group.