

ENDOMETRIOSIS

A Guide for Patients



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A glossary of italicized words is located at the end of this booklet.

INTRODUCTION

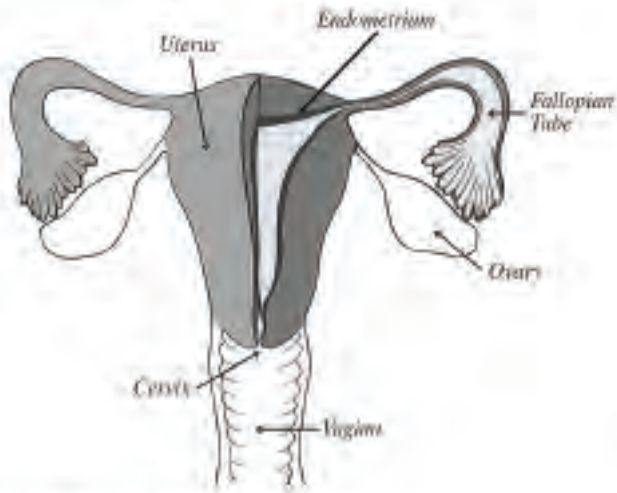
Women with endometriosis may experience infertility, pelvic pain, or both. This booklet will describe options for diagnosing and treating pain or infertility that may be attributed to endometriosis.

What is Endometriosis?

Endometriosis is a common condition that affects women during the reproductive years. It occurs when normal tissue from the *uterine* lining, the *endometrium*, attaches to organs in the pelvis and begins to grow. This displaced endometrial tissue causes irritation in the pelvis that may lead to pain and infertility.

Experts do not know why some women develop endometriosis. During each menstrual period, most of the uterine lining and blood is shed through the *cervix* and into the vagina. However, some of this tissue enters the pelvis through the *fallopian tubes*. Women who develop endometriosis may simply be unable to clear the pelvis of these cells.

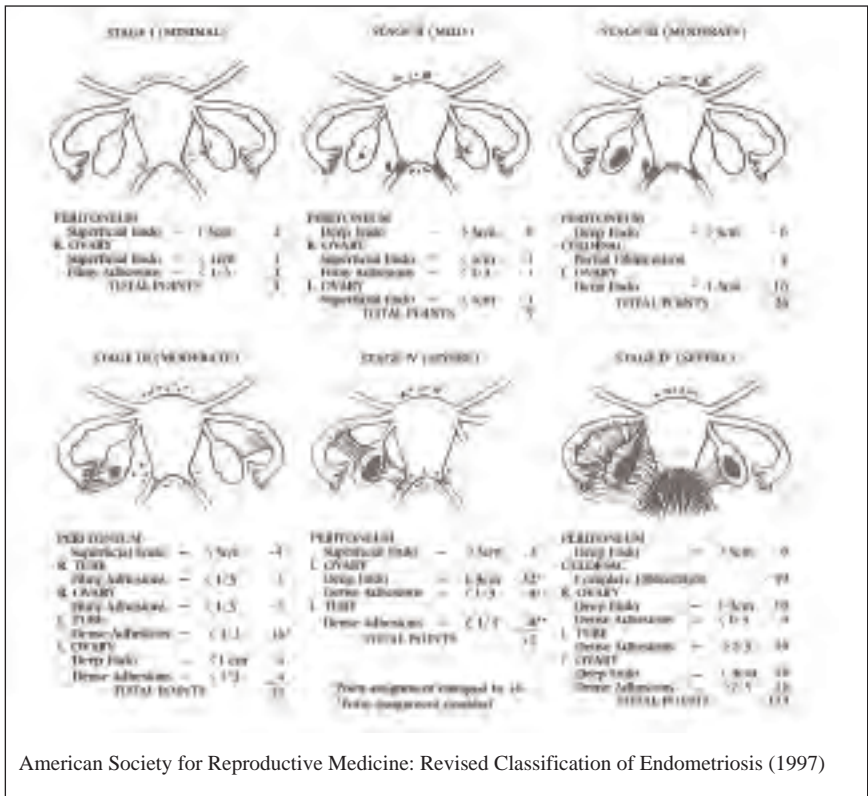
Early endometriosis implants look like small, flat patches, blebs or flecks sprinkled on the pelvic surface. The flecks can be clear, white, brown, red, black or blue. The severity and course of endometriosis is highly unpredictable. Some women may have a few endometriosis *implants* on the surface of the pelvis, the *peritoneum*, or pelvic organs, or it may invade the peritoneum and grow as *nodules*. Endometriosis may grow on the surface of the ovary as implants or invade inside the ovary and develop a blood filled cyst called an *endometrioma*, or a “chocolate cyst.” Chocolate cysts are so named because over time the blood they contain darkens to a deep reddish brown color. These cysts may be as small as a pea or grow to be larger than a grapefruit. Endometriosis may irritate surrounding tissue and produce internal scar tissue called *adhesions*. These adhesions can bind the pelvic organs together, cover them entirely, or involve nearby intestines. The adhesions may keep the *fallopian tube* from picking up the egg from the *ovary* during *ovulation*. Endometriosis may also grow into the walls of the intestine or into the tissue between the vagina and the rectum.



