Untreated endometriosis: what are the risks?

Endometriosis is a disease affecting millions of women throughout the world. For many, the condition goes unnoticed. But for others, it demands professional attention, especially when fertility is impaired or pain affects the lifestyle.

Endometriosis is a common disorder that affects women during their reproductive years. It has a prevalence of 0.5-5% in fertile and 25-40% in infertile women. It occurs when endometrial tissue, which lines the uterus, grows outside the uterine cavity. This misplaced tissue may implant and grow anywhere within the abdominal cavity, or rarely in distant sites such as the navel or lungs. This tissue may grow in small superficial patches called implants, in thicker, penetrating nodules; or it may form cysts in the ovary called endometriomas.

Highly unpredictable

Endometriosis is highly unpredictable. Some women may have a few isolated implants that never spread or grow, while in others the disease may spread throughout the pelvis, Endometriosis irritates surrounding tissue and may produce web-like growths of scar tissue called adhesions. This scar tissue can bind any of the pelvic organs to one another and may sometimes cover them entirely.

Many women who have endometriosis experience few or no symptoms. In fact, it is often diagnosed when a patient is undergoing pelvic surgery for other reasons. However, in some women, endometriosis may cause severe menstrual cramps, pain during intercourse, infertility, or other symptoms.

Endometriosis can usually be treated by medication or surgery designed to preserve fertility. However, a few patients may have symptoms so severe that the uterus and ovaries must be surgically removed. Fortunately for most patients, alternative treatments are available and hysterectomy is rarely necessary.

Sometimes labelled a 'career woman's disease'

Many specialists feel that endometriosis is more likely to be found in women who have never been pregnant. For this reason, the condition is sometimes labelled a "career woman's disease", because working women often delay pregnancy. But endometriosis cannot be so easily generalised. Sometimes it affects women who have had children and it can also occur in teenagers.

Endometrial tissue, whether it is inside or outside the uterus, responds to the rise and fall of oestrogen and progesterone produced by the ovaries during the reproductive cycle. The roles hormones play in the function of the reproductive organs will help you understand endometriosis, its diagnosis, and treatment.

Estrogen, progesterone and prostaglandins:

The cycle of ovarian hormone production has two phases. In the first half known as the follicular phase, estrogen plays a dominant role. During this phase, the egg, surround by a fluid-filled sac, matures inside the ovary. The sac is lined with cells that secrete hormones. This sac containing the egg is called a follicle. The follicle secretes a large amount of estrogen into the bloodstream, and the estrogen circulates to the uterus where it stimulates the endometrium to grow and thicken.

The second phase of hormone production begins at ovulation, midway through the cycle, when the follicle ruptures and releases the mature egg into the fallopian tube. The empty follicle becomes the corpus luteum, which produces large quantities of progesterone, as well as estrogen, throughout the second half of the cycle. Travelling through the bloodstream to the uterus, progesterone complements the work begun by estrogen as it stimulates endometrial cells to mature and makes it possible for a fertilized egg (embryo) to implant.

If no pregnancy occurs, production of estrogen and progesterone will fall 10 to 14 days after ovulation and the outer two-thirds of the endometrium will be shed from the uterus as the menstrual flow. The menstrual discharge contains endometrial tissue fragments and chemical products of endometrial cells. Among these products are a group of substances called prostaglandins. These substances stimulate the uterine muscles to contract and are largely responsible for menstrual cramping.

Endometriosis reacts to ovarian hormones in much the same way as the endometrium. Under the influence of estrogen and progesterone, the misplaced tissue swells and produces the same by-products, including prostaglandins. When hormone levels drop, the tissue may bleed. Unlike the normally situated endometrium that is shed from the body as menstrual discharge, this blood and tissue has no outlet. It remains to irritate the surrounding tissue.

What causes endometriosis?

No one factor is responsible for all cases of endometriosis, and it is likely that the disease has a multifaceted etiology. One of the earliest and most widely accepted explanations is Sampson's theory of retrograde menstruation. This classic theory proposes that, during menstruation, sloughed-off endometrial tissue is refluxed from the uterus through the fallopian tubes. These cells are capable of implanting and growing outside the uterus in the pelvic organs and lining or more distant sites. However, Sampson's theory provides only a partial explanation for the etiology of endometriosis. Virtually all women reflux menstrual fluid through the fallopian tubes, yet only some of them develop endometriosis. Therefore, this hypothesis cannot explain why retrograde menstruation, a physiologic occurrence, does not lead to endometriosis in all women.

