

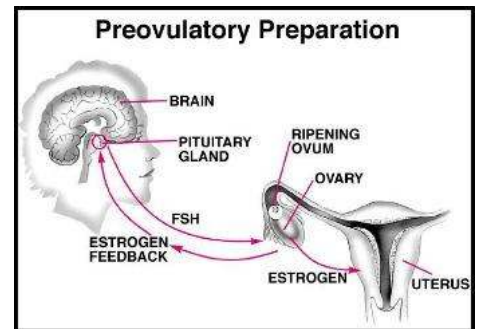
# Certified Fertility Counselor Course- Session 2- Follicular Phase and Hormones

## Follicular Phase

The follicular phase is the first half of the menstrual cycle, beginning on the first day of the menstrual cycle, and lasting until the day ovulation occurs. There are many factors that happen in this cycle in order for ovulation to occur.

This phase is also called the “proliferative phase”. The term follicular is based on the changes occurring in the ovaries while the synonym word proliferative (meaning multiplication) is based on the changes occurring in the endometrium of the uterus at the same time.

When a period arrives, it is due to the hormone’s estrogen and progesterone levels being low, indicating to your body that it is time to start a new cycle. The body will begin to shed the top layer of the endometrium (lining of the uterus) to make way for a healthier new lining. At the same time, your hormones are starting to prepare new eggs for ovulation. During the follicular phase the endometrium lining is between 7-8 mm thick.



At the start of your cycle, triggered by the low estrogen and progesterone levels, your pituitary gland (located at the base of the brain) starts producing a hormone known as GnRH (gonadotropin releasing hormone). GnRH stimulates the production of FSH (Follicular stimulating hormone) and LH (Luteinizing hormone).

Follicular stimulating hormone tells the ovaries to start preparing follicles for ovulation. As the FSH stimulates the follicles, they will begin to mature the eggs inside of them. Each follicle contains an egg. As the cycle progresses, one of the follicles will become the dominant follicle and the egg contained inside that follicle will be the one released for ovulation.

As the follicles mature, they also release estrogen. When the follicle first started out, it was with low levels of estrogen, so it gradually has to build. This release of estrogen from the follicles is how the body knows when it is time to ovulate. When estrogen levels have reached high enough, this signals the ovary and tells it that the egg is mature and ready to be released.

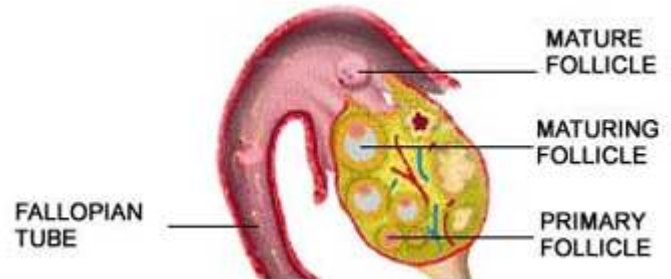
To make this happen the body also releases the hormone Luteinizing hormone. Luteinizing hormone surges at a high peak about thirty six hours prior to ovulation.

## Length of Follicular Phase and Follicle Size

The length of the follicular phase can vary, however the time it takes for follicles to mature is fourteen days. The average follicles that start to mature are between 10 to 20, so an individual will have between 10-20 eggs starting to mature on each ovary.

Each follicle will start to grow at a different rate, and retain a certain size before maturity. Follicles start out a small size in the beginning of the follicle phase, a size of 1-2 mm in diameter.

By day five the follicle has already reached 5 to 6 mm in diameter, and growing about 2 mm per day, until the follicle matures and reaches a size of between 20-26 mm in diameter.



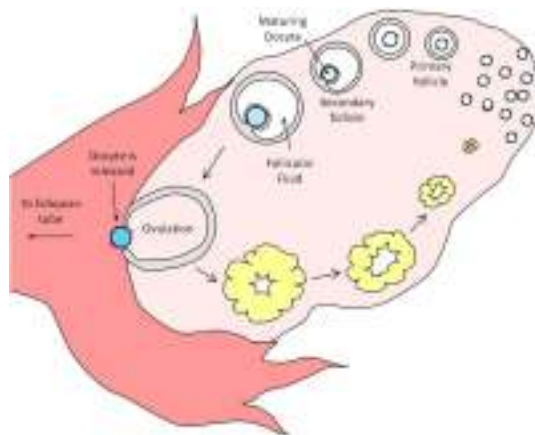
The size a follicle can be visible on an ultrasound is around 7 mm in diameter.

