

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

ABNORMAL UTERINE BLEEDING

A Guide for Patients



PATIENT INFORMATION SERIES

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

INTRODUCTION

Menstruation is considered normal when uterine bleeding occurs every 21 to 35 days and is not excessive. The normal duration of menstrual bleeding is between two and seven days. Abnormal uterine bleeding occurs when either the frequency or quantity of uterine bleeding differs from that mentioned above or the woman has spotting in between her menstrual periods. Abnormal uterine bleeding is caused by a variety of factors. The two main causes are structural abnormalities of the reproductive system and *ovulation* disorders.

NORMAL OVARIAN FUNCTION

In women of reproductive age, the *ovary* secretes *estrogen* and *progesterone* into the bloodstream. These two hormones prepare the *endometrium* (the lining of the *uterus*) for implantation of a fertilized egg. The *pituitary gland*, located at the base of the brain, influences ovarian hormone production and ovulation by secreting two hormones, *follicle stimulating hormone (FSH)* and *luteinizing hormone (LH)*. Following stimulation by FSH and LH, a *follicle* containing an immature egg begins to develop within the ovary. As the follicle enlarges, it secretes increasing amounts of estrogen. When a sufficient amount of estrogen is secreted, the pituitary gland releases a large amount of LH which causes the follicle to release its egg (ovulation). If the egg does not become fertilized or does not implant in the endometrium, the

secretion of estrogen and progesterone declines approximately two weeks after ovulation. With declining levels of estrogen and progesterone, the lining of the uterus is shed as the menstrual period. The cyclical release of FSH and LH from the pituitary gland is tightly regulated and easily disrupted. When the pituitary gland does not release appropriate quantities of FSH or LH, ovulation may not occur and the cycle may be disrupted.

In some women who do not ovulate, the endometrium is stimulated by continuous exposure to estrogen without sufficient levels of progesterone to allow for complete shedding of the endometrial lining. This may eventually result in irregular or heavy bleeding. If estrogen exposure is continuous, abnormal cells may develop within the endometrium that could eventually form endometrial cancer.

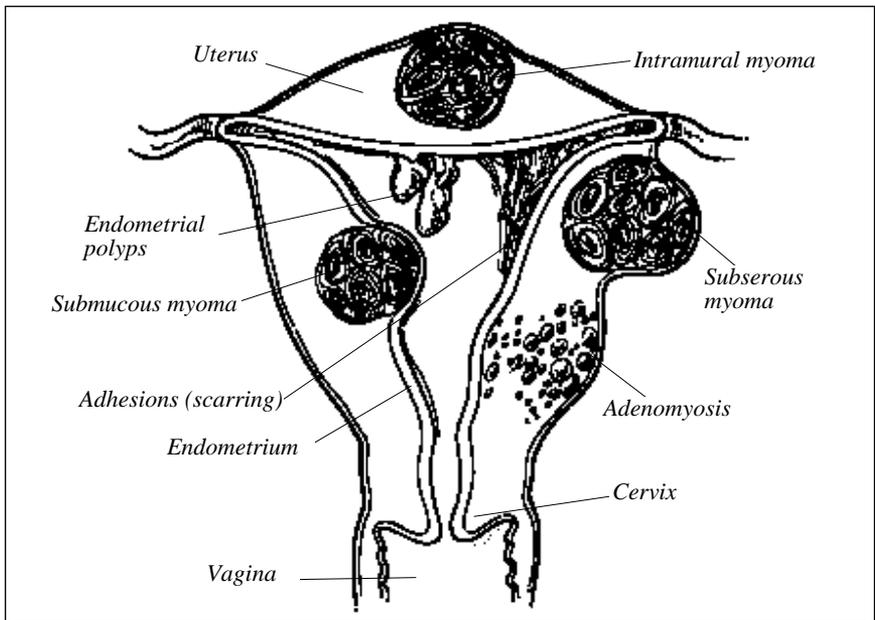


Figure 1. Causes of abnormal uterine bleeding.