An alternative hypothesis, the lymphatic and vascular metastasis theory, postulates that endometrial cells are transported to distant sites via the lymphatic and circulatory systems. Yet another explanation, the coelomic metaplasia theory, proposes that endometriosis develops from metaplasia of cells lining the pelvic peritoneum.

More recent research has focused on how the invading endometrial cells survive eradication by the immune system or accomplish neovascularisation (formation of new blood vessels). Numerous studies implicate dysfunction of the immune system in the pathogenesis of endometriosis. Research suggests that migrating endometrial cells can implant only in women who have deficient cell-mediated immunity. These women appear to lack the normal cellular immunity that destroys transplanted endometrial cells and prevents them from implanting.

Women with endometriosis also have been found to have increased generalised B-cell function and abnormal humoral immunity. Endometriosis is associated with the formation of autoantibodies to endometrial tissue. The peritoneal fluid from women with endometriosis also has been shown to contain multiple growth factors and cytokines, which may stimulate the growth of endometrial implants. These substances may create an environment that is toxic to sperm or embryos, providing a

possible explanation for the well-documented association between endometriosis and infertility.

More recently, researchers have speculated that environmental chemotoxins, such as 2,3,7,8-tetra-chloro-dibenzo-p-dioxin (TCDD; often called dioxin), may contribute to endometriosis. Evidence suggests that TCDD and dioxin-like compounds may be linked to the development of endometriosis in humans[14] and monkeys. Chemotoxins have been associated with decreases in human sperm count and fertility rates, and an increased risk of testicular, prostate, and breast cancer. Dioxin is among the environmental toxins known to affect the immune and reproductive systems. Exposure to TCDD or dioxin-like compounds has been shown to disrupt both immune function and the endocrine system, leading to reproductive toxicity.

Genetic factors also appear to contribute to the development of endometriosis. Studies suggest that first-degree relatives of women with endometriosis are more likely to develop the disease, have more severe manifestations, and tend to manifest symptoms earlier. Patients with a first-degree relative with endometriosis have an approximately 10-fold increased risk of developing the illness.

A positive correlation between endometriosis and age has been observed in women of reproductive age, suggesting that the disease risk increases with the cumulative number of menstrual cycles. The risk of endometriosis appears to be increased in women who have increased exposure to menstruation, such as those with shorter cycle length, heavier flow, longer duration of flow, and reduced parity. Women who delay childbirth also are at increased risk for endometriosis, perhaps because they are exposed to more uninterrupted menstrual cycles. Since endometrial tissue is estrogen-responsive, symptoms usually abate after menopause, when ovarian steroidogenesis ceases.

What does endometriosis look like?

Early implants look like small, flat patches or flecks of dark paint sprinkled on the pelvic surface. The small patches may remain unchanged, become scar tissue, or spontaneously disappear over a period of months. Endometriosis may invade the ovary, producing blood-filled cysts called endometriomas. With time, the blood darkens to a deep reddish-brown colour. Once a cyst has developed to this point, it is often described as a "chocolate cyst". These cysts may be smaller than a pea or larger than a grapefruit. Sudden pain may occur when a large cyst bleeds into itself or bursts. The spilled fluid may cause further inflammation and the development of scar tissue.

In some cases, bands of fibrous tissue (adhesions) may bind the uterus, fallopian tubes, ovaries, and nearby intestines together. The endometrial tissue may grow into the walls of the intestine or into the tissue that separates the rectum from the vagina. When endometrial tissue grows deeply into the uterine wall, it is called adenomyosis, and the uterus becomes slightly enlarged, reddish, softer than usual and tender. Occasionally, endometrial tissue can also invade the bladder wall. Although it may invade neighbouring tissue, endometriosis is not a cancer, and cancer rarely develops in endometriotic tissue.

Symptoms of endometriosis:

Menstrual cramps
Dysmenorrhoea or menstrual cramping may be a symptom of endometriosis. Primary dysmenorrhoea, which occurs during the early years of menstruation and tends to decrease with age and after childbearing, is usually unrelated to endometriosis. Secondary dysmenorrhoea, which occurs later in life and may increase with age, should be viewed as a possible warning sign of endometriosis.