Around day five, increasing amounts of LH are released to help the follicles mature. As these follicles in the ovaries mature, they also begin to produce estrogen. Estrogen works to stimulate more LH production which continues the maturation process of all these follicles.

About day 8 of the follicular phase, one of these developing follicles will emerge as the dominant one, out growing all the rest. This is the “mature” follicle. There is likely a chance that more are measuring just a little smaller. However all of these will begin to shrivel and disintegrate back down. Around the twelfth day of the follicular phase, the increasing level of estrogen is also causing the lining of the endometrium to thicken as it prepares for implantation of a fertilized egg.

Now should all the follicles grow at once, they will get exhausted in one cycle and none are left for the next. The result is premature menopause.

## Ovulatory Phase (The Week of Ovulation)



*The week of ovulation the follicles swell as they mature, causing fluid filled sacs in the ovary. This can cause discomfort as the dominant follicle grows. During this week, due to the rise of estrogen from the maturing follicles, an abundant amount of fertile cervical fluid, often called as “egg white” is secreted. This is a form of discharge, and would be the most fertile time during the cycle.*

## The Graafian Follicle

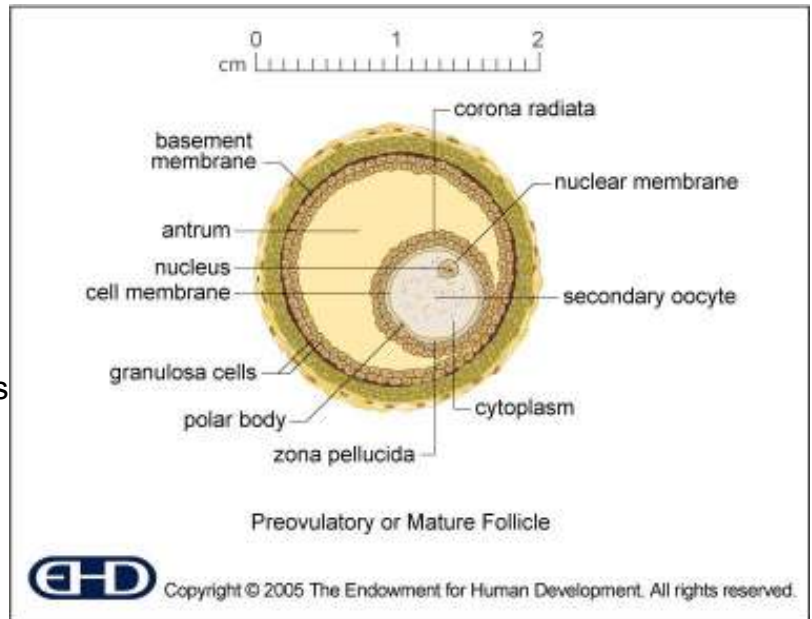
A Graafian follicle (ovarian follicle) is found inside an ovary and is basically a tiny cyst inside which an ovum develops. Women are born with many immature follicles, each containing an undeveloped ovum. Once puberty is reached and the menstruation begins, one ovum matures inside its containing follicle.

Graafian follicles start out as immature structures called primordial follicles. Follicles start out small in size during the first few days of the menstrual cycle. Then start to grow in size 1 to 2 mm per day in diameter.

There are between 10 to 20 follicles that start to mature on each ovary.

The “recruited” follicles then progress in development, as the granulosa cells multiply. The ovum (egg) will also increase in size and mature. Despite the current growth of the remaining smaller follicles, only one will mature to form the Graafian follicle while the others then start to shrink.

The fluid that fills inside the maturing follicle is called Antrum fluid. The mature ovum inside the follicle will burst out during ovulation, and antrum fluid will also release. Antrum fluid often causes irritation of the endometrium lining as it is Hyaluronic acid, causing some minor discomfort or cramping. This does not compromise conception.

