Amenorrhea is considered a type of abnormal menstrual bleeding characterized by the unexpected absence of menstrual bleeding, lasting three months or longer. Menstrual bleeding typically happens approximately once a month when blood and endometrial tissue, or tissue lining the inside of the uterus, sheds from the uterus through the vagina. Menstruation is expected to stop with pregnancy, breastfeeding, and menopause, or the natural cessation of the menstrual cycle at an older age. However, women may also experience amenorrhea because of an underlying health condition, including low body weight or polycystic ovarian syndrome, that may complicate fertility and contribute to decreased quality of life. According to the American College of Obstetricians and Gynecologists, one in twenty-five women experience amenorrhea as a menstrual disorder within their lives at times.

Amenorrhea is a sign of abnormal menstrual bleeding, a term that describes when a person experiences irregular symptoms during menstruation, the process that occurs at the start of the menstrual cycle. The menstrual cycle is a process that prepares the female body for pregnancy. The cycle is controlled by fluctuations in the amounts of the hormones estrogen and progesterone in the female body. Menstruation occurs at the start of the menstrual cycle, when the endometrium, or tissue lining the inside of the uterus, is thick, filled with blood. Typically, menstruation occurs every twenty-one to thirty-five days. During menstruation, estrogen and progesterone are low, which causes the uterus to shed the thick endometrium. After menstruation, the ovaries produce estrogen, allowing one of the two ovaries to release an egg cell in a process called ovulation. During ovulation, the egg cells travel through the fallopian tube, where it can meet a sperm cell. The sperm cell can then fertilize the egg cell. If the egg cell is fertilized, estrogen and progesterone rise, causing the endometrium to thicken. The fertilized egg cell later attaches itself to the thick endometrium inside of the uterus and pregnancy starts. If a sperm cell does not fertilize the egg cell, then the menstrual cycle begins again.

Amenorrhea is often the result of hormone imbalances in the body, and there are two types, called primary and secondary amenorrhea. Primary is typically characterized delayed menarche, or the first menstrual period, whereas secondary is typically characterized by the cessation of a period for at least three months. Primary amenorrhea is defined as a lack of a period by age sixteen or within five years of the first signs of puberty. That type of amenorrhea can also be attributed to changes in organs, glands, and hormones present during menstruation. People who are underweight may also develop primary amenorrhea. That is because low body weight often suppresses the function of the hypothalamus, a region of the brain that triggers the pituitary gland, which regulates vital body functions, to release hormones that are necessary for the menstrual cycle to work. Secondary amenorrhea is defined as the loss of a period for at least three months after regular bleeding. Secondary amenorrhea can also be characterized as a stop in bleeding for six months after bleeding was previously irregular. The causes of secondary amenorrhea include pregnancy, stress, illness, and excessive exercise. Stress can alter the functioning of the hypothalamus, and excessive exercise can include the interruption of a period because of low body fat, stress, and high energy expenditure.

Discussion of symptoms that are often indicative of amenorrhea is evident in some of the earliest texts. For example, Greek physician Hippocrates provided one of the first known descriptions of abnormal menstrual bleeding around 400 BCE, suggesting that abnormal menstrual bleeding causes disease. Greek philosopher Aristotle also discussed irregular menstrual bleeding, stating that women should menstruate on the same day every month, because everything in nature has order. According to Aristotle, if a woman experienced irregular menstrual bleeding, then it is not necessarily dangerous, but troublesome, since it may impair the woman’s ability to become pregnant.

According to physician Jane Woolcock, ideas similar to Aristotle’s remained popular for thousands of years since many people did not know why some women experience irregular menstrual bleeding. In 1847, English physician Fleetwood Churchill detailed his account of abnormal menstrual bleeding, in his book. In that book, Churchill attributes the cause of amenorrhea to the absence of the ovaries, referencing one woman who did not menstruate after the removal of her ovaries. He also references women who lack prominent breasts, have masculine characteristics such as a deep voice and facial hair, and have distorted reproductive organs as those who experience amenorrhea. For example, Churchill states that if the cervix, or lower part of the vagina, is impermeable, not allowing menstrual blood to leave the body, then a woman may place an artificial cervix inside her body as a treatment. Churchill writes that women can use a trocar, which is a small tube that physicians use to withdraw fluid from the body during surgery, as an artificial cervix.

