The Centre For Women's Reproductive Care

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Endometriosis

Endometriosis is a relatively common condition that can cause significant pain and suffering. At the other end of the scale, it can exist without any sign of its presence. Overall, between 3-10% of women aged between 15-45 years have endometriosis. In women who have difficulties conceiving, this is rises to about 25-35%.

It used to be believed that the disease is more common in goal-orientated, professional women over the age of 30, but this misconception is now well disproved. It does not usually occur before puberty (though it has been reported), and it can present for the first time in women who have already had children.

What exactly is endometriosis?

Endometriosis is small deposits of the womb lining that are located outside of the womb cavity. The most common place to find it is on the ovary, the back of the uterus and the ligamentous supports that hold the uterus in its normal position (uterosacral ligaments). It can also be found on the thin lining of the pelvic organs (the peritoneum), on the tubes, between the vagina and rectum (rectovaginal septum), in or on the bladder, in abdominal scars from previous surgery and even as far away from the pelvis as the lung!

Each time that you have a normal period, so this endometriosis does also, and this leads to cyclical swelling, stretching of tissues, inflammation and scarring. Eventually all the scarring and inflammation can lead to symptoms even when you're not having a period.

It is more common in women whose relatives have endometriosis, in women who have cycles shorter than 28 days and those who typically have a period lasting longer than a week. Many cases occur in women without these associations, of course, and not all women who fit into the above categories necessarily get endometriosis.

What causes endometriosis?

There are several theories behind this; one possible cause is called *retrograde menstruation*. Normally during a period the menstrual blood comes out of the cervix and into the vagina. In around 75% of women, a small amount of blood flows backwards down the fallopian tubes and into the pelvic cavity. This blood contains tiny seedlings of the lining of the womb - endometrium. It is not known why in some women this might implant and lead to endometriosis, but not in others - it may have something to do with a particular woman's immune response and ability to fight off & remove these seedlings.

The *metaplasia theory* suggests that because the uterus, tubes, peritoneum and part of the ovary are all developed from the same area in the fetus, some cells taking the wrong turn during development might cause endometriosis.

The *vascular theory* rests on the fact that endometrial tissue from the lining of the womb can be found in the blood stream. It might be that these small deposits end up in other areas far from the womb and grow from there. This would explain the rare finding of endometriosis in sites such as the lung.

Most likely there is no one simple answer to explain it, and the true cause is a composite of all these.

What problems can it cause?

The most common problems are:

- Pelvic pain
- Painful periods
- Pain during intercourse
- Infertility

The *pelvic pain* caused by endometriosis can be very variable. It may be like a dull ache located generally over the lower abdomen, or may be more severe. It can be more localised into the rectum (back passage) or cause urinary symptoms. Sometimes the degree of pain felt by a woman is not related to the extent of disease found when the endometriosis is diagnosed. Some women have very extensive endometriosis, but their pain & discomfort is minimal. Others have only a few spots noted and the pain is very disabling. In general, however, the more endometriosis that is present, the more likely you are to have symptoms.

Painful periods are often the first sign a woman might have that endometriosis is present. The pain usually begins a few days before the period is due and continues throughout the period. It is typically located in the centre of the pelvis, but can be one-sided. It may go into the back or down the legs.

Pain on intercourse is often worse with a particular position and especially with deep penetration. Many women experience an aching in the pelvis after intercourse.

The link between endometriosis and *infertility* is sometimes difficult to explain. When the disease is so bad that there is much scarring around the tubes, or there are ovarian cysts, it is not surprising that this might interfere with normal fertility. It is less clear how a few small spots of endometriosis might have a detrimental effect on attempts at pregnancy. Nevertheless, studies have found that endometriosis is more common in women who have difficulty conceiving, supporting the link. Also, another major study looking at treatment of mild to moderate endometriosis did find an improved fertility rate in women who received treatment.

Other symptoms

Although the above problems are most common, some women experience other symptoms related to where endometriosis might have implanted:

- painful bowel movements
- bloating
- constipation
- painful pelvic exams
- painful and frequent urination, or bleeding when passing water during the time of the period

Examination findings

A pelvic examination can sometimes suggest the presence of endometriosis. Typical findings depend on the severity of the disease and where it is located. A normal uterus is quite mobile, but the scarring of endometriosis can make it tender and fixed in the pelvis. There may be a swelling felt on one of the ovaries because of an endometriosis cyst. The uterosacral ligaments are one of the supports of the uterus where endometriosis can occur and these can be felt just above the cervix. Tender nodules in this area can suggest its presence.