CAUSES OF ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding (AUB) may be due to structural abnormalities of the uterus. Some of the more common structural causes of abnormal uterine bleeding include benign (non-cancerous) lesions of the uterus such as polyps, fibroids (myomas), and adenomyosis (Figure 1). Other causes include bleeding associated with early pregnancy, including miscarriage and ectopic pregnancy, and bleeding disorders which affect the ability of the blood to clot normally. Lesions of the cervix or vagina (benign and cancerous), chronic infections of the endometrial lining

(*endometritis*), scar tissue (*adhesions*) in the endometrium, and the use of an *intrauterine device (IUD)* may also be associated with abnormal uterine bleeding. Additional causes of abnormal bleeding include medications which can affect the normal release of estrogen and progesterone, chronic medical problems such as *diabetes mellitus* or disorders of the liver, kidney, *thyroid gland*, or *adrenal glands*, or other medical problems which can affect the production and metabolism of estrogen and progesterone. Emotional or physical stress as well as significant changes in body weight may disrupt the pituitary's release of FSH and LH and prevent ovulation.

Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding is the occurrence of uterine bleeding unrelated to structural abnormalities of the uterus or the endometrial lining. It is a diagnosis of exclusion made after structural causes of bleeding and chronic medical diseases have been ruled out. Other causes of abnormal bleeding must also be disproved, including pregnancy complications and medications which influence hormonal action or affect clotting. DUB occurs most commonly in the first five years after a woman starts menstruating and as she approaches *menopause*. The main cause of DUB is *anovulation*, the absence of ovulation and the orderly secretion of estrogen and progesterone. DUB may alert the woman and her physician to the fact that she is no longer ovulating normally.

DIAGNOSIS

Women who experience abnormal uterine bleeding should be evaluated by a physician. A medical history, discussion of possible contributing factors, and a detailed physical exam are usually necessary. A variety of diagnostic techniques are available for determining the cause of abnormal uterine bleeding.

Diagnostic Procedures

The doctor may recommend an *endometrial biopsy*, an office procedure, to examine a sample of the uterine lining to rule out abnormalities of the endometrium. *Hysteroscopy* is a useful procedure that allows visual inspection of the entire uterine cavity (Figure 2). It may allow the physician to identify specific areas within the endometrium which may be biopsied or removed with special instruments. Hysteroscopy may be performed under general anesthesia or as an office procedure. For more information on hysteroscopy, refer to the ASRM patient information booklet titled *Laparoscopy and Hysteroscopy*. In some circumstances, a *dilation and curettage (D&C)* may be recommended to further assess the endometrial tissue. D&C may also be recommended for control of persistent or heavy bleeding in women for whom other methods have been ineffective. Generally, however, a hysteroscopy is

performed prior to the D&C. A variety of techniques is available to visualize the uterus and pelvic organs. *Ultrasound* is a procedure which uses high-frequency sound waves to produce a picture of the pelvic structures. This is the most commonly employed imaging method for the pelvic organs and does not involve the use of x-rays. Less commonly, *computerized tomography (CT)* and *magnetic resonance imaging (MRI)* can be used to depict a three-dimensional image of internal organs including the uterus, although these procedures are rarely needed to determine the source of abnormal uterine bleeding.

Abnormalities of the endometrium may be detected by a *hysterosalpingogram (HSG)*. This entails the slow injection of an iodine-containing solution into the uterine cavity under x-ray guidance, so that the contours of the endometrium and *fallopian tubes* can be visualized.