Menstrual cramps are caused by contractions of uterine muscle initiated by prostaglandins released from endometrial tissue. These contractions facilitate the expulsion of menstrual fluid. While prostaglandins are released during menstruation directly into the ovaries or elsewhere in the pelvis, pain may be intensified because these pelvic tissues are sensitive to the effects of prostaglandins.

Most women who suffer from dysmenorrhoea do not have endometriosis. A puzzling feature of endometriosis is that the degree of pain is not a valid indicator of the extent of the disease. Some women with extensive endometriosis feel no pain at

all.

Two very effective treatments are available to relieve menstrual cramps associated with endometriosis. Birth control pills block ovulation and the production of progesterone, thus reducing the formation of prostaglandins. Prostaglandin inhibitors block prostaglandins production and often reduce or eliminate the pain. Ibuprofen, naproxen and aspirin are widely used as prostaglandin inhibitors. Although they relieve pain, prostaglandin inhibitors do not affect the endometriotic tissue and thus do not cure the disease. A woman with endometriosis may notice that as the disease progresses, her periods become more painful or the pain begins earlier or lasts longer.

Pain during intercourse
Endometriosis may cause pain during intercourse, a condition known as dyspareunia. The thrusting motion can produce pain in an ovary bound by scar tissue to the top of the vagina, or in a tender nodule of endometriosis on one of the uterosacral ligaments, which hold the uterus in place. Anchored near the top of the vagina, the uterosacral ligaments attach the lowermost portion of the uterus and cervix to the sacrum, the triangular bone at the base of the spine. Dyspareunia may also result from tender endometrial implants in the base of the pelvis near the top of the vagina.

Abnormal uterine bleeding
Most women who have endometriosis report no bleeding abnormalities. Occasionally, however, the disease is accompanied by vaginal bleeding at irregular intervals. Endometriosis may exist on the intestines, one the wall of the bladder, or in surgical scars. Rarely, these pockets may release blood into the bladder or bowel during the menstrual cycle.

Infertility
In some cases, infertility is a symptom of endometriosis. However, other factors such as poor quality sperm or ovulation disorders may be involved in a couple's infertility. Some women who have endometriosis are able to conceive, while others may be infertile due to endometriosis alone or a combination of factors.

Endometriosis may hinder conception in various ways. Endometriosis in the pelvis, for example, may inflame surrounding tissue and spur the growth of scar tissue or adhesions. Bands of scar tissue may bind the ovaries, fallopian tubes, and intestines together. Adhesions may interfere with the release of eggs from the ovaries or the pick-up of the egg by the fallopian tubes. If the ovaries are pulled away from the tubes, eggs may fail to enter the tubes on a regular basis after ovulation.

Researchers are investigating other possible links between endometriosis and infertility. Even implants located far from the tubes and ovaries can impair fertility, and there is evidence that something, perhaps prostaglandins or other chemicals, produced by these implants may interfere with ovulation, entry of the egg into the tube, and fertilization.

Studies have shown that the risk of miscarriage is higher for women with untreated endometriosis than in those without it. The increased risk does not seem to be present for women who have been treated. It is not known why women with endometriosis have an increased risk of miscarriage; however, chemicals that can be toxic to the embryo have been found in the abdominal fluid of women with endometriosis. Possible changes in the immune system might also explain the increased risk.

Diagnosis
The diagnosis of endometriosis cannot be made from symptoms alone. For unknown reasons, there is little correlation between the degree of a woman's pain symptoms and the anatomic extent of her endometriosis. Some women with anatomically severe endometriosis have no symptoms or complain only of infertility. Conversely, women whose disease appears minimal based on laparoscopic examination may complain of severe and debilitating pain. The reason for this paradox is not known.

