Menstrual cycle

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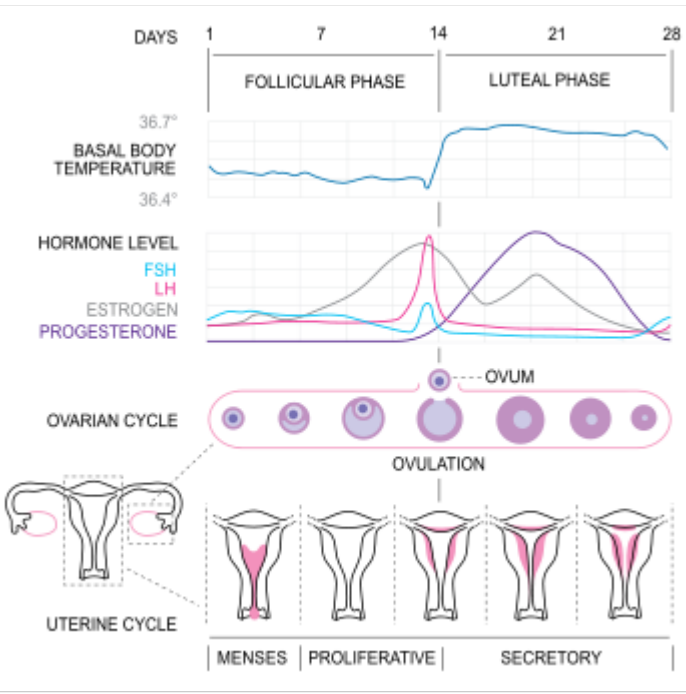
See also: Menstruation and Menstruation (mammal)



Menstrual cycle

The **menstrual cycle** is the scientific term for the physiological changes that can occur in fertile women. This article focuses on the human menstrual cycle.

The menstrual cycle, under the control of the endocrine system, is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase; although some sources use a different set of phases: menstruation, proliferative phase, and secretory phase.[1] Menstrual cycles are counted from the first day of menstrual bleeding. Hormonal contraception interferes with the normal hormonal changes with the aim of preventing reproduction.

Stimulated by gradually increasing amounts of estrogen in the follicular phase, discharges of blood (menses) slow then stop, and the lining of the uterus thickens. Follicles in the ovary begin developing under the influence of a complex interplay of hormones, and after several days one or occasionally two become dominant (non-dominant follicles atrophy and die). Approximately mid-cycle, 24–36 hours after the Luteinizing Hormone (LH) surges, the dominant follicle releases an ovum, or egg in an event called ovulation. After ovulation, the egg only lives for 24 hours or less without fertilization while the remains of the dominant follicle in the ovary become a corpus luteum; this body has a primary function of producing large amounts of progesterone. Under the influence of progesterone, the endometrium (uterine lining) changes to prepare for potential implantation of an embryo to establish a pregnancy. If implantation does not occur within approximately two weeks, the corpus luteum will involute, causing sharp drops in levels of both progesterone and estrogen. These hormone drops cause the uterus to shed its lining and egg in a process termed menstruation.

In the menstrual cycle, changes occur in the female reproductive system as well as other systems (which lead to breast tenderness or mood changes, for example). A woman's first menstruation is termed menarche, and occurs typically around age 12-13. The average age of menarche is about 12.5 years in the United States,[2] 12.72 in Canada,[3] 12.9 in the UK[4] and 13.06 ± 0.10 years in Iceland.[5] The end of a woman's reproductive phase is called the menopause, which commonly occurs somewhere between the ages of 45 and 55.

Contents

Terminology

The menarche is one of the later stages of puberty in girls. The average age of menarche in humans is 12–13 years, but is normal anywhere between ages 8 and 16. Factors such as heredity, diet and overall health can accelerate or delay menarche.[6] The cessation of menstrual cycles at the end of a woman's reproductive period is termed menopause. The average age of menopause in women is 52 years in industrialised countries such as the UK, with anywhere between 45 and 55 being common. Menopause before age 45 is considered *premature* in industrialised countries.[7] The age of menopause is largely a result of genetics; however, illnesses, certain surgeries, or medical treatments may cause menopause to occur earlier.[8]

