The Menstrual Cycle

A normal menstrual cycle is a result of the hormonal pathway from the hypothalamus to the pituitary to the ovary to the uterus. Each organ secretes specific hormone(s) that affect the next organ in the pathway. This pathway is called the hypothalamic-pituitary-gonadal axis.

The menstrual cycle is typically 28 days long and divided up into 3 phases. The 3 phases are known as the following:

1. Follicular Phase – Days 1-13
2. Ovulation – Day 14
3. Luteal Phase – Days 15-28

The follicular phase is the first half of the cycle and throughout this phase oocytes (eggs) grow on the ovaries. The length of this phase can vary depending on the total length of the cycle. For example: a normal 28 day cycle will have a 14 day follicular phase whereas a 32 day cycle will have an 18 day follicular phase. This phase is also called the proliferative (to grow) phase because throughout this phase the uterine lining begins to grow.

The ovulation phase occurs in the middle of the cycle and at this point a mature egg will ovulate (be released) from a follicle. This usually occurs around cycle day 14 in a normal 28 day menstrual cycle.

The Luteal phase is the second half of the cycle and it’s during this phase that an embryo may or may not implant onto the uterine wall. If embryo implantation occurs, a pregnancy will begin. If an embryo doesn’t implant, hormone levels will drop and a new cycle will begin. The Luteal phase is also known as the secretory
phase because progesterone is produced, which stimulates the development of the glands and arteries of the endometrium, causing it to become thick and spongy.

The follicular phase of a new menstrual cycle (1st day of menses) will begin as a result of both progesterone and estrogen significantly dropping in the bloodstream. This drop in hormone levels will occur in the late luteal phase if embryo implantation does not occur. The drop in progesterone and estrogen causes the uterine lining to slough and menses begins, marking the beginning of a new cycle. The low levels of both estrogen and progesterone in the blood will also send positive feedback to the hypothalamus in the brain to release a hormone called GnRH (gonadotropin releasing hormone). GnRH is secreted by the hypothalamus and travels to its own receptor (hormone docking station) found on the pituitary gland. The pituitary gland is also located in the brain. When GnRH binds to its own receptor on the pituitary, the pituitary gland will begin to secrete both FSH (follicle stimulating hormone) and LH (luteinizing hormone). Both FSH and LH secreted by the pituitary gland which travels to its own receptors found on the ovaries. The FSH and LH receptors are specifically found on the surface of egg containing follicles. When FSH and LH begin binding to its own receptors, the follicles begin to grow and the eggs within begin to mature. As the follicles grow throughout Follicular phase they primarily release the hormone estrogen. The estrogen produced by the ovaries acts on the uterus to begin uterine lining growth. The uterine lining is growing during the follicular phase (proliferative phase) in preparation for embryo implantation.

Each follicle found on the ovary contains an egg and is shaped like a sphere. On the surface of the follicle you will find two types of cells known as the granulosa cells and the theca cells. In the beginning of the the follicular phase, the granulosa cells contain only FSH receptors, whereas the theca cells contain only LH receptors. The
egg within the follicle has a nucleus known as the germinal vesicle. The germinal vesicle holds the chromosomal make up of the egg. The egg is also surrounded by a thin hard shell known as the zona pellucida.

Throughout the early part of the Follicular phase (cycle days 1-6), the ovaries will start growing many follicles. During the middle of the follicular phase (cycle day 7), one follicle will begin to grow larger than the rest of the follicles found on the ovaries. This naturally selected larger follicle is known as the Graafian follicle or the dominant follicle. Once this dominant follicle reaches 19-22 millimeters in diameter, the egg within will be mature and the ovulation phase will be begin.

When ovulation occurs (cycle day 14) the dominant follicle will rupture and the mature egg will be released. The ruptured follicle on the ovary will no longer contain an egg at this point but will immediately develop into a short-lived endocrine (hormone) organ called the corpus luteum. The formation of the corpus luteum marks the beginning of the luteal phase (cycle days 15-28) and plays a key role in producing both progesterone and estrogen. Progesterone maintains the endometrium (lining of the uterus) and is necessary for embryo implantation and pregnancy.