Danazol
The hormone derivative danazol is a medication frequently used to treat endometriosis. During treatment with danazol, estrogen levels are often reduced to low levels similar to natural menopause. This state is sometimes called pseudo-

menopause. Danazol is thought to work indirectly by affecting the hormones produced by the brain which cause ovulation, and directly by affecting endometrial implants. Danazol is similar to male-specific hormones and may have side effects. These include, but are not limited to, deepening of the voice, abnormal hair growth, reduced breast size, water retention, weight gain, acne, irregular vaginal bleeding, and muscle cramps. Danazol controls pain in the majority of patients with less extensive endometriosis and may eliminate small patches of the disease. Unfortunately, large ovarian endometriomas (cysts) are generally resistant to the drug. Danazol is an expensive medication usually prescribed for six or more months and is associated with a high incidence of side effects.

GnRH analogues
GnRH analogues comprise the newest class of hormones used for endometriosis treatment. After a few weeks of treatment, analogue use leads to depletion of the pituitary hormones that direct the ovary to release estrogen. Estrogen levels fall to menopausal levels, ovulation does not occur, the endometrium does not grow, and menstruation does not occur. This results in a state called reversible menopause. Side effects of these drugs are associated with a lack of estrogen and include hot flashes, vaginal dryness and loss of bone calcium. The medications are usually given for six months and can be administered daily or monthly injection or as a nasal spray. They are as effective as danazol in pain relief and in achieving pregnancy. Like danazol, large ovarian endometriomas (cysts) are generally resistant to GnRH analogues.

Progestins
Some doctors use progestins to treat endometriosis. Progestins are synthetic progesterone-like drugs prescribed as pills or injections. Side effects include water retention, mood swings, and irregular vaginal bleeding. They are considerably less expensive than other medications. One special drawback of the injectable form is that it may inhibit fertility for an unpredictable period of time after treatment is discontinued.

Surgery
Treating endometriosis with medication has definite limitations. Medication usually controls mild or moderate pain and may eliminate small patches of the disease. But large endometrial cysts in the ovary are less likely to respond, and drugs cannot remove scar tissue. Surgery to remove adhesions, implants, or endometriomas may be needed to relieve pain or improve fertility. Even with surgery, all endometriosis may not be eradicated and sometimes post-operative medical therapy is used.

As described earlier, laparoscopy can be used as a therapeutic tool. For example, fluid can be drained and small patches of endometriosis may be destroyed using a laser or electrical current. More extensive surgery is required when scar tissue is thick or involves delicate structures.

Some patients need a combination of medical and surgical treatment. If an infertile woman with endometriosis fails to conceive even after medical and surgical treatment, in vitro fertilization may be an option. Even women with extensive disease, whose ovaries are surrounded by adhesions, are candidates for in vitro fertilization. Ultrasound-guided techniques allow oocytes to be harvested in most cases.
While most women exhibit improvement with therapy, 20 to 50% of patients exhibit signs and symptoms of recurrence five to ten years after completion of initial therapy.

For a small number of patients who have no success with any treatments and who have completed their families, the ovaries may be removed to relieve severe and persisting pain. The uterus is also usually removed at this time (hysterectomy). Removing both ovaries minimises the chance of recurrence, although this leaves a woman in an estrogen-deficient state. To prevent the loss of bone calcium and other menopausal symptoms due to estrogen deficiency, most of these patients will need subsequent estrogen replacement therapy. The recurrence rate for endometriosis on estrogen replacement therapy is quite low, and the benefits of estrogen therapy are usually much greater than the potential risks.

Pregnancy
Although statistics are inconclusive as to whether pregnancy is therapeutic, many specialists have observed that endometriosis sometimes regresses during pregnancy. These doctors feel that the hormonal environment produced by pregnancy usually inhibits the disease. The condition may often return some time after pregnancy. However, many women with endometriosis have difficulty conceiving.

Psychological implications

Endometriosis is a disease that has emotional consequences for women. The pain can debilitate some women by affecting work and other relationships and disrupting normal activities. Sexual intercourse can be painful; some women lose interest in sex to avoid the discomfort. In addition, the hormonal treatments for endometriosis can affect sexuality and be emotionally difficult. The side effects of these medications, some of which mimic menopause, can cause depression and inhibit sexual desire in some women. The understanding and support of a partner, family and friends are important to any woman with endometriosis. Support groups have formed to help women with endometriosis and may be available in your area.

Conclusion

Choosing a qualified physician who is familiar with the latest developments in endometriosis management is the best strategy. The physician will recommend the most appropriate course of treatment based on your personal situation.

For more information on fertility treatment go to www.vitalab.com