

# Estrogen and the Menstrual Cycle in Humans <sup>[1]</sup>

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Estrogen is the primary sex [hormone](#) <sup>[3]</sup> in women and it functions during the reproductive menstrual cycle. Women have three major types of [estrogen](#) <sup>[4]</sup>: estrone, [estradiol](#) <sup>[5]</sup>, and estriol, which bind to and activate receptors within the body. Researchers discovered the three types of [estrogen](#) <sup>[4]</sup> over a period of seven years, contributing to more detailed descriptions of the menstrual cycle. Each type of [estrogen](#) <sup>[4]</sup> molecule contains a slightly different arrangement or number of atoms that in turn causes some of the estrogens to be more active than others. The different types of [estrogen](#) <sup>[4]</sup> peak and wane throughout women's reproductive cycles, from normal [menstruation](#) <sup>[6]</sup> to [pregnancy](#) <sup>[7]</sup> to the cessation of [menstruation](#) <sup>[6]</sup> (menopause). As scientists better explained the effects of estrogens, they used that information to develop oral contraceptives to control [pregnancy](#) <sup>[7]</sup>, to map the menstrual cycle, and to create [hormone](#) <sup>[3]</sup> therapies to regulate abnormal levels of [estrogen](#) <sup>[4]</sup>.

The estrogens ([estradiol](#) <sup>[5]</sup>, estrone, and estriol) are a group of biologically active steroid [hormones](#) <sup>[8]</sup>. As signaling molecules, [estradiol](#) <sup>[5]</sup>, estriol, and estrone bind to receptor molecules in cells to signal specific changes to occur within the body. The estrogens each attach to receptor molecules with a specific fit, like how one puzzle piece connects to another. Some of the [estrogen](#) <sup>[4]</sup> molecules function during the menstrual cycle, leading to changes in tissue thickness and menstrual bleeding. All three of the [estrogen](#) <sup>[4]</sup> molecules are similar in chemical structure and constituents. The similarities of the different estrogens arise because some [estrogen](#) <sup>[4]</sup> molecules are derivatives of the other, meaning that one [estrogen](#) <sup>[4]</sup> can lead to the creation of another. Each [estrogen](#) <sup>[4]</sup> molecule contains a similar base structure and varies minutely with the addition or elimination of specifically bound atoms, called functional groups. Researchers used the different functional groups to isolate and distinguish [estradiol](#) <sup>[5]</sup>, estrone, and estriol from one another.

In the 1920s, researchers debated about what item in the female body produced most of the [estrogen](#) <sup>[4]</sup>, then called the primary ovarian [hormone](#) <sup>[3]</sup>, during menstrual cycles. Some researchers said that the corpora lutea, which forms on the ovaries after [egg](#) <sup>[9]</sup> release, contained and produced the needed amount of [estrogen](#) <sup>[4]</sup> to complete the menstrual cycle. However, researchers Edward Adelbert Doisy and Edgar Allen hypothesized that the ovarian follicles primarily produced the levels of [estrogen](#) <sup>[4]</sup> needed to complete the cycle. In 1923 at [Washington University](#) <sup>[10]</sup> in St. Louis, Missouri, Allen and Doisy isolated [estrogen](#) <sup>[4]</sup> from ovarian follicle extracts and showed its effect in test animals. Their results showed that the ovarian follicles primarily produced [estrogen](#) <sup>[4]</sup> during the reproductive cycle. That discovery enabled future researchers to outline the follicular phase, the phase in the menstrual cycle that includes [egg](#) <sup>[9]</sup> development, to also include [estrogen](#) <sup>[4]</sup> production in the ovarian follicles. Later researchers showed that the increase in [estrogen](#) <sup>[4]</sup> levels led to the production of another [hormone](#) <sup>[3]</sup>, the [luteinizing hormone](#) <sup>[11]</sup>, which leads to the release of eggs from ovaries.

The three kinds of estrogen—estradiol, estrone, and, estriol—were discovered over time, with estrone being discovered first. In 1929, researchers Doisy, Clement D. Veler, and Sidney Thayer isolated pure crystalized estrone in the Laboratory of Biological Chemistry at the St. Louis University School of Medicine in St. Louis. The three researchers isolated estrone from the urine of pregnant women using distillation, a method that uses boiling point differences to evaporate one liquid from another; and extraction, the removal of one substance from another. At the Institute of Chemistry in Göttinge, Germany, Adolf Frederick Johann Butenandt also isolated estrone around the same time, receiving the Nobel Prize for Chemistry in 1939 for that achievement.