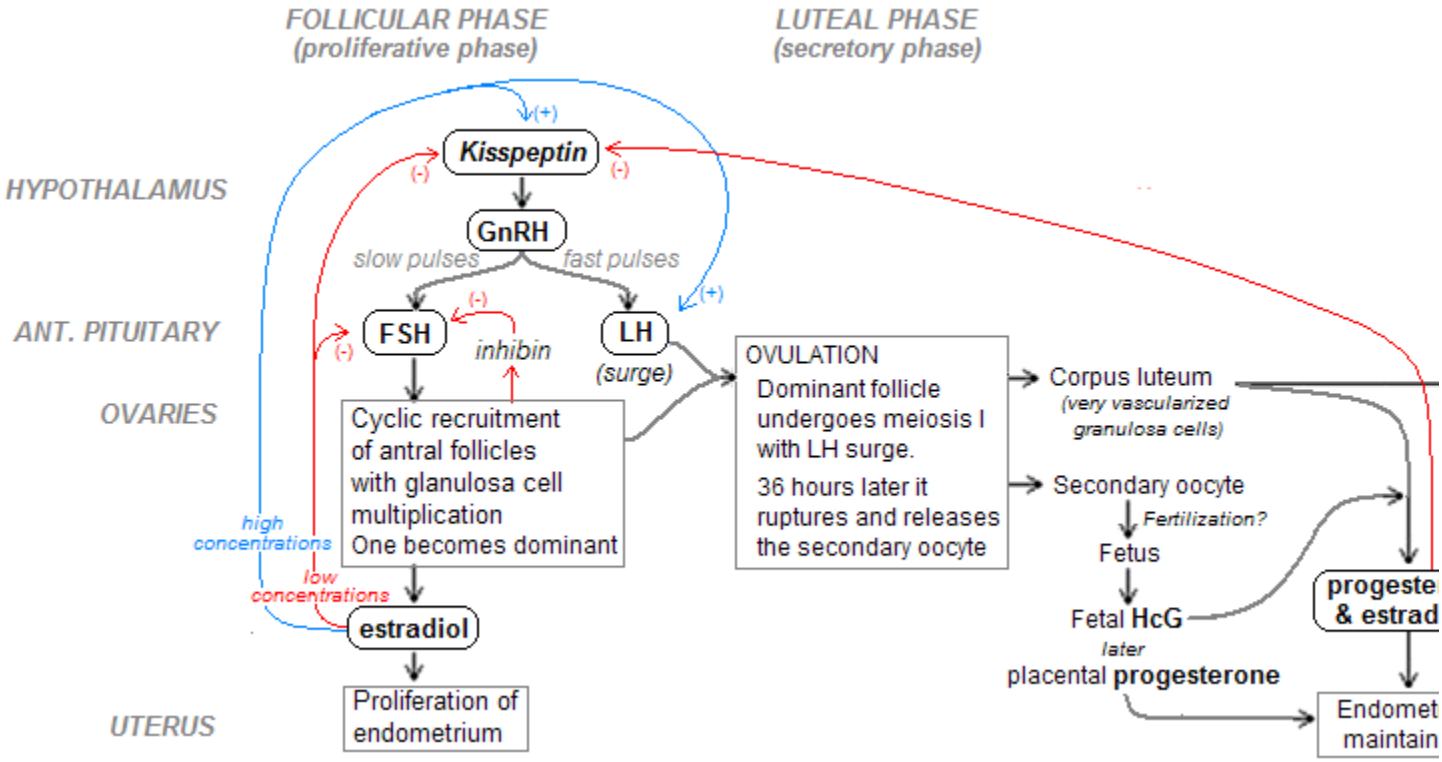
The length of a woman's menstrual cycle will typically vary, with some shorter cycles and some longer cycles. A woman who experiences variations of less than eight days between her longest cycles and shortest cycles is considered to have regular menstrual cycles. It is unusual for a woman to experience cycle length variations of less than four days. Length variation between eight and 20 days is considered as moderately irregular cycles. Variation of 21 days or more between a woman's shortest and longest cycle lengths is considered very irregular.[9]

Phases

The menstrual cycle can be divided into several different phases. The average length of each phase is shown below, the first three are related to changes in the lining of the uterus whereas the final three are related to processes occurring in the ovary:

Name of phase	**Average start day** assuming a 28-day cycle	**Average end day**
Menstrual phase (Menstruation)	1	4
Proliferative phase (Some sources include Menstruation in this phase)	5	13
Ovulatory phase (Ovulation)	13	16