In the nineteenth century, despite there being many detailed accounts of abnormal menstrual bleeding that are indicative of amenorrhea, how those symptoms manifested remained poorly understood. According to Woolcock, researchers and physicians...
often associated a lack of menstrual bleeding to certain social behaviors. An example, according to researcher Julie-Marie Strange, is that in 1856, English physician William Tyler Smith attributed menstruation \(^9\) to femininity, leading to social ideas that women who were diagnosed with amenorrhea lacked feminine qualities. Smith wrote that menarche and menopause mark the beginning and end of femininity. According to Strange, that understanding of menstruation \(^9\) represented social ideas that women who did not menstruate were not suitable for marriage, because those women lacked fertility. Strange also writes that during that time, some physicians even recommended that women who did not menstruate become engaged to reestablish the menstrual cycle. Later in 1887, physician Arthur Grayling found that an imperforate hymen, which covers the entire vaginal opening, may also cause some women to not menstruate. The hymen is tissue that incompletely covers the vaginal opening. However, in the case of one woman, Grayling found that the hymen completely covered the vaginal opening, meaning that menstrual blood could not leave the woman's body. After incising the hymen, Grayling wrote that the woman began to regularly menstruate and later was able to marry. Strange states that Grayling's report demonstrates the relationship between female reproductive health and marriageability that continued to persist throughout the nineteenth century.

During the twentieth century, as researchers provided more detailed accounts of hormones \(^{10}\) and the menstrual cycle, researchers better understood the pathology of amenorrhea. In 1923, researchers Edward Adelbert Doisy and Edgar Allen detailed the varying levels of estrogen \(^{11}\) during the menstrual cycle, after isolating the hormone \(^{18}\) from ovarian follicles. After Doisy and Allen were able to explain the relationship between estrogen \(^{11}\) and the menstrual cycle, the mechanisms by which amenorrhea occurs became clearer. In 1929, The Southern Medical Journal published an article, titled "Amenorrhea in Young Women," that discussed Doisy and Allen's work as it relates to amenorrhea. In that article, there is a description of several women who, after not menstruating for several months, received injections of the same hormone \(^{18}\) that Doisy and Allen isolated from ovarian follicles. Within the article, there are reports that those women later experienced varying menstrual bleeding patterns, lasting between two and six days. Because of the specificity of the medication and the variable outcomes, the article ends with advising women who are diagnosed to not receive hormone \(^{18}\) injections and rather make lifestyle changes to restore menstruation \(^{9}\).

Also, due to advancements in diagnostic techniques in the twentieth century, physicians were able to see the relationship between amenorrhea and other reproductive disorders, specifically polycystic ovarian syndrome, or PCOS. In 1935, in Chicago, Illinois, physicians Irving Freiler Stein and Michael Leventhal were among the first to describe PCOS according to Lorena I. Rasquin Leon, a medical doctor in Einstein Medical Center in Philadelphia, Pennsylvania. PCOS refers to the condition in which females have higher than typical levels of androgens \(^{39}\), or sex hormones \(^{34}\) that are typically present at higher levels in males. PCOS is also characterized by the presence of small fluid-filled sacs, called cysts, in the ovaries and is associated with amenorrhea. Stein and Leventhal found that their patients who had amenorrhea also displayed masculine characteristics and experienced infertility \(^{25}\). Stein and Leventhal diagnosed patients who presented similar symptoms with what they called Stein-Leventhal Syndrome. To further examine those patients, Stein developed a way to view the uterus \(^8\), ovaries, and fallopian tubes \(^{26}\) of the patients. He injected carbon dioxide gas and oil into the fallopian tubes \(^{26}\), which allowed him to produce an X-ray. Those X-rays showed that the patients had ovaries that were enlarged due to cyst growth. To examine the cysts, Stein surgically removed ovarian tissues from his patients and observed them under a microscope \(^{27}\). He found that the surgery to remove ovarian tissues was also therapeutic to their patients since some patients began to regularly menstruate, meaning symptoms of their amenorrhea were being treated, and others were able to become pregnant.