The Female Reproductive Organs. A basic knowledge of these organs and their functions is essential to understanding endometriosis.

Up to 10% of all women may have endometriosis. Many women who have endometriosis experience few or no symptoms. Some women experience severe menstrual cramps, chronic pelvic pain, or painful intercourse. In others, infertility may be the only symptom of endometriosis. Often, endometriosis is diagnosed when a woman has pelvic surgery because of a persistent ovarian cyst or other reasons. Endometriosis can affect women who have had children, and can occur in teenagers and young women. Some specialists feel that endometriosis is more likely to be found in women who have never been pregnant. Endometriosis may be found in 24% to 50% of women who experience infertility, and in more than 20% who have chronic pelvic pain.

Endometriosis is classified into one of four stages, I-minimal, II-mild, III-moderate, and IV-severe, depending on the location, extent, and depth of endometriosis implants, the presence and severity of adhesions, and presence and size of ovarian endometriomas. Most women have minimal or mild endometriosis, which is characterized by superficial implants and mild adhesions. Nevertheless, this degree of endometriosis is strongly associated with infertility, dysmenorrhea, and chronic pelvic pain. Moderate and severe endometriosis is characterized by chocolate cysts and more severe adhesions.



American Society for Reproductive Medicine: Revised Classification of Endometriosis (1997)

SYMPTOMS OF ENDOMETRIOSIS

Menstrual Cramps

Many women experience mild menstrual cramps, which are considered normal. When cramping is more severe it is called *dysmenorrhea*, and may be a symptom of endometriosis or other types of pelvic pathology such as uterine fibroids or *adenomyosis*. Severe cramping may cause nausea, vomiting, or diarrhea. *Primary dysmenorrhea* occurs during the early years of menstruation, tends to improve with age or after childbearing, and is usually not related to endometriosis. *Secondary dysmenorrhea* occurs later in life and may increase with age. This may be a warning sign of endometriosis, although some women with endometriosis feel no cramping at all.

Painful Intercourse

Endometriosis can cause pain during or after intercourse, a condition known as *dyspareunia*. Deep penetration can produce pain in an ovary bound by scar tissue to the top of the vagina. Pain also may be caused by bumping against a tender nodule of endometriosis behind the uterus or on the *uterosacral ligaments*, which connect the cervix to the *sacrum*.

Infertility

There is a large body of evidence that demonstrates an association between endometriosis and infertility. Endometriosis can be found in up to 50% of infertile women. Infertility patients with untreated mild endometriosis conceive on their own at a rate of 2% to 4.5% per month, compared to a 15% to 20% monthly fertility rate in normal couples. Infertility patients with moderate and severe endometriosis have monthly pregnancy rates of less than 2%. Even though endometriosis is strongly associated with infertility, not all women who have endometriosis are infertile. For example, many women undergoing tubal sterilization procedures are noted to have endometriosis.