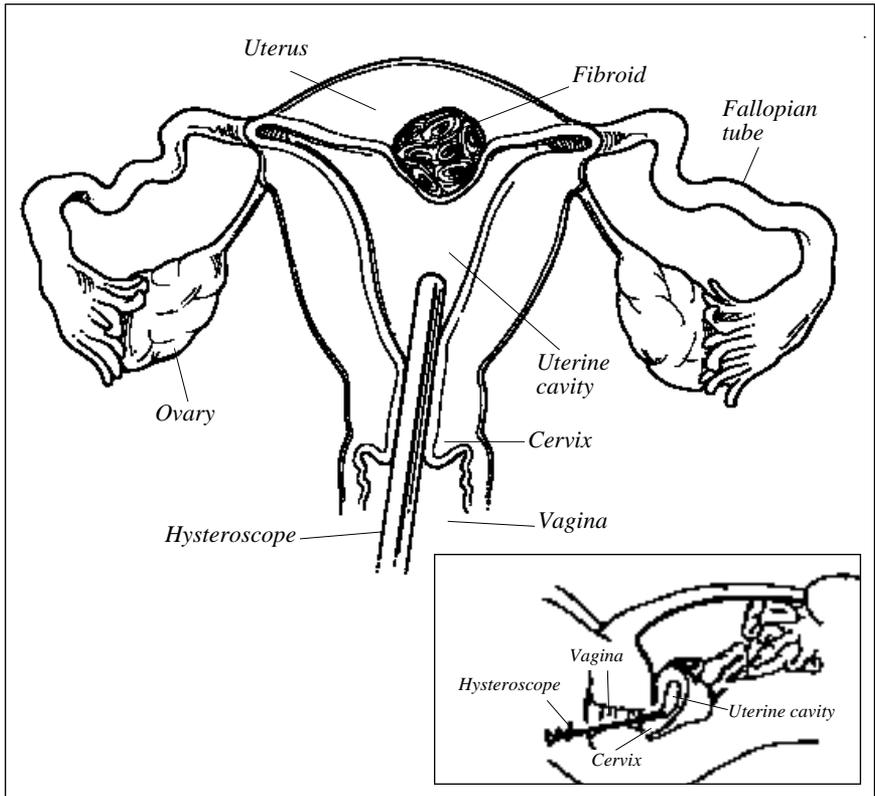


Figure 2. Frontal view of hysteroscopy. See inset for side view.

Laboratory Studies

Laboratory studies also aid in diagnosing abnormal uterine bleeding. Often a blood test will be obtained to check for *anemia* or a blood clotting disorder. When structural disturbances of the reproductive tract have been ruled out, a blood test to measure pituitary hormones, such as *prolactin*, FSH, and thyroid hormones may be performed. If there is evidence of increased *androgen* (male hormone) levels, the likely cause is *polycystic ovarian syndrome (PCOS)*. PCOS is often associated with irregular or heavy menstruation. For more information on PCOS, refer to the ASRM patient information booklet titled *Hirsutism and Polycystic Ovarian Syndrome*. Additional tests of the liver, kidney, pancreas, and other major organs may be useful, depending upon each woman's medical history. Laboratory studies for abnormal uterine bleeding will be based on the physician's clinical judgment as to the underlying cause of the bleeding.

TREATMENT

The individual therapy recommended will be tailored to the specific cause of abnormal bleeding. Structural abnormalities of the reproductive tract such as fibroids, polyps, or scar tissue can often be treated with hysteroscopy. Surgical instruments can be inserted through the *hysteroscope* to remove or correct structural abnormalities within the uterine cavity. Generally, patients can return to normal activities within 24 hours after a hysteroscopy. Serious complications are rare.

Individuals who have adequate levels of estrogen but who do not ovulate can be effectively treated with synthetic *progestins* such as medroxyprogesterone acetate (Provera®, Cycrin®, Amen®, Medroxyprogesterone® tablets) using dosages of 5 to 10 mg each day orally for seven to 12 days. Other progestins, including natural progesterone, are available as oral capsules, vaginal suppositories, or intramuscular injections, and are also effective for promoting complete shedding of the endometrial lining. In many instances, patients can be treated with low dose oral contraceptives (OCs), which provide both estrogen and progestins and promote regular menstruation. This may be a particularly useful choice for individuals who also desire birth control.

Menorrhagia

For women with *menorrhagia* (excessively prolonged or heavy menstruation), the administration of an estrogen alone may be recommended to temporarily stop the bleeding and stabilize the endometrial lining. Often the physician will recommend an endometrial biopsy under such circumstances. Estrogens can be administered orally, such as conjugated estrogens using dosages of 1.25 to 5 mg every six hours for a 12- to 24-hour period. Alternatively, intravenous estrogens at dosages of 20 to 25 mg can be administered every four to six hours to control heavy bleeding. After

several days to weeks of estrogen therapy, a progestational agent should be administered orally for 10 to 12 days to facilitate a controlled bleeding episode.

Heavy uterine bleeding may be controlled with the use of low dose OCs. A combination OC formulation may be administered as two to four tablets per day for up to seven days to control severe menorrhagia. Thereafter, an interruption of OC use for five to seven days may be recommended, and a controlled withdrawal flow generally occurs. Subsequently, low dose OCs may be used in a standard fashion to facilitate orderly menstrual bleeding. If OC therapy is used in women over the age of 40, reproductive tract abnormalities, malignancies, and medical conditions which may prevent the use of these medications should first be excluded.

Progestosert® IUDs are useful in treating DUB. Prostaglandin synthesis inhibitors, including ibuprofen and related compounds, have also been shown to reduce excessive menstrual bleeding in some women. This may be particularly useful in women with menorrhagia following the insertion of an IUD.

Occasionally, the physician may recommend the use of *GnRH analogs* to temporarily control excessive uterine bleeding, particularly for the treatment of severe menorrhagia, which may cause anemia. These compounds temporarily stop the release of FSH and LH from the pituitary gland and cause ovarian estrogen production to fall to menopausal levels. Short-term use of GnRH analogs in combination with iron supplementation may improve or correct the anemia.