Luteal phase (also known as Secretory phase)	16	28
Ischemic phase	27	28
Follicular phase	1	13



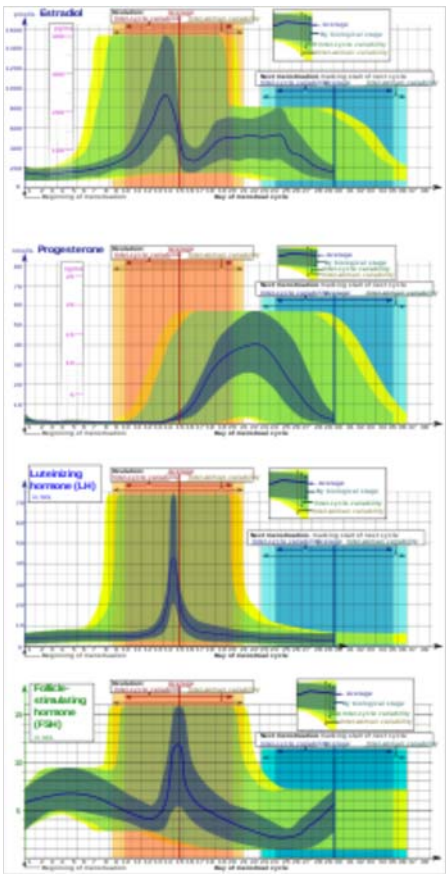
Menstruation

Main article: Menstruation

Menstruation is also called **menstrual bleeding**, **menses**, **catamenia** or a **period**. The flow of menses normally serves as a sign that a woman has not become pregnant. (However, this cannot be taken as certainty, as a number of factors can cause bleeding during pregnancy; some factors are specific to early pregnancy, and some can cause heavy flow.)[10][11][12]

Eumenorrhea denotes normal, regular menstruation that lasts for a few days (usually 3 to 5 days, but anywhere from 2 to 7 days is considered normal).[14][15] The average blood loss during menstruation is 35 milliliters with 10–80 ml considered normal.[16] (Because of this blood loss, women are more susceptible to iron deficiency than men are.)[17] An enzyme called plasmin inhibits clotting in the menstrual fluid.[18]

Painful cramping in the abdomen, back, or upper thighs is common during the first few days of menstruation (most women experience some pain during menstruation). Severe uterine pain during menstruation is known as dysmenorrhea, and it is most common among adolescents and younger women (affecting about 67.2% of adolescent females).[19] When menstruation begins, symptoms of premenstrual syndrome (PMS) such as breast tenderness and irritability generally decrease.[15] Many sanitary products are marketed to women for use during their menstruation.



Levels of estradiol (the main estrogen), progesterone, follicle-stimulating hormone and luteinizing hormone during the menstrual cycle, taking inter-cycle and inter-woman variability into account.[13]

Follicular phase

Main article: Follicular phase

This phase is also called the *proliferative phase* because a hormone causes the lining of the uterus to grow, or proliferate, during this time.[20]

Through the influence of a rise in follicle stimulating hormone (FSH) during the first days of the cycle, a few ovarian follicles are stimulated.[20] These follicles, which were present at birth[20] and have been developing for the better part of a year in a process known as folliculogenesis, compete with each other for dominance. Under the influence of several hormones, all but one of these follicles will stop growing, while one dominant follicle in the ovary will continue to maturity. The follicle that reaches maturity is called a tertiary, or Graafian, follicle, and it forms the ovum.[20]

As they mature, the follicles secrete increasing amounts of estradiol, an estrogen. The estrogens initiate the formation of a new layer of endometrium in the uterus, histologically identified as the proliferative endometrium. The estrogen also stimulates crypts in the cervix to produce fertile cervical mucus, which may be noticed by women practicing fertility awareness.[21]

Ovulation

Main article: Ovulation

During the follicular phase, estradiol suppresses production of luteinizing hormone (LH) from the anterior pituitary gland. When the egg has nearly matured, levels of estradiol reach a threshold above which they stimulate production of LH. These opposite responses of LH to estradiol may be enabled by the presence of two different estrogen receptors in the hypothalamus: estrogen receptor alpha, which is responsible for the negative feedback estradiol-LH loop, and estrogen receptor beta, which is responsible for the positive estradiol-LH relationship.[22] In the average cycle this LH surge starts around cycle day 12 and may last 48 hours.