A cause and effect relationship between endometriosis and reduced fertility is presumed but not proven. It is not known how minimal and mild endometriosis reduces fertility when there are no adhesions. It is presumed that endometriosis alters the pelvic environment in subtle but important ways. Theories include inflammation, altered immune system, hormonal changes, abnormal function of the fallopian tube, or impaired fertilization and implantation. It is easier to understand how moderate and severe endometriosis reduces fertility, since major pelvic adhesions, when present, may prevent the release of eggs, block sperm entry into the fallopian tube, and prevent the fallopian tube's ability to pick up eggs during ovulation.

HOW IS ENDOMETRIOSIS DIAGNOSED?

Endometriosis cannot be diagnosed by symptoms alone. Your physician may suspect endometriosis if you are having fertility problems, severe menstrual cramps, pain during intercourse, or chronic pelvic pain. It may also be suspected when there is a persistent ovarian cyst. Endometriosis is often found in close family members like a mother or sister. Remember, however, that many women with endometriosis have no symptoms at all.

Pelvic Exam

Certain findings of a pelvic examination may lead your physician to suspect endometriosis. The doctor may feel a tender nodule behind the cervix during a combined vaginal and rectal exam, or the uterus may be tilted back or *retroverted*. One or both ovaries may be enlarged or fixed in position. Occasionally, endometriosis implants may be visible in the vagina or the cervix. Although your physician may suspect endometriosis, based on your history and the results of a pelvic exam, surgery is needed to confirm endometriosis.

Laparoscopy

Laparoscopy is an outpatient surgical procedure that enables the physician to see the pelvic organs and look for endometriosis. During laparoscopy, a thin camera called a laparoscope is inserted into the abdomen through a small incision near the navel. The laparoscope allows the surgeon to see the surface of the uterus, fallopian tubes, ovaries, and other pelvic organs. For more information on laparoscopy, please see the ASRM booklet entitled, *Laparoscopy and Hysteroscopy*.

The extent of endometriosis is evaluated during laparoscopy. A clinical staging system is used to describe the extent of endometriosis, adhesions, and endometrioma cysts in the ovary. A score of 1-15 indicates minimal or mild endometriosis, and a score of 16 or higher indicates moderate or severe disease. The staging system, however, does not correlate well with a woman's chance of conceiving with fertility treatment or the degree of pain that she experiences.

Your physician may decide to treat your endometriosis during the laparoscopy. Additional small incisions allow your physician to insert surgical instruments. Endometriosis may be coagulated, vaporized, burned or excised, and scar tissue or ovarian cysts may be removed. During laparoscopy, your doctor can determine if your fallopian tubes are open by injecting dye through the cervix into the uterus. If the tubes are open, the dye will flow out the ends of the fallopian tubes.

Other Diagnostic Procedures

In special cases, your doctor may use special imaging techniques such as *ultrasound*, *computerized tomography (CT scan)*, or *magnetic resonance imaging (MRI)* to gather more information about your pelvis. These procedures can identify cysts and help characterize the fluid within an ovarian cyst, although an endometrioma cyst and a normal *corpus luteum* cyst may have a similar appearance. These tests are useful when evaluating women experiencing infertility and/or chronic pelvic pain.

TREATMENT OF PAIN

Your doctor will consider your symptoms, physical examination, test results, and your goals and concerns before advising treatment. Women with mild symptoms may benefit from lifestyle changes, or require no treatment at all. Hormonal therapy may be suggested when pain interferes with family, work, or daily activities, since these therapies usually reduce pelvic pain and dyspareunia in more than 80% of women in whom endometriosis is diagnosed. Since several effective treatments are available, the choice is made based on side effects and cost. Hormonal treatments are not effective for large ovarian endometriomas, and surgery is necessary. Surgery also may be indicated when medical treatment is unsuccessful or when medical conditions prohibit the use of hormone treatments.

Lifestyle Modifications

Some women have found that their pain is improved by exercise and relaxation techniques. Although natural supplements have not been shown to reduce endometriosis-related pain, over-the-counter, non-steroidal, anti-inflammatory medications, like ibuprofen and naproxen, reduce painful menstrual cramps. When painful intercourse is a problem, changing positions prevents pain caused by deep penetration. In spite of these measures, medical treatment is frequently needed.