The egg will be swooped into the fallopian tube by the fimbria (fingerlike tentacles at the end of fallopian tube). This begins the eggs journey through the fallopian tube into uterus. Given sexual intercourse was performed at the optimal time; sperm will start penetrating the outer shell of the egg 12-24 hours post ovulation. Once the egg reaches the mid-fallopian tube area, a single sperm will have completely penetrated the outer shell of the egg and fertilization (DNA duplication) will have occurred. Thirty hours post ovulation the newly fertilized egg will become a zygote (two cell embryo). Three days post ovulation the embryo will have grown to be an eight cell embryo. Four to five days post ovulation the embryo will be have developed into a blastocyst (embryo comprised of 70-100 cells). On day five or six post ovulation (cycle day 20 &21) the blactosycst may or may not
implant onto the uterine wall. If embryo implantation does occur, the embryo itself will begin releasing a hormone called HCG (human chorionic gonadotropin).

HCG in the bloodstream will trigger the corpus luteum to stay functioning until the placenta is able to sustain the pregnancy on its own. The corpus luteum produces both progesterone and estrogen therefore these hormones stay constant in the bloodstream, resulting in a missed period. Remember it’s the significant drop in progesterone and estrogen in the blood that triggers the uterine lining to shed and the start of a new cycle. If embryo implantation does not occur, HCG will never be produced and eventually the corpus luteum will die off, leading to a drop in progesterone and estrogen and the start of a new cycle.

Side Notes:

It’s interesting to point out at that this point that this how a birth control pill works. We have all heard that birth control pills trick the body into thinking it’s pregnant. To further explain this, all birth control pills are made up of both estrogen and progesterone and women are instructed to take them every day at the same time to avoid pregnancy. When women take the pill every day, they maintain constant levels of progesterone and estrogen in the body, which leads to suppression of GnRH at a hypothalamus level. GnRH suppression results in FSH & LH suppression which leads to follicular growth suppression. When women discontinue their pills each month the estrogen and progesterone drop in the bloodstream and menses begins.

It’s also interesting to point out that when women use an at home pregnancy tests, the test is trying detect the hormone HCG. If HCG is detected in the urine, this means an embryo has implanted on the uterine wall and a pregnancy has occurred.
Menstrual Cycle Hormones

GnRH is basically ten amino acids contacted together, better known as a decapeptide. The hormones native elimination half life is only 2 to 4 minutes. In a medical context, half life is defined as the time it takes the blood plasma concentration of a substance to halve its steady state. GnRH (gonadotropin releasing hormone) is produced in the hypothalamus and binds to own receptor found on the pituitary gland. Because GnRH has such an ultra short half life, the hypothalamus continuously pumps out the hormone to maintain sufficient levels in the blood. The frequency and the quantity of GnRH that is pumped out of the hypothalamus vary widely depending on what phase (follicular, ovulation, luteal) the menstrual cycle is in. If GnRH is not pumping out of the hypothalamus just right, the pituitary will not function correctly, which may lead to ovulation problems.

The frequency and quantity at which GnRH pumps out of the hypothalamus is regulated by the blood levels of estrogen, progesterone, FSH, LH, and GnRH itself.

Side Note: Understanding the elimination half lives of these native hormones is critical to understanding how the fertility drugs work in the body and why doctors prescribe what they do.

LH’s native elimination half life is approximately 30 minutes, whereas FSH’s half life is about 3 hours.

Follicular phase FSH levels vary during a natural menstrual cycle. Increased estrogen levels throughout the cycle exert negative feedback of FSH production. It’s theorized that FSH levels vary in a menstrual cycle in an effort to naturally select out the strongest of follicle for ovulation. The strongest follicle would be defined as having the most FSH receptors.
During the ovulation phase FSH will surge to twice its baseline concentration. FSH is low during the luteal phase but then begins to slowly rise just before the start of menses.