Since those advancements during the twentieth century, amenorrhea is more clearly known as a menstrual disorder that causes irregular or no menstrual bleeding as a result of interference with the hypothalamic-pituitary-ovarian, or HPO, axis in the brain. The HPO axis is a regulated system that controls female reproduction. For menstruation \(^9\), it controls the production of gonadotropic hormones \(^{10}\), which are secreted from reproductive glands including the ovaries, and steroid hormones \(^{10}\). The production of hormones \(^{10}\) is needed to proceed with ovulation \(^{19}\) and preparing the endometrium \(^{13}\) for pregnancy \(^7\). However, certain things may interfere with the regular functioning of the HPO axis, such as tumors, which are abnormal tissue growths, or mutations in genes \(^{28}\) that cause the HPO axis to not develop properly. Most commonly, the HPO axis stops functioning because of hormone \(^{18}\) imbalances, which can be caused by natural occurrences like pregnancy \(^7\) or menopause, or by more extreme circumstances such as low body weight or high intensity exercises. Such interferences can cause primary or secondary amenorrhea.

Amenorrhea can be diagnosed by tracking the date of a woman's last menstrual period but also by using a variety of diagnostic tests. There are different laboratory tests that can detect amounts of estrogens and androgens \(^{23}\) in the blood to check for a hormone \(^{18}\) imbalance. Similarly, a physician may administer a progesterone \(^{12}\) challenge test. Progesterone is another type of sex hormone \(^{18}\) that helps prepare a woman's body for conception \(^{26}\) and pregnancy \(^7\), and is needed to regulate the monthly menstrual cycle. During a progesterone \(^{19}\) challenge test, a woman takes a ten mg oral dose of medroxyprogesterone acetate, or synthetic progesterone \(^{19}\), each day for five to ten days. Alternatively, she may receive one 100 to 200 mg injection of progestin \(^{40}\), another type of synthetic progesterone \(^{12}\). If the woman bleeds for two to seven days after taking the test, then the test is positive, indicating that the woman has enough estrogen \(^{11}\) in her body but does not ovulate, which may often be due to PCOS. If the test is negative and no bleeding occurs, then the woman has low levels of estrogen \(^{11}\), which can be a sign of ovarian failure. Thus, the progesterone \(^{12}\) challenge test can help physicians identify underlying conditions that cause a patient's amenorrhea. Also, in cases of possible PCOS, a physician may use an ultrasound \(^{31}\) to check for cysts in the ovaries.
If a woman experiences primary or secondary amenorrhea, then she may receive hormone therapy or make lifestyle changes to restore her periods. If a physician finds that a patient’s ovaries are not producing enough progesterone or estrogen, they can administer hormone therapies to restore the levels of these hormones and restore periods. If stress, rapid weight loss, strenuous exercise, or PCOS is the cause of amenorrhea, then women can also make lifestyle choices, changing their diets and exercise, to restore their periods.

One example of a hormone therapy used to restore menstruation in women who are diagnosed with amenorrhea is the use of birth control pills, which are subject to religious and social controversy due to their contraceptive effects. During the 1950s, physician John Rock led clinical trials of one of the first birth control pills, called Envoid, and was a supporter of the pill’s use to regulate abnormal menstrual bleeding. During those clinical trials, Rock found that Envoid successfully suppressed ovulation. In 1957, the US Food and Drug Administration, or FDA, approved the pill’s use as a treatment for menstrual disorders, including amenorrhea, and infertility. Following that, Rock advocated for the Roman Catholic Church, which opposes the use of contraceptives, to approve the use of Envoid, and in 1958, Pope Pius XII agreed. Pius XII approved the use of Envoid for menstrual disorders, stating that if the pill’s primary use is for the treatment of menstrual disorders, then any contraceptive effects are unintended.

In 1964, the Church reevaluated its position on birth control pills, following the papacy of Pius XII. In 1968, Pope Paul VI sent a papal letter to all bishops of the Roman Catholic Church, titled Humanae vitae (Of Human Life), in which he reiterated the Church’s acceptance of the use of birth control pills as a treatment for menstrual disorders, only if such disorders cause bodily harm. However, the St. Louis Guild of the Catholic Medical Association, which is a group of Catholic physicians in St. Louis, Missouri, maintains that the use of birth control pills as a treatment is, what they refer to as, suboptimal medicine. Despite religious opposition, in 2011, the Guttmacher Institute, which is an organization that researches and promotes reproductive health policies, found that among women who use birth control pills, twenty-eight percent reported amenorrhea, demonstrating that women use hormonal therapies for reasons other than contraception.

In 2019, Cleveland Clinic in Cleveland, Ohio reported that three to thirty-five percent of women worldwide experience a menstrual disorder, including amenorrhea. Women who experience amenorrhea often have an underlying health condition, including low body weight or PCOS, that may complicate fertility. For that reason, early detection and treatment like hormone therapy or lifestyle changes are used to restore menstruation.

Sources

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