Diagnostic laparoscopy

To confirm endometriosis requires a diagnostic laparoscopy. This is where a small telescope is passed through the umbilicus to gain access to the pelvis. A picture of the pelvis is viewed on a TV screen and the presence of endometriosis and its stage assessed. There is an information sheet on the website containing more information on diagnostic laparoscopy. Ultrasound is useful to help diagnose endometriosis cysts of the ovary.

At laparoscopy the appearance of endometriosis is quite variable. It can take one of the following appearances:

- blue or black powder-burn lesions
- red, blue, white or non-pigmented lesions
- scarring and peritoneal defects
- ovarian cysts

In more advanced cases of endometriosis there might be web-like scar tissue, *adhesions*, sticking the ovary to the side of the pelvis or the tube to the uterus, distorting the normal position of the pelvic organs. Even if the endometriosis is silent, adhesions can cause pain, particularly if they affect the bowel or the ovary. Stretching of the ovary and surrounding adhesions when an egg is developing toward midcycle will cause pain & make it sensitive during intercourse. Similarly the normal movement of the bowel as food passes through can lead to pressure symptoms if it is stuck down in adhesions.

Endometriosis can affect the ovary with the development of benign ovarian cysts called *endometriomas*. These can be as small as a grape or as large as grapefruit. Bleeding into the cysts leads to collection of old, dark-brown coloured blood and this is why they are sometimes called 'chocolate cysts'. A woman may suddenly feel pain if there is bleeding into an endometrioma with stretching of the capsule. Similarly if an endometrioma bursts, the blood spilled will cause irritation and can lead to the development of adhesions.

Staging of endometriosis

Endometriosis is staged depending upon the amount present, the areas it involves and the presence of secondary scarring. Staging is graded by the revised American Fertility Society score. Mild disease (rAFS stage I and II) is generally limited to small to medium-sized lesions with variable degrees of penetration. More severe disease (rAFS stage III and IV) suggests the presence of adhesions around the ovaries, tubal disruption and ovarian endometriomas.

Treatments

There are several options for treating endometriosis, and each has its place for different women's disease. The options are as follows:

- No treatment at all
- Management of symptoms
- Medical management
- Conservative surgery
- Radical surgery

If endometriosis is found, for example, at the time of laparoscopic sterilisation and it is only mild, causing no symptoms at all, then it is quite reasonable to leave well alone and avoid any treatment at all. Some surgeons might burn it away at the time of diagnosis even if it isn't causing symptoms at that time.

Symptom management

Management of the symptoms means using painkillers to make the painful periods more tolerable or for cyclical pain if it is not too bad. Hormones called ‘prostaglandins’ which make the uterus contract cause some of the pain. Ibuprofen and mefanamic acid (Ponstan) are anti-inflammatory drugs that reduce levels of prostaglandins and often help with the pain. If there is not prompt response to analgesics, it is sensible to move onto some hormonal treatment, that will actually shrink the endometriosis itself, or to consider one of the surgical approaches.

Assisted conception

If endometriosis is associated with infertility, another way of 'managing the symptoms' is to use assisted conception (in-vitro fertilisation or IVF, sometimes called 'test-tube baby'). This won't deal with the endometriosis, but the approach might be suitable for a woman with minimal other symptoms, who is older & doesn't have as much time to undergo prolonged treatments or sit around on a waiting list for surgery. Also, if other treatments have failed and infertility persists, assisted conception is usually the only remaining option.

Medical and Treatments

Treatment of endometriosis with drugs can result in great improvement of symptoms such as painful periods, pain on intercourse and pelvic pain. Three important facts must be understood before choosing a medical treatment:

- Medical treatment does not improve the chances for pregnancy and, as it is a hormonally contraceptive treatment, just delays it further.

- Medical treatment suppresses endometriosis, rather than removing it and is effective only for short-term management of symptoms, the active endometriosis returning gradually over 12-24 months after stopping.

- The various medical treatment options are of equal effectiveness in treating endometriosis, but the cost and side effects vary.