In addition to estrone, Doisy also isolated estriol from hundreds of gallons of urine from pregnant women in 1930, discovering a second [estrogen](#) <sup>[4]</sup>. In 1936, Doisy alongside researchers Donald W. MacCorquodale and Stanley S. Thayer isolated the third type of [estrogen](#) <sup>[4]</sup>, [estradiol](#) <sup>[5]</sup>, from [pig](#) <sup>[12]</sup> ovaries. Estradiol was later found in [humans](#) <sup>[13]</sup>. The structure of [estradiol](#) <sup>[5]</sup> is similar to estrone, but instead of the double bonded oxygen atom, the molecule contains a single bonded oxygen atom. The isolation of [estradiol](#) <sup>[5]</sup>, the [estrogen](#) <sup>[4]</sup> most involved in the reproductive menstrual cycle, enabled researchers to create [hormone](#) <sup>[3]</sup> therapies and oral contraceptives. Doisy also researched Vitamin K, for which he went on to win the [Nobel Prize in Physiology or Medicine](#) <sup>[14]</sup> in 1943.

Later, researchers used Doisy's methods to create [hormone](#) <sup>[3]</sup> therapies for women who lacked proper levels of [estradiol](#) <sup>[5]</sup>. Researchers could cause changes in the menstrual cycle, as they had the ability to give women [estradiol](#) <sup>[5]</sup>, the most biologically active [estrogen](#) <sup>[4]</sup> [hormone](#) <sup>[3]</sup> that predominates during the menstrual cycle.

In 1946 in New York City, New York, physicians Hans Wiesbader and William Filler demonstrated their ability to induce changes in the menstrual cycle when they gave lab made (synthetic) [estradiol](#) <sup>[5]</sup> to women with problems arising from menopause. In the mid twentieth century, researchers synthesized [estradiol](#) <sup>[5]</sup>-like molecules from other products, creating compounds like ethinyl [estradiol](#) <sup>[5]</sup>, which caused the same reactions within the body as natural [estradiol](#) <sup>[5]</sup>. Wiesbader and Filler sought to help women

suffering from menopause, the cessation of a regular menstrual flow, by giving them the [hormone](#)<sup>[3]</sup> ethinyl [estradiol](#)<sup>[5]</sup>. Menopause in women can cause the vaginal tissue to thin and the natural buildup of [endometrium](#)<sup>[15]</sup> tissue in the [uterus](#)<sup>[16]</sup> to cease, along with symptoms like hot flashes. When women took the [hormone](#)<sup>[3]</sup> ethinyl [estradiol](#)<sup>[5]</sup> orally in pill form, the [hormone](#)<sup>[3]</sup> thickened vaginal walls and uterine linings, and it removed hot-flash symptoms in some women during the clinical tests. Research with [estrogen](#)<sup>[4]</sup> [hormones](#)<sup>[8]</sup> continued.

The isolation of [estradiol](#)<sup>[5]</sup> by Doisy, MacCorquodale, and Thayer also enabled researchers to create oral contraceptives, approved in 1960 in the US by the [Food and Drug Administration](#)<sup>[17]</sup> in Washington, DC. The isolation of [estradiol](#)<sup>[5]</sup> led researchers to describe the structure and function of the [hormone](#)<sup>[3]</sup>, which helped chemists to cheaply synthesize [estradiol](#)<sup>[5]</sup>-like [hormones](#)<sup>[8]</sup> for commercial use. With the advent of synthesized [estradiol](#)<sup>[5]</sup>, researchers made oral contraceptives available to women to prevent [pregnancy](#)<sup>[7]</sup>. Oral contraceptives function to prevent [pregnancy](#)<sup>[7]</sup> by altering the menstrual cycle. Those alterations prevent ovaries from releasing eggs and keep the tissue of the [uterus](#)<sup>[16]</sup> thin, reducing the chances of a possible [fertilized egg](#)<sup>[18]</sup> from implanting in the [uterus](#)<sup>[16]</sup>. The menstrual cycle is controlled by [estradiol](#)<sup>[5]</sup> and other [hormones](#)<sup>[8]</sup>. With the discovery that [estradiol](#)<sup>[5]</sup> functions throughout a woman's reproductive cycle, researchers described the cycle in a greater detail.