Hormonal Contraceptives

When used for contraception, birth control pills are taken daily for three weeks, followed by a week without pills to permit menstrual flow. Birth control pills often reduce menstrual cramping and pelvic pain that may be associated with endometriosis.

Birth control pills may also be prescribed continuously without pausing for menstrual periods. This may be effective when menstrual cramps are still bothersome despite using birth control pills. Side effects of this approach include fluid retention and irregular spotting or bleeding. Serious side effects of birth control pills are very rare and include stroke, vascular problems, and heart disease. It should also be noted that endometriosis may be diagnosed in women taking birth control pills, and that birth control pills have never been shown to prevent the development of endometriosis. No data is currently available concerning the effect of transdermal contraceptive patches and vaginal contraceptive rings upon endometriosis.

Progestins

Progestins are synthetic medications that have *progesterone*-like activity upon the endometrium, the uterine lining. Many progestins have been demonstrated to reduce endometriosis-associated pelvic pain. The most common side effects of progestin therapy are irregular uterine bleeding, weight gain, water retention, breast tenderness, headaches, nausea, and mood changes, particularly depression. Progestins are considerably less expensive than other medications, and may be prescribed as pills, injections, or the levonorgestrel-containing intrauterine contraceptive devices (IUDs). Drawbacks of the injectable form known as depot-medroxyprogesterone acetate (depo Provera) is that it may inhibit fertility for many months after treatment is discontinued, and that its use for longer than six months may cause a significant loss of bone mineral density and place a woman at risk for osteoporosis.

GnRH Analogs

GnRH analogs, particularly *GnRH agonists*, cause *estrogen* levels to fall to menopausal levels, and menstruation does not occur. These drugs are highly effective for painful endometriosis. Side effects include menopausal symptoms: hot flashes, vaginal dryness, and loss of calcium from the bones. The medications are usually given for six months. Low-dose estrogen-progestin hormone therapy or progestins alone may be added when prolonged treatment is needed, or if menopausal symptoms are severe. Calcium supplementation and exercise are recommended to reduce the loss of bone density that occurs with therapy. Most bone density loss is temporary and is regained after treatment is stopped. In a recent comparative trial, GnRH agonist therapy with depot-leuprolide acetate and progestin therapy with depot medroxyprogesterone acetate for subcutaneous injection (DMPA-SC) were equally effective in reducing endometriosis-associated pain; and both medications maintained

clinical improvement for 12 months following the end of treatment. DMPC-SC was associated with less bone loss and fewer hot flashes than depot-leuprolide.

Danazol

Danazol, a medication that is similar to male hormones, is also highly effective for endometriosis pain. Common side effects may include water retention, acne, irregular vaginal bleeding, muscle cramps, and temporarily reduced breast size. Uncommon, but irreversible side effects include deepening of the voice and growth of facial or body hair. Danazol is less frequently used to treat endometriosis today than 20 years ago because medications such as GnRH agonists are equally effective, but have a more favorable side effect profile than danazol.

Surgery for Pain

Surgical treatment of endometriosis is often performed when endometriosis is diagnosed. During laparoscopy, the doctor may remove adhesions, endometriosis nodules, and ovarian cysts. Laparoscopy is often used to treat recurrent endometriosis when the goal is to preserve future fertility. Sometimes the severity of endometriosis is such that major surgery is advised to remove endometriosis and adhesions. Ovarian cystectomy is superior to cyst drainage for treating pain and prevention of recurrent cysts.

Overall, fertility-preserving endometriosis surgery improves pain for 60% to 80% of women. After surgery, medical therapy may be needed to control symptoms of endometriosis since 40% to 80% of women experience recurrent pain symptoms within two years of surgery. Recurrent symptoms occur within five to 10 years in more than 50% of women after completing a six-month course of medical treatment. Long-term management of endometriosis-related pain is usually necessary.

Hysterectomy, with removal of the ovaries, is an effective approach after childbearing is completed. This surgery provides final relief from endometriosis-related pain in more than 90% of women. In contrast, if one or both ovaries are preserved, there is a much greater chance that symptoms will recur, and additional surgery will be required. If needed, low-dose hormone therapy reduces hot flashes and menopausal symptoms that occur after hysterectomy with bilateral removal of the ovaries.