An ovary about to release an egg.

The release of LH matures the egg and weakens the wall of the follicle in the ovary, causing the fully developed follicle to release its secondary oocyte.[20] The secondary oocyte promptly matures into an ootid and then becomes a mature ovum. The mature ovum has a diameter of about 0.2 mm.[23]

Which of the two ovaries—left or right—ovulates appears essentially random; no known left and right co-ordination exists.[24] Occasionally, both ovaries will release an egg;[24] if both eggs are fertilized, the result is fraternal twins.[25]

After being released from the ovary and into the peritoneal space, the egg is swept into the fallopian tube by the fimbria, which is a fringe of tissue at the end of each fallopian tube. After about a day, an unfertilized egg will disintegrate or dissolve in the fallopian tube.[20]

Fertilization by a spermatozoon, when it occurs, usually takes place in the ampulla, the widest section of the fallopian tubes. A fertilized egg immediately begins the process of embryogenesis, or development. The developing embryo takes about three days to reach the uterus and another three days to implant into the endometrium.[20] It has usually reached the blastocyst stage at the time of implantation.

In some women, ovulation features a characteristic pain called *mittelschmerz* (German term meaning *middle pain*).[15] The sudden change in hormones at the time of ovulation sometimes also causes light mid-cycle blood flow.[26]

Luteal phase

Main article: Luteal phase

The luteal phase is also called the *secretory phase*. An important role is played by the corpus luteum, the solid body formed in an ovary after the egg has been released from the ovary into the fallopian tube. This body continues to grow for some time after ovulation and produces significant amounts of hormones, particularly progesterone.[20] Progesterone plays a vital role in making the endometrium receptive to implantation of the blastocyst and supportive of the early pregnancy; it also has the side effect of raising the woman's basal body temperature.[27] There is a noted secretion of prolactin towards the end of the secretory phase.[*citation needed*]

After ovulation, the pituitary hormones FSH and LH cause the remaining parts of the dominant follicle to transform into the corpus luteum, which produces progesterone. The increased progesterone in the adrenals starts to induce the production of estrogen. The hormones produced by the corpus luteum also suppress production of the FSH and LH that the corpus luteum needs to maintain itself. Consequently, the level of FSH

and LH fall quickly over time, and the corpus luteum subsequently atrophies.[20] Falling levels of progesterone trigger menstruation and the beginning of the next cycle. From the time of ovulation until progesterone withdrawal has caused menstruation to begin, the process typically takes about two weeks, with 14 days considered normal. For an individual woman, the follicular phase often varies in length from cycle to cycle; by contrast, the length of her luteal phase will be fairly consistent from cycle to cycle.[28]

The loss of the corpus luteum can be prevented by fertilization of the egg; the resulting embryo produces human chorionic gonadotropin (hCG), which is very similar to LH and which can preserve the corpus luteum. Because the hormone is unique to the embryo, most pregnancy tests look for the presence of hCG.[20]

Length

Although many people believe the average menstrual cycle takes 28 days, a large study of more than 30,000 cycles from more than 2300 women showed that the mean cycle length was 29.1 with a standard deviation of 7.5 days and a 95% prediction interval of between 15 and 45 days.[29] In that study, the subset of data with cycle lengths between 15 and 45 days had an average length of 28.1 days with a standard deviation of 4 days. A smaller study of 140 women performed in 2006 found a mean cycle length of 28.9 days.[30]

The variability of menstrual cycle lengths is highest for women under 25 years of age and is lowest, that is, most regular, for ages 35 to 39.[29] Subsequently, the variability increases slightly for women aged 40 to 44.[29] Usually, length variation between eight and 20 days in a woman is considered as moderately irregular menstrual cycles.[9] Variation of 21 days or more is considered very irregular.[9]

It has long been thought that cycle length is associated with the moon. A 1979 study of 305 women found that approximately one-third of the subjects had lunar period cycles, i.e., a mean cycle length of 29.5 days plus or minus 1 day. Almost two-thirds of the subjects started their cycle in the brighter half of the lunar cycle, significantly more than would be expected by random distribution.[31] Another study found a statistically significant number of menstruations occurred around the new moon.[32]

Fertile window

Main article: fertility testing

The most fertile period (the time with the highest likelihood of pregnancy resulting from sexual intercourse) covers the time from some 5 days before until 1–2 days after ovulation.[33] In a 28 day cycle with a 14-day luteal phase, this corresponds to the second and the beginning of the third week. A variety of methods have been developed to help individual women estimate the relatively fertile and the relatively infertile days in the cycle: these systems are called fertility awareness.