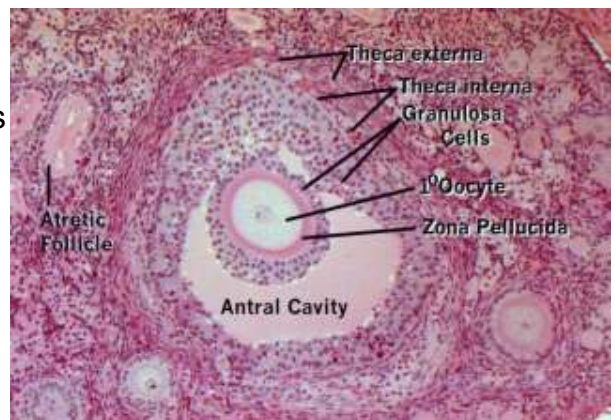


## Parts of Follicle

Zona Pellucida - surrounds the oocyte (egg) and is located between the oocyte and the follicular cells.

Corona Radiata - The first layer of the follicular (granulosa) cells outside the zona pellucida.

Antrum - The fluid filled space (liquor folliculi) of a secondary follicle. This fluid is rich in Hyaluronic acid.

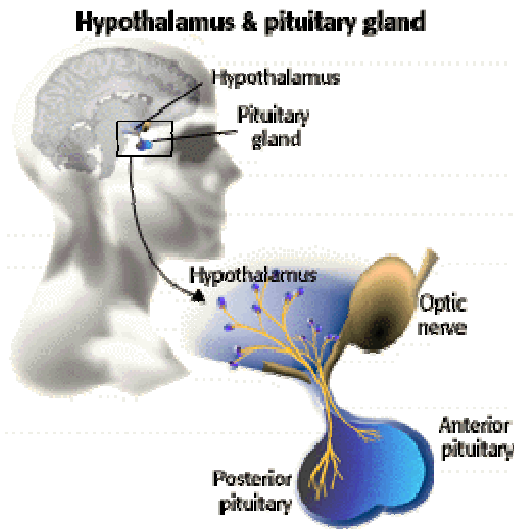


Theca Internia - These cells are endocrine-like and border the membrana granulosa. They function in the production of estrogen.

Theca Externa - Fibroblast resembling cells just outside the theca interna.

## Hormones during the Follicular Phase

Each part of the reproductive structure is controlled by the Anterior Pituitary gland. The pituitary gland is made up of two parts, the first part being the anterior which releases



hormones for the reproductive phase, and the posterior which releases two other hormones oxytocin and antidiuretic hormone. The pituitary gland is an endocrine gland, helping to regulate a wide variety of the body's functions.

Even though the pituitary is about the size of a pea in the brain, it's known as the "master gland" of the body.

The *hypothalamus* is a part of the brain that controls the autonomic nervous system and the secretions of hormones by the pituitary gland. Through these nerve and hormone channels, the hypothalamus regulates many vital biological processes, including body temperature, blood pressure, thirst, hunger, and the sleep-wake cycle.

There are six main hormones that the Anterior Pituitary gland produces, and seven main hormones the hypothalamus produces.

### The Anterior Pituitary Releases these Hormones-

- *Follicle Stimulating Hormone* - Stimulates the ovaries to produce an ovum (egg) for fertilization. Also causes an increase in oestrogen.
- *Growth Hormone* - Well known effect in children is to increase height. Controls the amount of muscle and fat in the body.
- *Luteinizing Hormone* - Triggers ovulation. (In men it stimulates cells in the testes to produce testosterone) also known as GnRH.
- *Prolactin* - Together with other hormones, prolactin stimulates the breasts to produce milk. However also found in women who aren't pregnant, and men.
- *Thyroid-Stimulating Hormone* - TSH stimulates the thyroid gland to produce its own hormone, triiodothyronine (T3) and thyroxine (T4). These hormones help to control many bodily functions including heart rate, temperature and metabolism.
- *Adrenocorticotrophic Hormone* - (ACTH) is secreted from the anterior pituitary in response to corticotrophin-releasing hormone from the hypothalamus. Corticotrophin-releasing hormone is secreted in response to many types of stress, which makes sense in view of the "stress management" functions of glucocorticoids.