Surgical approaches include removal of fibroids, polyps, and scar tissue with the use of the hysteroscope. Surgical removal of fibroids may be recommended for women with menorrhagia who fail to respond to hormonal therapy. The type of surgical technique will depend upon both the size and location of the fibroids. Hysteroscopic removal of uterine fibroids, also known as *myomectomy*, via an abdominal incision (*laparotomy*), and *hysterectomy* (abdominal or vaginal) are surgical options that may be considered. For more information on fibroids, refer to the ASRM patient information booklet titled *Uterine Fibroids*.

Additionally, *endometrial ablation* via the hysteroscope may be recommended for women who no longer desire fertility. This procedure, which is performed under general anesthesia, uses electrosurgical techniques or a laser beam to destroy the endometrial lining and generally corrects heavy menstrual flow. It is important to exclude serious endometrial lesions prior to performing this procedure. Although the goal is to stop menstrual bleeding completely, most often menstrual periods simply become lighter following this procedure. Because endometrial ablation is a newer technique, its long-term safety remains to be determined.

Only rarely will a hysterectomy be recommended for DUB. This should only be considered for patients who have had both an unsuccessful D&C and hormonal therapy, or when a thorough diagnostic evaluation has failed to reveal specific or correctable abnormalities.

Pituitary and Glandular Dysfunction

Disorders of the pituitary and thyroid glands can cause anovulation and menstrual irregularity. Individuals with inadequate production of thyroid hormone (hypo-

thyroidism) can be treated with daily oral replacement of thyroid hormone. Excess thyroid hormone production (hyperthyroidism) may be treated with oral medications, radioactive iodine, or surgical removal of all or part of the thyroid gland. The treatment of hyperprolactinemia (excessive release of prolactin from the pituitary) is generally treated with the oral medication *bromocriptine*. Individuals with elevated levels of prolactin may be advised to have an imaging study, such as a CT scan or MRI, of the pituitary gland to determine if there is evidence of a pituitary lesion. Pituitary *adenomas* are the most common benign tumors of the pituitary gland and are often associated with excessive release of prolactin. If pituitary adenomas are large, they may be treated surgically. An elevated FSH level may indicate impending ovarian failure, either due to menopause or to early menopause, also known as premature ovarian failure (POF). For more information on POF, refer to the ASRM patient information booklet titled *Early Menopause (Premature Ovarian Failure)*.

Polycystic Ovarian Syndrome (PCOS)

Patients with PCOS must have their therapy individualized depending upon whether their goal is restoration of fertility or regular menstruation. For individuals with irregular uterine bleeding who are not currently attempting to get pregnant, intermittent progestin therapy (medroxyprogesterone acetate 5 to 10 mg orally for 10 to 14 days a month) or oral contraceptives may be recommended to establish regular menstruation. Women with PCOS who are attempting to get pregnant are generally treated with *clomiphene citrate*. If clomiphene is ineffective, alternative treatment programs can be recommended. PCOS can be associated with high blood pressure, heart disease, acne, excess body hair (hirsutism), obesity, and diabetes mellitus, so proper medical attention and treatment are important. For further information on PCOS and fertility treatment for patients with PCOS, refer to the ASRM patient information booklets titled *Hirsutism and Polycystic Ovarian Syndrome* and *Ovulation Drugs*.

SUMMARY

Abnormal uterine bleeding is a common problem in reproductive aged women that can usually be corrected with surgery or medication. Surgery may be able to correct structural causes of abnormal bleeding. If there are no structural causes, medical therapy can often restore regular menstrual cycles. Whatever the cause of abnormal uterine bleeding, the many treatments available today can usually resolve the problem.

GLOSSARY

Adenoma. A benign (non-cancerous) growth of cells that usually does not invade adjacent tissue. A pituitary adenoma can disrupt ovulation and menstruation and is often associated with excessive prolactin production.

Adenomyosis. A benign (non-cancerous) invasion of endometrial tissue into the muscular wall (myometrium) of the uterus; is associated with painful or heavy menstrual periods.

Adhesions (scar tissue). Bands of fibrous scar tissue that may bind the pelvic organs and/or loops of bowel together. Adhesions can result from previous infections, endometriosis, or previous surgeries.

Adrenal glands. Glands located above each kidney that secrete a large variety of hormones (cortisol, adrenaline, and others) that help the body withstand stress and regulate metabolism. Altered function of these glands can disrupt menstruation, cause inappropriate hair growth, and affect blood pressure.