Pregnancy

Although it has not been proven that pregnancy is therapeutic, endometriosis often regresses during pregnancy. The hormonal environment produced by pregnancy may inhibit the condition. However, endometriosis often returns some time after pregnancy. A woman must carefully consider her immediate and long-term goals before choosing pregnancy as a treatment for endometriosis.

Team Approach to Pain

Some women continue to experience severe pain in spite of hormonal and surgical treatments. When pain persists, a multidisciplinary "team" approach may be helpful. This approach combines the expertise of a group of specialist physicians at a "pain center," along with mental health specialists, counselors and physical therapists. Nerve blocks, acupuncture, or other treatments may be beneficial.

Investigational Drug Treatments for Endometriosis

A number of new drugs are under research and development for endometriosis. Antiprogestins, such as mifepristone and onapristone, have had success in small studies. These medications work by modulating the estrogen and progesterone receptors in endometriosis implants and cause atrophy of endometriosis. Selective estrogen receptor modulators (SERMs) may be effective by virtue of their antiestrogen effect. Raloxifene is the SERM that currently shows some promise. In contrast, tamoxifen, another SERM, may cause endometriosis to worsen. Aromatase inhibitors, medications that inhibit aromatase, an enzyme that is required for estrogen synthesis, have had success in small studies and case reports. Anastrozole and letrozole are two examples of aromatase inhibitors undergoing investigation. Leukotriene antagonists theoretically will improve dysmenorrhea by modulating the activity of leukotrienes, immune chemicals that contribute to inflammation and pain. Other immune modulators are under investigation in animal models as potential therapies for endometriosis. These include loxoribine, levamisole, interleukin-12, and interferon-a-2b.

TREATMENT OF INFERTILITY

The entire infertility evaluation should be completed before considering treatment for endometriosis. For infertile women with suspected minimal or mild endometriosis, a decision must be made whether to perform laparoscopy before starting treatments to enhance fertility. Clearly, factors such as a woman's age, duration of infertility, and pelvic pain must be considered. Other infertility factors may co-exist and impact success rates and treatment outcome. If pain also is a concern, laparoscopy and surgical treatment seem prudent. In addition, laparoscopy and possible laparotomy are recommended when moderate or severe endometriosis is suspected, if no other cause for infertility has been found.

Surgery for Infertility

Laparoscopic treatment of minimal and mild endometriosis has been associated with a small but significant improvement in pregnancy rates. In the largest study to date, 29% of women who had their endometriosis treated conceived over nine months, in contrast to only 17% of women whose endometriosis was diagnosed, but not treated during laparoscopy. Although this is a modest treatment benefit, it suggests that there is a period of enhanced fertility after laparoscopic treatment

of endometriosis. Treatment of moderate and severe endometriosis by laparoscopy and/or laparotomy increases pregnancy rates for women in whom no other causes of infertility have been found. There is no evidence that the outcome is improved by any method used to treat endometriosis, such as electro-surgery, laser, excision or ablation.

Medical Therapy for Infertility

Whereas medical therapy is effective for relieving pain associated with endometriosis, there is no evidence that medical treatment of endometriosis by birth control pills, progestins, GnRH analogs, or danazol improves fertility. Furthermore, surgery combined with medical therapy has not been shown to enhance fertility. Instead, medical treatment before or after surgery may unnecessarily delay further fertility therapy. Nevertheless, these treatments are effective in reducing pelvic pain and painful intercourse associated with endometriosis. Therefore, hormonal suppression may improve comfort and sexual activity in infertile women with endometriosis and pelvic pain, thereby improving fertility after the completion of the treatment.

Expectant Management

A "watchful waiting" approach, also called expectant management, may be an option for younger women after surgery for endometriosis. Up to 40% of women may conceive during the first eight to nine months after laparoscopic management of minimal or mild endometriosis. Fertility-enhancing treatments may be offered as an alternative to expectant management, or if pregnancy fails to occur within a reasonable period. A woman's age is an important factor in deciding treatment. Women age 35 and older have lower fertility potential and higher chances of miscarriage. The decrease in fertility due to endometriosis and age may be additive. Therefore, more aggressive fertility treatments seem reasonable in older women with endometriosis. Watchful waiting is not a good option for women with infertility associated with severe endometriosis.