The menstrual cycle prepares a woman's body for possible [pregnancy](#)<sup>[7]</sup>, producing an [egg](#)<sup>[9]</sup> and a layer of nourishing uterine tissue. The menstrual cycle begins anew if the recently produced [egg](#)<sup>[9]</sup> remains unfertilized or if a [fertilized egg](#)<sup>[18]</sup> does not implant to the [uterus](#)<sup>[16]</sup>. In [humans](#)<sup>[13]</sup>, each menstrual cycle lasts for approximately twenty-eight days but typically varies between individuals, as some women have longer cycles and others have shorter cycles. Professionals quantify each cycle's length by measuring the time in days that it spans from beginning to end. The monthly cycle starts on day one with normal bleeding ([menstruation](#)<sup>[6]</sup>) and ends around day twenty-eight, just before the onset of the next [menstruation](#)<sup>[6]</sup> if a [fertilized egg](#)<sup>[18]</sup> has not implanted. If a [fertilized egg](#)<sup>[18]</sup> implants to the uterine wall, the menstrual cycle stops and [pregnancy](#)<sup>[7]</sup> begins. In [humans](#)<sup>[13]</sup>, four regulating [hormones](#)<sup>[8]</sup> control the menstrual cycle by initiating and ending a series of stepwise phases. The four [hormones](#)<sup>[8]</sup> include [luteinizing hormone](#)<sup>[11]</sup>, [follicle stimulating hormone](#)<sup>[19]</sup>, [progesterone](#)<sup>[20]</sup>, and [estrogen](#)<sup>[4]</sup>. The phases that make up the menstrual cycle include the follicular phase, the ovulatory phase, and the luteal phase.

The first phase, the follicular phase, begins the menstrual cycle in [humans](#)<sup>[13]</sup>, lasting on average thirteen to fourteen days. Egg development and menstrual bleeding both occur during the follicular phase. At the beginning of the follicular phase, the tissue that lines the inside of the [uterus](#)<sup>[16]</sup> ([endometrium](#)<sup>[15]</sup>) is thick and full of nutrients that are ready to support and nourish a [fertilized egg](#)<sup>[18]</sup>. However, if an [egg](#)<sup>[9]</sup> does not implant, the [uterus](#)<sup>[16]</sup> shreds the [endometrium](#)<sup>[15]</sup>. The shedding of the uterine lining is one of the many changes that occur during the menstrual cycle.

When the menstrual cycle begins, [estradiol](#)<sup>[5]</sup> and [progesterone](#)<sup>[20]</sup> levels drop. That drop in [hormone](#)<sup>[3]</sup> levels signals the [endometrium](#)<sup>[15]</sup> layer to shed, resulting in menstrual bleeding. During menstrual bleeding, the level of follicle-stimulating [hormone](#)<sup>[3]</sup> (FSH) increases and stimulates the growth of multiple ovarian follicles. Each follicle contains a developing [egg](#)<sup>[9]</sup>. Later in the follicular phase, FSH levels start to decrease and only one follicle grows to maturation (the dominant ovarian follicle). The dominant ovarian follicle begins producing [estradiol](#)<sup>[5]</sup> during the follicular phase. When it begins to produce [estradiol](#)<sup>[5]</sup>, the remaining stimulated follicles break down. The increase in [estradiol](#)<sup>[5]</sup> stimulates the production of [luteinizing hormone](#)<sup>[3]</sup>, which begins the next stage of a menstrual cycle.

The next phase, the ovulatory phase, lasts approximately sixteen to thirty-two hours and begins with a sharp increase in [luteinizing hormone](#)<sup>[11]</sup> caused by [estradiol](#)<sup>[5]</sup> at the end of the follicular phase. The surge in [luteinizing hormone](#)<sup>[11]</sup> level causes the dominant ovarian follicle to increase in size, eventually to the point that it ruptures, releasing a mature [egg](#)<sup>[9]</sup> from one of the two ovaries that women have. The release of an [egg](#)<sup>[9]</sup> is called [ovulation](#)<sup>[21]</sup>. Ovulation occurs approximately fourteen days before the onset of a woman's next menstrual period. The released [egg](#)<sup>[9]</sup> travels down the fallopian tube, which connects the [ovary](#)<sup>[22]</sup> to the [uterus](#)<sup>[16]</sup>. Once in the fallopian tube, the [egg](#)<sup>[9]</sup> can be fertilized by [sperm](#)<sup>[23]</sup>. If the [egg](#)<sup>[9]</sup> becomes fertilized and implants in the [uterus](#)<sup>[16]</sup>, the cycle stops and [pregnancy](#)<sup>[7]</sup> occurs. Regardless of whether or not the [egg](#)<sup>[9]</sup> becomes fertilized, the menstrual cycle continues to the luteal phase.