Androgen. In men, androgens are the “male” hormones produced by the testes which are responsible for encouraging masculine characteristics. In women, androgens are produced in small amounts by both the adrenal glands and ovaries. In women, excess amounts of androgens can lead to irregular menstrual periods, obesity, excessive growth of body hair (hirsutism), and infertility.

Anemia. A reduction in the number of red blood cells, which carry oxygen in the body. Anemia is characterized by weakness or listlessness.

Anovulation. Absent ovulation. Failure of the ovary to ovulate regularly.

Bromocriptine. A drug used to suppress the production of prolactin by the pituitary gland. The brand name is Parlodel®.

Cervix. The lower narrow end of the uterus that connects the uterine cavity to the vagina.

Clomiphene citrate. An oral anti-estrogen drug used to induce ovulation in the female. It is also sometimes used to increase testosterone levels in the infertile male, which may, in turn, improve sperm production. The brand names are Clomid® and Serophene®.

Computerized tomography (CT). An x-ray imaging technique that creates a three-dimensional image of internal organs.

Diabetes mellitus. A condition due to abnormal production of insulin resulting in abnormally elevated blood glucose (sugar) levels.

Dilation and curettage (D&C). An outpatient surgical procedure during which the cervix is dilated and the lining of the uterus is scraped out. The tissue is often used for microscopic examination for the presence of abnormality or pregnancy tissue.

Dysfunctional uterine bleeding (DUB). Abnormal uterine bleeding with no evidence of mechanical or structural cause. The most common cause of DUB is deficient or excessive production of estrogen and/or progesterone.

Ectopic pregnancy. A pregnancy that implants outside of the uterus, usually in the fallopian tube. The tube may rupture or bleed as the pregnancy grows and create or

result in a serious medical situation.

Endometrial ablation. A hysteroscopic procedure used to remove most of the endometrium (uterine lining); sometimes used to treat abnormal uterine bleeding.

Endometrial biopsy. Removal of a small piece of tissue from the endometrium (lining of the uterus) for microscopic examination. The results may indicate whether or not the endometrium is at the appropriate stage for successful implantation of a fertilized egg (embryo) and/or if it is inflamed or diseased.

Endometritis. An inflammation of the endometrium caused by bacterial invasion.

Endometrium. The lining of the uterus that is shed each month as the menstrual period. As the monthly cycle progresses, the endometrium thickens and thus provides a nourishing site for the implantation of a fertilized egg.

Estrogen. The female sex hormones produced by the ovaries which are responsible for the development of female sex characteristics. Estrogens are largely responsible for stimulating the uterine lining to thicken during the first half of the menstrual cycle in preparation for ovulation and possible pregnancy. They are also important for healthy bones and overall health. A small amount of these hormones is also produced in the male when testosterone is converted to estrogen.

Fallopian tubes. A pair of hollow tubes attached one on each side of the uterus through which the egg travels from the ovary to the uterus. Fertilization usually occurs in the fallopian tube. The fallopian tube is the most common site of ectopic pregnancy.

Fibroids. Benign (non-cancerous) tumors of the uterine muscle wall that can cause abnormal uterine bleeding. Also known as leiomyomas or myomas.

Follicle. A fluid-filled sac located just beneath the surface of the ovary that contains an egg (oocyte) and cells that produce hormones. The follicle increases in size and volume during the first half of the menstrual cycle. At ovulation, the follicle matures and ruptures, releasing the egg. As the follicle matures, it can be visualized by ultrasound.

Follicle stimulating hormone (FSH). In women, FSH is the pituitary hormone responsible for stimulating follicular cells in the ovary to grow, stimulating egg development and the production of the female hormone estrogen. In the male, FSH is the pituitary hormone which travels through the bloodstream to the testes and helps stimulate them to manufacture sperm. FSH can also be given as a medication. The brand name is Metrodin®.

GnRH analog. A long-acting drug that blocks the release of hormones, stops ovulation, and decreases the body's production of estrogen. Prolonged use of GnRH analogs causes decreased hormone production and menopausal levels of estrogen. The brand names are Lupron®, Depo Lupron®, Synarel®, and Zolodex®.

Hysterectomy. The surgical removal of the uterus. Hysterectomy may be performed through an abdominal incision (laparotomy), through the vagina (vaginal hysterectomy), or through laparoscopy assisted vaginal hysterectomy (LAVH). Sometimes the ovaries and fallopian tubes are also removed.