Fertility awareness methods that rely on cycle length records alone are called calendar-based methods.[34] Methods that require observation of one or more of the three primary fertility signs (basal body temperature, cervical mucus, and cervical position)[35] are known as symptoms-based methods.[34] Urine test kits are available that detect the LH surge that occurs 24 to 36 hours before ovulation; these are known as ovulation predictor kits (OPKs).[36] Computerized devices that interpret basal body temperatures, urinary test results, or changes in saliva are called fertility monitors.

A woman's fertility is also affected by her age.[37] As a woman's total egg supply is formed in fetal life,[38] to be

ovulated decades later, it has been suggested that this long lifetime may make the chromatin of eggs more vulnerable to division problems, breakage, and mutation than the chromatin of sperm, which are produced continuously during a man's reproductive life. However, despite this hypothesis, a similar paternal age effect has also been observed.

Effect on other systems

Some women with neurological conditions experience increased activity of their conditions at about the same time during each menstrual cycle. For example, drops in estrogen levels have been known to trigger migraines (a neurological syndrome, migraines),[39] especially when the woman who suffers migraines is also taking the birth control pill. Many women with epilepsy have more seizures in a pattern linked to the menstrual cycle; this is called "catamenial epilepsy".[40] Different patterns seem to exist (such as seizures coinciding with the time of menstruation, or coinciding with the time of ovulation), and the frequency with which they occur has not been firmly established. Using one particular definition, one group of scientists found that around one-third of women with intractable partial epilepsy have catamenial epilepsy.[40][41][42] An effect of hormones has been proposed, in which progesterone declines and estrogen increases would trigger seizures.[43] Recently, studies have shown that high doses of estrogen can cause or worsen seizures, whereas high doses of progestrone can act like an antiepileptic drug.[44] Studies by medical journals have found that women experiencing menses are 1.68 times more likely to commit suicide.[45]

Mice have been used as an experimental system to investigate possible mechanisms by which levels of sex steroid hormones might regulate nervous system function. During the part of the mouse estrous cycle when progesterone is highest, the level of nerve-cell GABA receptor subtype delta was high. Since these GABA receptors are inhibitory, nerve cells with more delta receptors are less likely to fire than cells with lower numbers of delta receptors. During the part of the mouse estrous cycle when estrogen levels are higher than progesterone levels, the number of delta receptors decrease, increasing nerve cell activity, in turn increasing anxiety and seizure susceptibility.[46]

Estrogen levels may affect thyroid behavior.[47] For example, during the luteal phase (when estrogen levels are lower), the velocity of blood flow in the thyroid is lower than during the follicular phase (when estrogen levels are higher).[48]

Among women living closely together, it was once thought that the onsets of menstruation tend to synchronize. This effect was first described in 1971, and possibly explained by the action of pheromones in 1998.[49] Subsequent research has called this hypothesis into question.[50]

Cycle abnormalities and disorders

Main article: Menstrual disorder

Infrequent or irregular ovulation is called *oligoovulation*.[51] The absence of ovulation is called *anovulation*. Normal menstrual flow can occur without ovulation preceding it: an anovulatory cycle. In some cycles, follicular development may start but not be completed; nevertheless, estrogens will form and will stimulate the uterine lining. Anovulatory flow resulting from a very thick endometrium caused by prolonged, continued high estrogen levels is called *estrogen breakthrough bleeding*. Anovulatory bleeding triggered by a sudden drop in estrogen levels is called changes.[52] Anovulatory cycles commonly occur before menopause (perimenopause) and in women with polycystic ovary syndrome.[53]

Very little flow (less than 10 ml) is called *hypomenorrhea*. Regular cycles with intervals of 21 days or fewer are *polymenorrhea*; frequent but irregular menstruation is known as *metrorrhagia*. Sudden heavy flows or amounts greater than 80 ml are termed *menorrhagia*.[54] Heavy menstruation that occurs frequently and irregularly is *menometrorrhagia*. The term for cycles with intervals exceeding 35 days is *oligomenorrhea*.[55] Amenorrhea refers to more than three[54] to six[55] months without menses (while not being pregnant) during a woman's reproductive years.