The aim of medical treatment is to break the cycle of stimulation and bleeding. By stopping the ovary's usual hormonal cycle and reducing oestrogen levels, the endometriosis deposits shrink down and become inactive. The endometriosis is still there, and will gradually become reactivated when the normal menstrual cycle starts again. Ovarian endometriomas of greater than 3cm diameter are unlikely to respond to medical treatment, and similarly if there is a significant amount of adhesions - these will respond best to laparoscopic breakdown (called *adhesiolysis*).

It was initially thought that use of the more 'powerful' treatments, such as GnRH agonists, was more likely to cure the endometriosis or result in a greater improvement in symptoms. Studies have compared the various options and it is now clear that they are all pretty much the same in terms of improvement of symptoms.

Each drug will be discussed in turn, but continuous use of the combined contraceptive pill or progestogens are usually the best options with the lowest chance of side effects. Medical treatments are typically used for 6-12 months, except for the contraceptive pill, which can be used as long as needed.

Contraceptive pill

The Pill is one of the most commonly used treatments for endometriosis, and is a good choice for young women with mild disease who also require effective contraception. Despite its long-established use, there has been only one study on the use of the Pill for endometriosis. It compared the Pill with GnRH agonists and found an equal improvement with both drugs with regards to pelvic pain, painful periods and painful sex. There was a trend towards the Pill being better at controlling painful periods and GnRH agonists being best for improving painful intercourse.

In the above study the Pill was used cyclically, but many gynaecologists suggest that it is better taken continuously, with no withdrawal bleed in between each packet. This doesn't do your body any harm and there is no 'build-up' of blood as might be expected, since one of the hormones it contains keeps the lining of the womb quite thin.

If used continuously, it should be for 6-12 months, but breakthrough spotting is not uncommon after a few months and you can either have a seven day break at the end of the next packet or your doctor might prescribe some additional oestrogen for a week, which helps to refresh the lining of the womb.

Progestogens

Progestogens are the most commonly used medical treatment and are effective in about 80% of cases. Examples include the drugs *medroxyprogesterone acetate* (Provera), *dydrogesterone* and *norethisterone*. They work by thinning out and shrinking down the endometriosis and also by suppressing the normal cycle of the ovary. They can be used either continuously or in a cyclical way (eg. taken for 3 weeks, with one week off). Depot Provera, the injection form of the drug commonly used 3-monthly for contraception also works, but its use is limited in women wishing pregnancy as it can delay ovulation some time after the last injection (up to 12 months).

Side effects of progestogens can include: irregular bleeding or breakthrough spotting - which affects around one third of users, weight gain, breast tenderness, water retention and rarely depression. This list of side effects is just what is possible, many people don't have any ill effects at all and it would be unlikely that all would be experienced at once! Once again, breakthrough bleeding can be managed with a short course of oestrogen tablets.

It has long been known that progestogens can alter the blood lipids (fats) in an unfavourable way, which might theoretically lead to an increased risk of blood clots (thrombosis). Two recent studies have provided more evidence that this could be the case. Although they looked at progestogens used for period problems, the doses used are similar as would be for endometriosis, and the risk of thrombosis was around 5-fold higher than expected. Whilst this is an acceptable risk for women not already at risk for thrombosis, if you have other risk factors (eg. a previous clot or a strong family history) then an alternative treatment might be preferable.

The Mirena Intra Uterine System

One way of administering progestogen to the pelvis is in the form of a medicated intra uterine device called the Mirena. Although developed as a contraceptive this device has found many other gynaecological uses in the treatment of heavy menstrual periods and pelvic pain. Many studies have demonstrated that it is as effective as other medications in the control of endometriosis and it can significantly reduce the risk of recurrence after surgery.

The main advantage of the Mirena is that the drug is concentrated in the pelvis where it is needed and only small amounts circulate throughout the body in the blood stream. Unwanted side effects such as mood change, sore breasts, weight gain and bloating are less common although they can still occur. Irregular bleeding is common but menstrual periods are usually substantially reduced in amount.

One disadvantage of the Mirena is that it is not really suited to a uterus that has not borne a pregnancy. However for women who have completed their family it is an excellent means of both contraception and control of endometriosis without the need to take medication. The device is fitted in a doctors surgery in a procedure that takes only minutes and its medication lasts for five years.

