Estrogen and the Menstrual Cycle in Humans [1]

By: Van Iten, Brendan Keywords: Hormones [2]

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

The estrogens (estradiol [5], estrone, and estriol) are a group of biologically active steroid hormones [8]. As signaling molecules, estradiol [5], 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 [4] molecules function during the menstrual cycle, leading to changes in tissue thickness and menstrual bleeding. All three of the estrogen [4] molecules are similar in chemical structure and constituents. The similarities of the different estrogens arise because some estrogen [4] molecules are derivatives of the other, meaning that one estrogen [4] can lead to the creation of another. Each estrogen [4] 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 [5], estrone, and estriol from one another.

In the 1920s, researchers debated about what item in the female body produced most of the estrogen [4], then called the primary ovarian hormone [3], during menstrual cycles. Some researchers said that the corpora lutea, which forms on the ovaries after egg [9] release, contained and produced the needed amount of estrogen [4] to complete the menstrual cycle. However, researchers Edward Adelbert Doisy and Edgar Allen hypothesized that the ovarian follicles primarily produced the levels of estrogen [4] needed to complete the cycle. In 1923 at Washington University [10] in St. Louis, Missouri, Allen and Doisy isolated estrogen [4] from ovarian follicle extracts and showed its effect in test animals. Their results showed that the ovarian follicles primarily produced estrogen [4] during the reproductive cycle. That discovery enabled future researchers to outline the follicular phase, the phase in the menstrual cycle that includes egg [9] development, to also include estrogen [4] production in the ovarian follicles. Later researchers showed that the increase in estrogen [4] levels led to the production of another hormone [3], the luteinizing hormone [11], 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 [4]. In 1936, Doisy alongside researchers Donald W. MacCorquodale and Stanley S. Thayer isolated the third type of estrogen [4], estradiol [5], from pig [12] ovaries. Estradiol was later found in humans [13]. The structure of estradiol [5] is similar to estrone, but instead of the double bonded oxygen atom, the molecule contains a single bonded oxygen atom. The isolation of estradiol [5], the estrogen [4] most involved in the reproductive menstrual cycle, enabled researchers to create hormone [3] therapies and oral contraceptives. Doisy also researched Vitamin K, for which he went on to win the Nobel Prize in Physiology or Medicine [14] in 1943.

Later, researchers used Doisy's methods to create hormone [3] therapies for women who lacked proper levels of estradiol [5]. Researchers could cause changes in the menstrual cycle, as they had the ability to give women estradiol [5], the most biologically active estrogen [4] hormone [3] 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 [5] to women with problems arising from menopause. In the mid twentieth century, researchers synthesized estradiol [5]-like molecules from other products, creating compounds like ethinyl estradiol [5], which caused the same reactions within the body as natural estradiol [5]. Wiesbader and Filler sought to help women

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

The isolation of estradiol [5] by Doisy, MacCorquodale, and Thayer also enabled researchers to create oral contraceptives, approved in 1960 in the US by the Food and Drug Administration [17] in Washington, DC. The isolation of estradiol [5] led researchers to describe the structure and function of the hormone [3], which helped chemists to cheaply synthesize estradiol [5]-like hormones [8] for commercial use. With the advent of synthesized estradiol [5], researchers made oral contraceptives available to women to prevent pregnancy [7]. Oral contraceptives function to prevent pregnancy [7] by altering the menstrual cycle. Those alterations prevent ovaries from releasing eggs and keep the tissue of the uterus [16] thin, reducing the chances of a possible fertilized egg [18] from implanting in the uterus [16]. The menstrual cycle is controlled by estradiol [5] and other hormones [8]. With the discovery that estradiol [5] 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 [7], producing an egg [9] and a layer of nourishing uterine tissue. The menstrual cycle begins anew if the recently produced egg [9] remains unfertilized or if a fertilized egg [18] does not implant to the uterus [16]. In humans [13], 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 [6]) and ends around day twenty-eight, just before the onset of the next menstruation [6] if a fertilized egg [18] has not implanted. If a fertilized egg [18] implants to the uterine wall, the menstrual cycle stops and pregnancy [7] begins. In humans [13], four regulating hormones [8] control the menstrual cycle by initiating and ending a series of stepwise phases. The four hormones [8] include luteinizing hormone [11], follicle stimulating hormone [19], progesterone [20], and estrogen [4]. 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 [13], 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 [16] (endometrium [15]) is thick and full of nutrients that are ready to support and nourish a fertilized egg [18]. However, if an egg [9] does not implant, the uterus [16] shreds the endometrium [15]. The shedding of the uterine lining is one of the many changes that occur during the menstrual cycle.

When the menstrual cycle begins, estradiol [5] and progesterone [20] levels drop. That drop in hormone [3] levels signals the endometrium [15] layer to shed, resulting in menstrual bleeding. During menstrual bleeding, the level of follicle-stimulating hormone [3] (FSH) increases and stimulates the growth of multiple ovarian follicles. Each follicle contains a developing egg [9]. 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 [5] during the follicular phase. When it begins to produce estradiol [5], the remaining stimulated follicles break down. The increase in estradiol [5] stimulates the production of luteinizing hormone [3], 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 [11] caused by estradiol [5] at the end of the follicular phase. The surge in luteinizing hormone [11] level causes the dominant ovarian follicle to increase in size, eventually to the point that it ruptures, releasing a mature egg [9] from one of the two ovaries that women have. The release of an egg [9] is called ovulation [21]. Ovulation occurs approximately fourteen days before the onset of a woman's next menstrual period. The released egg [9] travels down the fallopian tube, which connects the ovary [22] to the uterus [16]. Once in the fallopian tube, the egg [9] can be fertilized by sperm [23]. If the egg [9] becomes fertilized and implants in the uterus [16], the cycle stops and pregnancy [7] occurs. Regardless of whether or not the egg [9] becomes fertilized, the menstrual cycle continues to the luteal phase.

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

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

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

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Subject

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