FERTILITY ENHANCING TREATMENTS

Controlled Ovarian Hyperstimulation and Intrauterine Insemination

Several studies have shown that fertility is enhanced in women with minimal or mild endometriosis by controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI). This treatment is also called superovulation with IUI. Without treatment, women with minimal/mild endometriosis-related infertility have spontaneous pregnancy rates of 2% to 4.5% per month. The monthly pregnancy rate with intrauterine insemination alone for endometriosis is approximately 5%, and it is approximately 4% to 7% per month for clomiphene citrate, human menopausal gonadotropin (HMG), or follicle stimulating hormone (FSH) injections, when used without intrauterine insemination. However, clomiphene plus IUI improves the monthly pregnancy

rates to approximately 9% to 10%, at least for the first four treatment cycles. HMG or FSH plus IUI improves the success to 9% to 15% per month. COH with clomiphene plus IUI carries a 5% to 15% risk of twins. Multiple pregnancy and ovarian hyperstimulation are risks associated with HMG IUI therapy.

Assisted Reproductive Technology

In general, couples diagnosed with endometriosis have success rates with assisted reproductive technology (ART) procedures such as in vitro fertilization and embryo transfer (IVF-ET) that are similar to those for couples with other causes of infertility. Success rates for ART procedures vary greatly depending on a woman's age. Nationally, live birth rates for IVF-ET are approximately 30% to 35% for women under age 35, 25% from ages 35 to 37, 15% to 20% from ages 38 to 40, and about 10% between 41 and 42.

IVF-ET is the most effective treatment for moderate or severe endometriosis, particularly if surgery fails to restore fertility. Some physicians recommend long-term pretreatment with GnRH analogs before starting IVF in women with severe endometriosis, since some, but not all, studies have shown that this approach may improve IVF-ET outcomes.

CONCLUSION

Endometriosis affects millions of women throughout the world. It demands professional attention, especially when fertility is impaired or pain affects lifestyle. Endometriosis may be a lifelong problem, since pain frequently recurs after therapy, and endometriomas may also recur. It therefore has the potential to disrupt quality of life and cause significant emotional distress. A woman's age, duration of infertility, pelvic pain, and stage of endometriosis are taken into account when formulating an infertility treatment plan. Choosing a qualified specialist - one who is familiar with the latest developments in endometriosis management - is your best strategy. The physician you choose will recommend the most appropriate course of treatment based on your personal situation.

Let Us Know What You Think

Email your comments on this booklet to asrm@asrm.org. In the subject line, type "Attention: Patient Education Committee"

GLOSSARY

Adenomyosis. A benign (non-cancerous) invasion of endometrial tissue into the uterine wall.

Adhesions. Bands of fibrous tissues that bind the abdominal or pelvic organs together.

Assisted reproductive technology (ART). A fertility-enhancing procedure that most commonly refers to in vitro fertilization and embryo transfer. Also includes procedures in which unfertilized eggs and sperm are placed into the fallopian tube (gamete intrafallopian transfer - GIFT), or fertilized eggs are placed into the fallopian tube (zygote intrafallopian transfer - ZIFT).

Biopsy. The removal of a tissue sample for microscopic examination. The term also refers to the tissue removed.

Cervix. The lower part of the uterus that opens into the vagina.

Clomiphene. A fertility pill used to promote ovulation, often of more than one egg.

Controlled ovarian hyperstimulation (COH). Treatment with clomiphene, human menopausal gonadotropin or follicle stimulating hormone injections to cause more than one egg to develop and release during ovulation.

Computerized tomography (CT scan). A technique of x-ray imaging that creates a three-dimensional image.

Corpus luteum. A yellow body in the ovary that forms from a follicle after ovulation; the follicle has matured, ruptured, and released its egg. The corpus luteum produces progesterone and estrogen during the second half of a normal menstrual cycle.

Danazol. A synthetic weak male hormone that blocks ovulation and suppresses estrogen levels; used to treat endometriosis.