GnRH agonists

GnRH stands for *Gonadotrophin Releasing Hormone* and an *agonist* is a drug that acts the same way as the body's own hormone. The body normally makes GnRH in a small gland in the brain (the pituitary) and it is this hormone that stimulates the ovary to develop eggs and produce oestrogen, leading to the normal menstrual cycle. If you give GnRH agonists, this floods the system and confuses the delicately controlled balance, leading to a complete block of egg development, oestrogen production and menstrual cycle. It effectively makes you 'menopausal' for the short time that you use the treatment and without the oestrogen stimulation, endometriosis shrinks down and becomes inactive.

Examples of GnRH agonists include: goserelin (Zoladex), nafarelin (Synarel), Buserelin (Suprecur) and leuprorelin (Prostap). They are all either given by injection or nasal spray - tablet forms are unfortunately not available.

GnRH agonists are effective in relieving symptoms in 80-90% of patients and the best affect is in small areas of endometriosis. Although ovarian endometriomas will shrink down by around 20%, surgery remains the optimum treatment for the more severe disease. Studies looking at the effectiveness of GnRH agonists have found that the benefit is comparable with the other forms of medical treatment.

GnRH agonists work by lowering oestrogen levels and the main side effects of the treatment are due to this: hot flushes, reduced sex drive, vaginal dryness, emotional symptoms, depression and headaches. It really is like going through the menopause for a short time. The other main problem limiting longer courses than 6 months is that bone thinning is a side effect, with around 5-6% reduction in bone density in the spine. This is completely reversed by 9 months after stopping treatment.

There is now good evidence that the use of *add-back* hormone replacement therapy (HRT) is effective in preventing the bone thinning and the unpleasant side effects of GnRH treatment. The HRT used can be a normal cyclical oestrogen/progestogen one, a continuous 'no bleed' preparation or a newer type such as tibolone (Livial). It can be started at the same time as the GnRH agonist and does not diminish the effect of the treatment. It might seem surprising that using oestrogen replacement doesn't undo the effect of the GnRH, but there appears to be a threshold level of oestrogen where endometriosis will be stimulated, and HRT doesn't reach that level, but is enough to prevent the side effects.

Danazol

Danazol is a drug that was once used as first-line medical treatment for endometriosis and it is effective in 80-90% of cases. Fortunately, there is now good evidence demonstrating other drugs as equally effective, as Danazol can have some quite unpleasant side effects. It works by preventing ovulation and reducing oestrogen levels as well as having a directly suppressive effect on the endometriosis itself.

It has some properties that are similar to the male hormone testosterone and possible side effects include: weight gain, water retention, tiredness, decreased breast size, hot flushes, acne, oily skin, growth of facial hair and emotional symptoms. Although some side effects are experienced by about 80% of users, they are only troublesome enough to make women stop treatment in 10% of cases. It can irreversibly deepen the voice. It is also important to use an effective contraceptive, as accidental use in early pregnancy can masculinise a female fetus.

Gestrinone

Gestrinone is a treatment used more commonly in Europe. It works in much the same way as Danazol with similar, but milder, side effects. It is taken twice weekly and around 85% of women do not have any periods at all when on treatment.

Surgical Treatment

Surgical treatment for endometriosis is usually carried out in one of the following situations:

- At the time of diagnosis for mild to moderate endometriosis
- If medical treatment hasn't worked
- If subfertility is a problem
- If there is moderate to severe endometriosis, particularly with endometriomas
- When endometriosis recurs

Surgery can either be conservative or radical. The aim of conservative surgery is to return the appearance of the pelvis to as normal as possible. This means destroying any endometriotic deposits, removing ovarian cysts, dividing adhesions and removing as little healthy tissue as possible.

Radical surgery means doing a hysterectomy with removal of both ovaries and is reserved for women with very severe symptoms, who have not responded to medical treatment or conservative operations. Sometimes, if there are other reasons to carry out a hysterectomy it is done earlier than this.

Treatment at the time of diagnosis

This approach is rapidly becoming standard practice in the management of endometriosis. It is typically carried out where the endometriosis discovered is mild to moderate and the extra time required to do the surgery will be able to be accommodated within the operating list planned. A further keyhole into the abdomen is often needed.