LH levels remain low during the follicular phase but play an important role in producing the hormone estrogen. LH begins to surge 34-36 hours before ovulation and reaches its peak 10-12 hours before ovulation. The peak LH level will reach 3 times its baseline value established in the follicular phase. The LH surge last in between 1-3 days in length. LH levels are low during the luteal phase but then begin to slowly rise just before the start of menses.
How FSH and LH Work at an Ovarian Level

Follicular Phase

LH is produced by the pituitary gland and travels to own receptor (hormone docking station) found on the ovary. To be more specific LH binds to its own receptors found on the theca cells. Remember theca cells are found all over the surface of the egg containing follicles. In response to LH, theca cells produce androgens.

FSH is produced by the pituitary gland and travels to own receptor found on the ovary. To be more specific FSH binds to its own receptors found on the granulosa cells. Remember granulosa cells are also found on the surface of the egg containing follicles. When FSH binds to its own receptor, an enzyme is produced called aromatase. The presence of aromatase in the blood will convert androgens into estrogens. As LH rises in the late follicular phase, androgen production increases which leads to an increase in estrogen production. This cellular mechanism to produce estrogen is referred to as the two cell theory in the study of reproductive endocrinology.

Estrogens work to help grow the uterine lining in preparation of embryo implantation.

Approaching Ovulation

When estrogen levels start to plateau, it will trigger the beginning of the LH surge.

Throughout the follicular phase LH receptors are only found on the theca cells. As the menstrual cycle approaches ovulation, FSH and estrogen production induce the appearance of LH receptors on the granulosa cells. Now when LH binds to its own receptor on the granulosa cells, cholesterol will be converted directly into progesterone. This is called luteinization of the granulosa cells. This preovulatory rise in progesterone enhances
the activity of proteolytic (to aid in the breakdown) enzymes that are responsible for follicular rupture (ovulation).

To avoid any confusion at this point, it should be mentioned that progesterone production occurs at two different times during the menstrual cycle.

1. Preovulatory rise in progesterone occurs when luteinization of the granulosa cells occurs in the late follicular phase.

2. Post ovulation triggers the formation of the corpus luteum (ruptured follicle on ovary), which is mainly responsible for producing progesterone and estrogen in the luteal phase. The progesterone being produced post ovulation is responsible for creating a sticking uterine environment for embryo implantation.

Estrogen is a key hormone in the menstrual cycle that affects many different organs. During the follicular phase growing follicles produce estrogen. Estrogen’s main role in the follicular phase is to help grow the uterine lining in preparation for embryo implantation.

Estrogen levels in the first half of follicular phase are low, generally less than 50 pg/ml. About 7 days prior ovulation, the estrogen levels start rising rapidly, reaching peak levels of 200 to 300 pg/ml. The rise in estrogen levels correlates directly with follicular growth.

During the luteal phase a second rise in estrogen occurs, reaching its peak in the midpoint of luteal phase. This rise reflects estrogen secretion by the corpus luteum. Estrogen’s role at this point in the cycle is to aid in
sustaining a pregnancy if embryo implantation occurs. Estrogen levels will fall back to baseline if a pregnancy does not occur.

Throughout the follicular phase serum concentrations of progesterone are very low. At the time of the LH surge progesterone concentrations start to rise. This rise occurs over the next 4 to 5 days and reaches its peak approximately 7 days after ovulation. Progesterone levels of 10 pg/ml indicate good corpus luteum function. Progesterone levels will fall back to baseline in the late luteal phase if a pregnancy does not occur.

Adequate progesterone production is necessary in the luteal phase to establish embryo implantation and sustain pregnancy. Progesterone also acts within the ovary to suppress new follicular growth in the luteal phase. High progesterone levels inhibit GnRH production at a hypothalamic level, which leads to pituitary suppression of both FSH and LH.
Luteal Phase

The corpus luteum (ruptured follicle on ovary) will only survive for 13 to 14 days if a pregnancy doesn’t occur. Remember that the survival of the corpus luteum depends on embryo implantation and the production of HCG (human chorionic gonadotropin). If the corpus luteum dies, estrogen and progesterone will significantly drop in the bloodstream and new cycle will begin.

On the other hand if embryo implantation does occur, the embryonic cells themselves will produce the hormone HCG, which signals the corpus luteum to stay alive. The corpus luteum will continue producing progesterone and estrogen to sustain the pregnancy until the placenta is fully established (about 10-12 weeks).