Ovulation suppression

Hormonal contraception

Main article: Hormonal contraception

Half-used blister pack of a combined oral contraceptive. The white pills are placebos, mainly for the purpose of reminding the woman to continue taking the pills.

While some forms of birth control do not affect the menstrual cycle, hormonal contraceptives work by disrupting it. Progestogen negative feedback decreases the pulse frequency of gonadotropin-releasing hormone (GnRH) release by the hypothalamus, which decreases the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary. Decreased levels of FSH inhibit follicular development, preventing an increase in estradiol levels. Progestogen negative feedback and the lack of estrogen positive feedback on LH release prevent a mid-cycle LH surge. Inhibition of follicular development and the absence of a LH surge prevent ovulation.[56][57][58]

The degree of ovulation suppression in progestogen-only contraceptives depends on the progestogen activity and dose. Low dose progestogen-only contraceptives—traditional progestogen only pills, subdermal implants Norplant and Jadelle, and intrauterine system Mirena—inhibit ovulation in ~50% of cycles and rely mainly on other effects, such as thickening of cervical mucus, for their contraceptive effectiveness.[59] Intermediate dose progestogen-only contraceptives—the progestogen-only pill Cerazette and the subdermal implant Implanon—allow some follicular development but more consistently inhibit ovulation in 97–99% of cycles. The same cervical mucus changes occur as with very low dose progestogens. High dose progestogen-only contraceptives—the injectables Depo-Provera and Noristerat—completely inhibit follicular development and ovulation.[59]

Combined hormonal contraceptives include both an estrogen and a progestogen. Estrogen negative feedback on the anterior pituitary greatly decreases the release of FSH, which makes combined hormonal contraceptives more effective at inhibiting follicular development and preventing ovulation. Estrogen also reduces the incidence of irregular breakthrough bleeding.[56][57][58] Several combined hormonal contraceptives—the pill, NuvaRing, and the contraceptive patch—are usually used in a way that causes regular withdrawal bleeding. In a normal cycle, menstruation occurs when estrogen and progesterone levels drop rapidly.[27] Temporarily discontinuing use of combined hormonal contraceptives (a placebo week, not using patch or ring for a week) has a similar effect of causing the uterine lining to shed. If withdrawal bleeding is not desired, combined hormonal contraceptives may be taken continuously, although this increases the risk of breakthrough bleeding.

Lactational amenorrhea

Main article: Lactational amenorrhea method

Breastfeeding causes negative feedback to occur on pulse secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH). Depending on the strength of the negative feedback, breastfeeding women may experience complete suppression of follicular development, follicular development but no ovulation, or normal menstrual cycles may resume.[60] Suppression of ovulation is more likely when suckling occurs more frequently.[61] The production of prolactin in response to suckling is important to maintaining lactational amenorrhea.[62] On average, women who are fully breastfeeding whose infants suckle frequently experience a return of menstruation at fourteen and a half months postpartum. There is a wide range of response between individual breastfeeding women, however, with some experiencing return of menstruation at two months and others remaining amenorrheic for up to 42 months postpartum.[63]

Etymological and biological associations

Nightlighting and the moon

See also: Culture and menstruation and Lunar effect

The word "menstruation" is etymologically related to "moon". The terms "menstruation" and "menses" are derived from the Latin *mensis* (month), which in turn relates to the Greek *mene* (moon) and to the roots of the English words *month* and *moon*.[64]

Some authors believe women in traditional societies without nightlighting ovulated with the full moon and menstruated with the new moon,[65] and one author documents the controversial attempts to use the association to improve the Rhythm Method of regulating conception.[64][66]

A few studies in both humans [67] and other animals[68] have found that artificial light at night does influence the menstrual cycle in humans and the estrus cycle in mice (cycles are more regular in the absence of artificial light at night). It has also been suggested that bright light exposure in the morning promotes more regular cycles.[69] One author has suggested that sensitivity of women's cycles to nightlighting is caused by nutritional deficiencies of certain vitamins and minerals.[70]

Some studies show a correlation between the human menstrual cycle and the lunar cycle, while a meta-analysis of studies from 1996 showed no correlation.[71][72][73][74][75][76] Dogon villagers did not have electric lighting and spent most nights outdoors, talking and sleeping; so they were an ideal population for detecting a lunar influence: none, however, was found.[77]

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