Hysterosalpingogram (HSG). An x-ray procedure in which a special iodine-containing dye is injected through the cervix into the uterine cavity to illustrate the

inner shape of the uterus and degree of openness (patency) of the fallopian tubes.

Hysteroscope. A thin, lighted, telescope-like instrument which is inserted through the vagina and cervix into the uterine cavity to allow viewing of the inside of the uterus.

Hysteroscopy. The insertion of a long, thin, lighted telescope-like instrument, called a hysteroscope, through the cervix and into the uterus to examine the inside of the uterus. Hysteroscopy can be used to both diagnose and surgically treat uterine conditions.

Intrauterine device (IUD). A contraceptive device placed within the uterus; may also be used to prevent scar tissue formation following uterine surgery.

Laparotomy. Major abdominal surgery through an incision in the abdominal wall.

Lesions. Growths or abnormalities of normal anatomy. Examples include scar tissue, polyps, and uterine fibroids.

Luteinizing hormone (LH). In women, the pituitary hormone that triggers ovulation and stimulates the corpus luteum of the ovary to secrete progesterone and other hormones during the second half of the menstrual cycle. In men, LH is the pituitary hormone which stimulates the testes to produce the male hormone testosterone.

Magnetic resonance imaging (MRI). A diagnostic procedure that absorbs energy from specific high-frequency radio waves. The picture produced by measurement of these waves can be used to form precise images of internal organs without the use of x-ray techniques.

Menopause. Natural cessation of ovarian function and menstruation. Menopause can occur between the ages of 42 and 56 but usually occurs around the age of 51, when the ovaries stop producing eggs and estrogen levels decline.

Menorrhagia. Regular but heavy menstrual bleeding which is excessive in either amount (greater than 80 cc – approximately five tablespoons) or duration (greater than seven days).

Myomas. Benign (non-cancerous) tumors of the uterine muscle wall that can cause abnormal uterine bleeding and miscarriage. Also see fibroids.

Myomectomy. The surgical removal of myomas (fibroids) from the uterus.

Ovaries. The two female sex glands in the pelvis, located one on each side of the uterus. The ovaries produce eggs and hormones including estrogen, progesterone, and androgens.

Ovulation. The release of a mature egg from its developing follicle in the outer layer of the ovary. This usually occurs approximately 14 days before the next menstrual period (the 14th day of a 28-day cycle).

Pituitary gland. A small hormone-producing gland located just beneath the hypothalamus in the brain which controls the ovaries, thyroid, and adrenal glands. Ovarian function is controlled through the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Disorders of this gland may lead to irregular or absent ovulation in the female and abnormal or absent sperm production in the male.

Polycystic ovarian syndrome (PCOS). A condition in which the ovaries contain many cystic follicles that are associated with chronic anovulation and overproduction of androgens (male hormones). The cystic follicles exist presumably because the eggs are not expelled at the time of ovulation. Symptoms may include irregular

menstrual periods, obesity, excessive growth of central body hair (hirsutism), and infertility. PCOS can also be associated with heart disease, hypertension, or diabetes. Also called Stein-Leventhal syndrome.

Polyps. A general term that describes any mass of tissue which bulges or projects outward or upward from the normal surface level.

Progesterone. A female hormone usually secreted by the corpus luteum after ovulation during the second half of the menstrual cycle (luteal phase). It prepares the lining of the uterus (endometrium) for implantation of a fertilized egg and also allows for complete shedding of the endometrium at the time of menstruation. In the event of pregnancy, the progesterone level remains stable beginning a week or so after conception.

Progestins. A synthetic hormone that has an action similar to progesterone. Synonymous with progestational hormones.

Prolactin. A hormone normally secreted by the pituitary gland into the bloodstream for the purpose of maintaining milk production during lactation. When secreted in excessive amounts, it may lead to irregular or absent menstrual periods and may produce a milk-like discharge from the breasts.

Thyroid gland. A large, two-lobed, endocrine gland located in front of and on either side of the trachea (windpipe) in the neck that secretes the hormone thyroxin into the bloodstream. Thyroxin maintains normal body growth and metabolism.

Ultrasound. A picture of internal organs produced by high frequency sound waves viewed as an image on a video screen; used to monitor growth of ovarian follicles or a fetus and to retrieve eggs. Ultrasound can be either performed abdominally or vaginally.

Uterus (womb). The hollow, muscular female reproductive organ in the pelvis where an embryo implants and grows during pregnancy. The lining of the uterus, called the endometrium, produces the monthly menstrual blood flow when there is no pregnancy.

NOTES

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