Dysmenorrhea. Painful menstrual cramps.

Dyspareunia. Painful intercourse; sometimes a symptom of endometriosis.

Endometrioma. A blood-filled "chocolate" cyst that can occur when endometriosis tissue develops in the ovary.

Endometrium. The lining of the uterus that is shed each month during menstruation.

Estrogen. A hormone produced mainly by the ovaries. Estrogen is largely responsible for stimulating the endometrium to thicken and prepare for pregnancy during the first half of the menstrual cycle.

Expectant management. Period of "watchful waiting" without active treatment.

Fallopian tubes. A pair of organs attached to the uterus. The egg travels from the ovary to the uterus through a narrow passageway inside the tubes, and natural fertilization occurs in the fallopian tubes.

Follicle. A small, spherical cyst located under the surface of the ovary. It contains the egg, the surrounding layer of cells, and fluid. The follicle enlarges during the first half of the menstrual cycle. At ovulation, the mature follicle releases the egg.

Follicle stimulating hormone (FSH). A hormone that stimulates growth of the follicle. May be used as a fertility injection to promote ovulation, often of more than one egg.

GnRH analogs. Synthetic chemicals similar to gonadotropin-releasing hormone, the natural hormone that prompts the pituitary gland to stimulate the ovaries to produce estrogen and progesterone. Prolonged use of GnRH analogs causes menopausal levels of estrogen.

Human menopausal gonadotropin (HMG). A fertility injection used to promote ovulation, often of more than one egg.

Implants. Small, flat patches of endometrial-like cells growing outside their normal location.

In vitro fertilization and embryo transfer (IVF-ET). A procedure in which eggs are fertilized in a laboratory and one or more embryo is placed into the uterus.

Intrauterine insemination (IUI). An office procedure in which prepared sperm cells are placed into the uterus.

Laparoscope. A thin camera used to inspect the organs in the pelvis and abdomen.

Laparoscopy. A procedure in which a surgeon inserts a laparoscope through a small incision in or below the navel. This allows the doctor to inspect the uterus, fallopian tubes, ovaries and other organs in the pelvis and abdomen. Additional incisions may be made for inserting surgical instruments.

Laparotomy. A procedure in which a surgeon makes an incision in the abdomen, usually several inches long, in order to treat conditions such as extensive endometriosis.

Magnetic resonance imaging (MRI). A diagnostic imaging procedure that absorbs energy from high frequency radio waves.

Nodules. Penetrating knot-like collections of endometriosis.

Oocyte. The female sex cell; the egg.

Ovary. One of two female glands that contains eggs and produces estrogen and progesterone.

Ovulation. Release of the egg from the ovary.

Peritoneum. A clear tissue that lines the pelvic and abdominal cavity.

Primary dysmenorrhea. Pain associated with menstrual periods that decreases with age.

Progesterone. An ovarian hormone secreted by the corpus luteum during the second half of the menstrual cycle.

Progestin. A synthetic hormone that is similar to progesterone.

Prostaglandins. Hormone-like chemicals produced in large amounts by endometrial cells. They stimulate the uterine muscles to contract and are largely responsible for menstrual cramps.

Pseudo-menopause. A hormonal state created by taking medication and characterized by low estrogen levels similar to those found at menopause.

Retroverted uterus. A uterus that is tilted backwards. This is found in approximately 10% of normal women.

Reversible menopause. A hormonal state in which estrogen levels fall to menopause levels; ovulation and menstruation do not occur. Reversible menopause is created by taking GnRH analogs.

Sacrum. The last vertebrae of the spinal column; the base of the spine.

Secondary dysmenorrhea. Pain associated with menstrual periods that begins later in a woman's reproductive life span. It may be due to an abnormal condition such as endometriosis or infection.

Superovulation. Treatment with clomiphene, human menopausal gonadotropin or follicle stimulating hormone injections to cause more than one egg to develop and release during ovulation.

Ultrasound. A technology that uses high-frequency sound waves to form an image of internal organs.

Uterosacral ligaments. Ligaments that attach to the lowest part of the uterus and the cervix to the sacrum.

Uterus. The muscular organ in which a pregnancy develops.



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