Laparoscopic management of endometriosis

Mild to moderate disease

The endometriosis spots are destroyed by *diathermy*, where an electric current is passed down a fine probe burning the lesion. Some surgeons use *laser* to evaporate the endometriosis.

Fine adhesions can be cut using small scissors. Bleeding is usually minimal and having avoided an open operation means that the risk of subsequent adhesion development is reduced. Laparoscopic management also has the advantage of needing a minimal hospital stay, it is usually possible to go home the same or following day.

Improvement in pain symptoms following this type of surgery can be expected in 70% of cases, more so if the location of adhesions divided corresponds to the area of maximum pain.

There has been only one good quality study of the effect of surgical treatment of mild to moderate endometriosis on subfertility. It found that laparoscopic destruction of lesions resulted in a 13% increase in pregnancy rate - equivalent to, on average, a benefit for one out of every eight women receiving treatment.

Moderate to severe disease

Where endometriosis is more than a few spots, and in particular where there is more severe scarring or an ovarian endometrioma, there is still the option of laparoscopic treatment in some hospitals. In the UK, it is usually only an option in the larger, central hospitals or where a local Gynaecologist has a special interest in laparoscopy. The aim of laparoscopy, as usual, is to restore things back to normal. For endometriomas this will mean shelling out and removing the cyst from the underlying normal ovary tissue. An alternative is to make a hole in the cyst wall, empty out the 'chocolate' collection of blood and diathermy the cyst base so all endometriotic deposits are destroyed.

Removal of endometriomas and division of scar tissue can be expected to improve the pain symptoms of endometriosis. The success of surgery in improving subfertility is related to the severity of endometriosis in the first place. It is difficult to give exact estimations, but women with moderate disease can expect pregnancy success rates of around 60%, whereas the comparable figure with more severe disease is around 35%. If a pregnancy does not occur within 2 years of surgery for endometriosis, the chances of success are poor, and referral for in-vitro fertilisation should be made.

Open surgery

This is the usual method of approaching the more severe degrees of endometriosis, particularly where endometriomas are large and there is more extensive scarring involving the bowel and bladder.

Hysterectomy is an end-stage treatment for women who have completed their family and where endometriosis is severe. It is usual to suggest removal of the ovaries, particularly in a woman who is over the age of 40 or where the disease is particularly severe. Hormone replacement therapy will protect the bones and avoid the menopausal symptoms.

Using drugs with surgery

Overall the evidence to support drug treatment **before** surgery is not good. 3-6 months of drugs prior to surgery may make endometriomas smaller and therefore more accessible by laparoscopy, helping avoid the need for an open operation. There is nothing to suggest that it improves fertility rates or pain after the operation, however.

The use of drugs **after** conservative surgery in women wanting pregnancy does not improve pregnancy rates, but just adds delay. For women who have pain there is some evidence that pain is improved with a course of drug treatment following surgery, but it may just be limited to the period whilst the drugs are taken (as would be expected given the results of studies on long-term effect of medical treatment alone). This may be useful if it helps reduce pain whilst recovering from surgery - indeed it will take 2-3 months in any case for the true benefit from surgery to become apparent, as things gradually heal.

Recurrence of endometriosis after surgery

Recurrence rate for endometriosis has been estimated to be 10% per year by one author, another study found it to recur in 40% of women within 5 years after conservative surgery.

There is a 6 times higher risk of recurrence after hysterectomy if the ovaries are not removed. Even in women who have the ovaries removed, there is a small (0.01%) risk of further recurrence, usually involving the bowel.

Risks of laparoscopy

Keyhole surgery is generally very safe, especially in experienced hands, but it is important to be understood that any laparoscopy carries with it some degree of risk, as do all operations. When placing the laparoscope into the abdomen, there is a small risk of accidental injury to bowel, the bladder or blood vessels leading to haemorrhage - this risk is inherent in the procedure. It is greater if the surgery is more advanced involving dividing of adhesions, diathermy of endometriosis, removal of cysts, etc.

Large studies have found that complications might affect around 1/370 diagnostic laparoscopies and 1/50-100 where more prolonged and difficult operation is necessary. Not all of these complications will have serious implications, but it might mean an unexpected open operation and a longer hospital stay. Complications are more common where there have been multiple previous open surgeries.

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