The luteal phase lasts for approximately fourteen days after [ovulation](#)<sup>[21]</sup> and ends the menstrual cycle. During the luteal phase, the ruptured site on the [ovary](#)<sup>[22]</sup>, where the dominant ovarian follicle released an [egg](#)<sup>[9]</sup>, closes and develops into the [corpus luteum](#)<sup>[24]</sup>. The [corpus luteum](#)<sup>[24]</sup> produces a slight amount of [estradiol](#)<sup>[5]</sup> and a much larger amount of [progesterone](#)<sup>[20]</sup>. Levels of [estradiol](#)<sup>[5]</sup> during the luteal phase are high and, together with [progesterone](#)<sup>[20]</sup>, cause the [endometrium](#)<sup>[15]</sup> to thicken to provide nutrients and a place for adhesion if an [egg](#)<sup>[9]</sup> is fertilized and becomes an embryo. The increase in levels of [estradiol](#)<sup>[5]</sup> and [progesterone](#)<sup>[20]</sup> also causes the milk ducts in the breasts to dilate and become larger, resulting in swelling and possible breast soreness prior to the onset of [menstruation](#)<sup>[6]</sup>. If an embryo implants to the [endometrium](#)<sup>[15]</sup>, the corpus luteum functions until the [placenta](#)<sup>[25]</sup>, which nourishes the [fetus](#)<sup>[26]</sup>, develops to take over [hormone](#)<sup>[3]</sup> production in the twelfth or thirteenth weeks of [pregnancy](#)<sup>[7]</sup>. If a [fertilized egg](#)<sup>[18]</sup> does not implant, the [corpus luteum](#)<sup>[24]</sup> degrades around ten days after its initial development and stops secreting [progesterone](#)<sup>[20]</sup>. The luteal phase ends right before the beginning of the next menstrual period or before the onset of [pregnancy](#)<sup>[7]</sup>. The follicular phase occurs next, starting the menstrual cycle all over again.

Estradiol functions during the menstrual cycle. The drop in [estradiol](#)<sup>[5]</sup> levels during the follicular phase causes the [endometrium](#)<sup>[15]</sup> layer of the [uterus](#)<sup>[16]</sup> to shed, beginning [menstruation](#)<sup>[6]</sup>. In the later ovulatory phase, the dominant ovarian follicle produces

[estradiol](#)<sup>[5]</sup>, which increases [luteinizing hormone](#)<sup>[11]</sup> levels, rupturing the ovarian follicle, which releases an [egg](#)<sup>[9]</sup>. The corpus luteum during the final luteal phase produces the [hormone](#)<sup>[3]</sup> [estradiol](#)<sup>[5]</sup> in increasing amounts, which then thickens the [endometrium](#)<sup>[15]</sup>, enabling the menstrual cycle to start over again. During [pregnancy](#)<sup>[7]</sup>, the [placenta](#)<sup>[25]</sup> produces more estriol than [estradiol](#)<sup>[5]</sup>. Making estriol the dominant [estrogen](#)<sup>[4]</sup> measured in blood concentration levels. Estrone increases in concentration and is produced more than [estradiol](#)<sup>[5]</sup> when a woman enters menopause, when [menstruation](#)<sup>[6]</sup> and the menstrual cycle stop.

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Estrogen is the primary sex hormone in women and it functions during the reproductive menstrual cycle. Women have three major types of estrogen: estrone, estradiol, and estriol, which bind to and activate receptors within the body. Researchers discovered the three types of estrogen over a period of seven years, contributing to more detailed descriptions of the menstrual cycle. Each type of estrogen molecule contains a slightly different arrangement or number of atoms that in turn causes some of the estrogens to be more active than others. The different types of estrogen peak and wane throughout women's reproductive cycles, from normal menstruation to pregnancy to the cessation of menstruation (menopause). As scientists better explained the effects of estrogens, they used that information to develop oral contraceptives to control pregnancy, to map the menstrual cycle, and to create hormone therapies to regulate abnormal levels of estrogen.

## Subject

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## Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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## Last Modified

Wednesday, July 4, 2018 - 04:40

## DC Date Accessioned

Wednesday, June 22, 2016 - 01:04

## DC Date Available

Wednesday, June 22, 2016 - 01:04

## DC Date Created

2016-06-22

## DC Date Created Standard

Wednesday, June 22, 2016 - 07:00

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