## The Hypothalamus Hormones

- *Thyrotropin Releasing Hormone* - (TRH) is a tripeptide produced by the hypothalamus. Stimulates the pituitary gland and release of thyroid stimulating hormone (Thyrotropin). Thyrotropin then stimulates the thyroid gland to synthesize and release thyroid hormones.
- *Prolactin Releasing Hormone* - (PRH) is a polypeptide hormone that originates in the hypothalamus and stimulates the secretions of prolactin in the pituitary gland.
- *Prolactin Releasing-Inhibiting Hormone* - (PIH) is a hormone which inhibits the secretion of the hormone prolactin from the pituitary gland.
- *Corticotrophin Releasing Hormone* - (CRH) is secreted by the paraventricular nucleus of the hypothalamus in response to stress. (*Reduction of this protein has been observed in association with Alzheimer disease, and autosomal recessive hypothalamic corticotrophin deficiency has multiple and potentially fatal metabolic consequences including hypoglycemia and hepatitis.*)
- *Gonadotropin Releasing Hormone* (GnRH) - Is produced and secreted by specialized nerve cells in the hypothalamus of the brain. It is released into tiny blood vessels that carry this hormone from the brain to the pituitary gland where it stimulates the production of two more hormones – **follicle stimulating hormone and luteinizing hormone**.
- *Growth Hormone Releasing Hormone* - (GHRH) is the releasing hormone for the growth hormone. It first appears in the human hypothalamus between 18 and 29 weeks of gestation, and corresponds to the start of production of growth hormone and other somatotropes in the fetus.
- *Somatostatin* - (SS) (also known as growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF)) or somatotropin release-inhibiting hormone which is a peptide hormone that regulates the endocrine system.

## How the Hormones all Connect

- GnRH is released by the hypothalamus. It stimulates the release of FSH and LH (*gonadotropins are protein hormones secreted by gonadotrope cells of the anterior pituitary of vertebrates*) during the follicular phase of the menstrual cycle stimulating the release of FSH from the pituitary gland. In the ovulatory phase, it stimulates the release of LH.
- FSH hormone is produced by the Pituitary gland, and stimulates the growth follicles.
- LH which is produced by the Pituitary gland stimulates the follicle to release the egg, and the testes to release sperm. LH also stimulates the endometrium to grow and thicken.

## Estrogen and the Role of Testosterone

The estrogenic hormones are uniquely responsible for the growth and development of female sexual characteristics and reproduction in women. The term estrogen includes a group of chemically similar hormones that work together. These include estrone, estradiol (the most abundant in women of reproductive state), and estriol. Overall, estrogen is produced in the ovaries, adrenal glands and fat tissues. Estradiol and estrone forms are produced primarily in the ovaries and premenopausal women, and estriol is produced by the placenta during pregnancy.

In women, estrogen circulates in the bloodstream and binds to estrogen receptors (a group of proteins found inside cells) on cells in targeted tissues, affecting not only the breast and uterus, but also the brain, bone, heart, liver, and other tissues. Estrogen controls growth of the uterine lining during the follicular phase of the menstrual cycle, causes changes in the breasts during puberty, pregnancy, and regulates various metabolic processes including bone growth and cholesterol levels.

During the ovulatory phase of the menstrual cycle, the pituitary gland in the brain generates hormones that cause the ovum to grow and be released from the follicle each cycle. As well as the follicle develops, it produces estrogen which causes the lining of the uterus to thicken.

## **The Three Estrogens Explained**

There are three varieties of estrogen in a woman's body. The three are estrone (E1), estradiol (E2), and estriol (E3). *Estrone* is produced primarily from androstenedione originating from the gonads or the adrenal cortex. In premenopausal women, more than 50 percent of the estrone is secreted by the ovaries. Estrone is considered a weaker form of estrogenic hormone synthesized and used to treat estrogen deficiency, it's also spelled *oestrone*. Typically produced by belly fat cells, and is the major estrogenic form found in naturally menopausal women.

*Estriol* is one of the three major naturally occurring estrogens, the others being estradiol and estrone. Estriol is produced almost exclusively during pregnancy and is the major estrogen produced in the normal human fetus. During pregnancy the production of estriol depends on an intact maternal-placental-fetal unit. Fetal-placental production of estriol leads to a progressive rise in maternal circulating levels reaching a late-gestational peak several orders of magnitude greater than non-pregnant levels.

*Estradiol* is the predominant sex hormone present in women. It is also present in males and at a higher level because it is being constantly produced. However in women it is only produced about 3 of 30 days of the menstrual cycle. Estradiol has not only a critical impact on reproductive and sexual function, but also affects other organs including the bones. Estradiol is derived from cholesterol. A fraction of the androstenedione is converted to testosterone. During the reproductive years, most estradiol in women is produced by the granulosa cells of the ovaries by the aromatization of androstenedione (produced in the theca folliculi cells) to estrone, followed by conversion of estrone to estradiol by 17 $\beta$ -hydroxysteroid dehydrogenase. Smaller amounts of estradiol in women is produced by the adrenal cortex, and (in men) by the testes.

Now that we know the different roles of the three main estrogen hormones, we must look at how they connect. Granulosa cells are the first to respond to rising follicle stimulating hormone levels during the first few days of the follicular phase. Follicles secrete androstenedione, which is converted into estradiol (E2). Enhanced E2 production stimulates granulosa cell development through inhibin, which results in a drop of the FSH production, preventing the additional development of follicles. Although inhibin is a marker used to evaluate follicle reserve, FSH is responsible for inducing granulosa cells to develop and increase the production of E2.

## Testosterone

Traditionally, testosterone is known as the male hormone, it is better known as the sex hormone. In women, testosterone peaks during the follicular phase before ovulation causing a surge in “sexual desire”. Testosterone builds on the femininity of estrogen to inspire and drives libido. The combination of testosterone with estrogen allows a woman to feel her most attractive, responding and initiating sex.

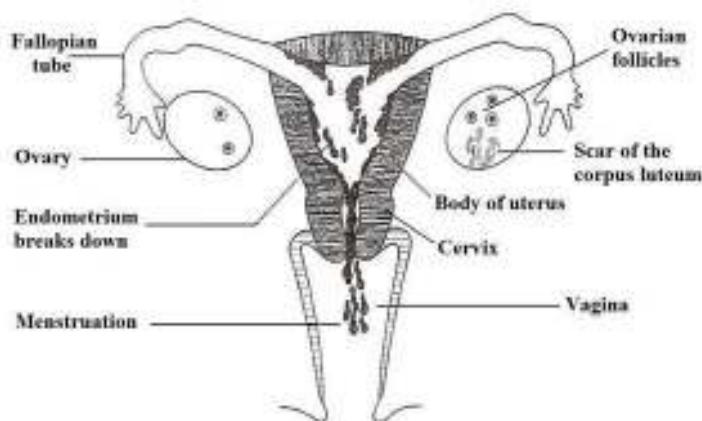
Testosterone in women is produced by the adrenal glands and ovaries. The adrenal glands lie above the kidneys and produce several different hormones. The inner core of the adrenal glands produces stress hormones, while the outer layer produces androgens, which is the family of “male” steroids that includes testosterone. Therefore the adrenal glands are a source of testosterone for both women and men. Testosterone is classified as a steroid hormone because it is released to all cells.

The ovaries make testosterone, but most of it is immediately converted to estrogen. So in women the adrenal glands are the primary source for testosterone. Women who have too much adrenal-derived testosterone suffer from irregular menstrual cycles, shrinkage of the breasts, acne, excess thick hair on the face or other parts of the body, and typical male muscle development. After menopause, when the ovaries sharply reduce estrogen production, conversion of adrenal-derived testosterone to estrogen becomes an important source of female hormone.

## Endometrium Lining During the Follicular Phase

Day one of the menstrual cycle is the shedding of the endometrial lining. This is where the follicular phase begins, and a new endometrial lining will start to form.

Right around when the menstrual bleeding stops, the endometrium lining should be about 3 mm thick. During this time, the two hormones in the beginning of the follicular phase are oestrogen and progesterone, and since the levels are low, this allows FSH (Follicle Stimulating Hormone) from the pituitary gland to stimulate a few follicles in the ovary and grow. Estrogen from the growing follicles stimulates proliferation of the endometrium. Estrogen also stimulates the cells in the cervix to secrete fertile cervical mucus approaching the ovulatory phase.



As the estrogen continues to be produced by the developing follicles, the endometrium lining will continue to thicken. In the ovary, one of the developing follicles then becomes dominant and continues to grow turning into a Graafian follicle (mature follicle), and the other developing follicles become atretic. The rising blood estrogen level produced by the Graafian follicle then stimulates further growth of the endometrium. Normally the thickness reaches from 6 to 13 mm by the time of ovulation. If the lining is thicker than 15 mm, the embryo may have trouble implanting.

## Four Main Causes for too Thin of Lining

Perimenopause and Menopause - The endometrium is reliant on adequate levels of estrogen during the follicular phase. In fact, women who have amenorrhea often have thin uterine lining due to low estrogen levels. The most common cause of low estrogen is perimenopause and menopause. This is where normal hormone levels begin to decline as a woman ages.

Inadequate blood flow - There are a variety of reasons blood flow to the uterus may be compromised. If the uterus is not receiving adequate blood flow (as estrogen travels through the blood), it may not be able to create a thick enough endometrium lining each cycle.

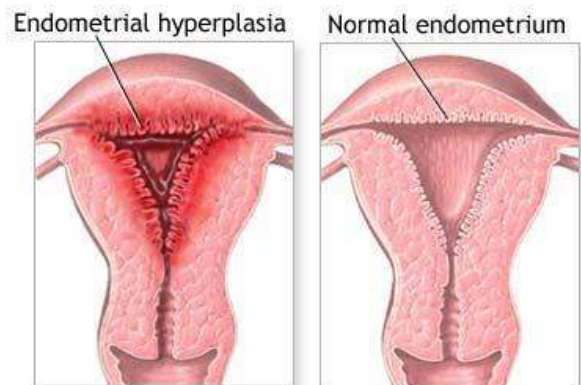
Poor health of the endometrium lining - This could be caused from damage of infection, surgery (such as scar tissue), illness may even cause damage to the tissues of the endometrium. This damage can also compromise blood flow, and possibly how the endometrium functions.

Long term use of birth control contraceptives - Some long term use of birth control contraceptives may also cause too thin of lining. Some contraceptives containing higher amounts of Progestin (progesterone) have been linked to thinning the uterine lining. The longer the use, the increased change for weak/thin lining.

## Factors for Thickened Uterine Lining

While it is normal for the endometrium to thicken during the follicular phase, abnormal thickening of the uterine lining is a medical condition called endometrial hyperplasia.

Since estrogen is responsible for building the uterine lining, the maintenance and control of this growth is carried out in the presence of progesterone (produced during the second half of menstrual cycle). An overgrowth of uterine lining occurs when there is too much estrogen and too little progesterone causing thickening of the endometrium.



ADAM.

Some causes include:

- Diabetes
- Estrogen hormone therapy without progesterone
- Polycystic Ovarian Syndrome
- Obesity
- Anovulation
- Abnormally short menstrual cycle



## CERTIFIED FERTILITY COUNSELOR COURSE - SESSION 2 – QUESTION & ANSWERS

NAME: \_\_\_\_\_

ADDRESS: \_\_\_\_\_

PHONE: \_\_\_\_\_

FAX: \_\_\_\_\_

E-MAIL: \_\_\_\_\_

Please be sure to fill out the information above, complete the test and e-mail it back to us at [myeggandme@amandabears.com](mailto:myeggandme@amandabears.com). We will grade your question & answer session and will let you know if we have any questions or concerns.

1. What's another name for follicular phase?
2. What is the size of the follicle around day five, and at what rate does it continue to grow?
3. Around what day does the dominant follicle develop?
4. What hormone helps the follicles mature, and what hormone does the follicle produce?
5. What are immature follicles called? What are mature follicles called?
6. What happens to the follicles that do not develop into a mature follicle?
7. What is the fluid called inside the mature follicle, and what does it contain?
8. What are the five parts of a follicle?
9. What is the anterior pituitary gland, and what does it control?
10. Name and define the hormones produced by the anterior pituitary gland.
11. What is the hypothalamus?
12. What hormones are controlled by the hypothalamus?
13. What is the role of GnRH?
14. Explain how the anterior pituitary hormones all connect?
15. Name all three main estrogens.
16. Which estrogen is weaker, and where is it found?
17. Explain how estradiol connects to the reproductive system.
18. How is testosterone produced in both men and women?
19. How does the endometrium lining thicken, and what is the normal thickness?
20. What can cause too thin of endometrium lining?
21. What can cause too thick of endometrium lining?
22. What are the causes of thick endometrial lining?