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Chapter 2

Normal Menstrual Cycle

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Additional information is available at the end of the chapter

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Abstract

Normal menstrual cycle represents a coordinated serial event, repeated month by month, at regular intervals, in which the hypothalamus participates along with the secretion of GnRH, the pituitary gland secreting follicle stimulating hormone and luteinizing hormone (LH), and the ovary which responds to those hormones, recruiting a dominant follicle and secreting estradiol and inhibin A. Estradiol stimulates endometrial proliferation and production of cervix mucus. A peak of estradiol triggers discharge of LH, responsible for ovulation and posterior secretion of progesterone by the corpus luteum, which in turn, involutionates 14 days later if it does not receive the stimulation of hCG (pregnancy). Normal menstrual cycles last 28 ± 7 days, being accepted a fluctuation of ±2 days in the same woman, as a normal pattern, what is described as a regular cycle. Normality of these events would allow to achieve a successful embrionary implantation in the case of looking for pregnancy. For this it is required that an adequate ovule to be fertilized is reached by a capacitated spermatozoon, during the ovulatory stage. Spermatozoon can survive as long as 5 days at feminine genital tractum, but the ovum is possible to be fecundated only during 12–24 hours. Fecundation occurs at the distal third of the fallopian tube and the fecundated zygote arrives in the state of a morula, to be implanted at the endometrium 4 days later. Once the state of blastocyst is reached, it is detached from its shaggy area (hatching) and it is implanted in a receptive endometrium when the window of implantation is open (days 7–9) postovulation. The first marker of pregnancy is the detection in maternal blood of β-hCG. No more than the 25% of fertile couples exposed to pregnancy can achieve gestation at the month of exposure.

Keywords: menstrual cycle, fertility, concepcional cycle

1. Definition of normality

Menstrual cycle lasts 28 ± 7 days. Just a third of patients have cycles every 28 days and 82% fluctuations among 22 and 32 days [1].

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A cycle is known as regular when the frequency has a variation of no more than 2 days. The lasting of each cycle is calculated since the first day of menstruation until the previous day of next menstruation. The cycle frequency is regulated by the hypothalamus-pituitary-gonadal axis; hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) must reach their effectors at the ovarian level where a dominant follicle must be recruited and developed, secrete estradiol, in enough amounts to obtain endometrial receptivity but also participating directly in a feedback-regulated control of the cycle.

Cycles show more irregularity in the extremes of the reproductive lifespan, during the first 2 years from the menarche and during the perimenopausal transition. The ovarian cycle has two stages separated by ovulation, the first, from the beginning of the cycle to ovulation, is called the follicular or proliferative phase. The second, between ovulation and the next menstruation, is called the luteal phase or secretory phase.

The follicular phase is characterized by the maturation of the follicle containing an ovule and a retinue of follicular cells, which are responsible for transforming androstenedione into estradiol, which in turn is released and, among many other actions, stimulates endometrial renewal.

The luteal phase, named because the follicular cavity that left the ovule after hatching, is transformed into a corpus luteum and continues to produce estrogen, but it also releases important amounts of progesterone. The luteal phase is preceded by a significant increase in LH, and ovulation marks its onset; then, it lasts ±14 fairly constant days when comparing different women. During this phase, the average total body temperature of women is constantly 0.5°C higher than in the follicular phase.

If there is no embryo implantation, the endometrium is detached giving rise to menstrual flow, which has normal volume parameters, up to 80 mL, in duration, 3–8 days, content, absence of clots and symptoms, and absence of pain.

It is considered that the conserved cyclicity expresses that the hypothalamic-pituitary-gonadal axis is healthy. The ovaries do not alternate to ovulate.

2. Important concepts

Ovarian reserve: *it corresponds to the number of follicles that a woman has and it is defined during fetal life and then the number of follicles goes slowing down gradually.*

When is born, each woman counts with a fixed number of ova, which are getting lost with the past of years (atresia) Delaying maternity is nonrecommendable, since at higher age the risk of not having ovum of a good quality at the moment when a pregnancy is planned.

In a woman fertility, among 38–40 years is lower than at 25–30 years. Atresia of oocytes is a continuous process that never stops not even with the use of anovulatory or pregnancy.

Oocyte atresia: *it is the mechanism of follicular apoptosis that seems to contribute to the selection of optimal ovules.* During the early fetal stage, about 7,000,000 oocytes are formed in the ovary.

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Before birth, the ovular reserve has been reduced to one-third by mechanisms of apoptosis (programmed death).

At birth, only 1–2 million oocytes remain in the ovary and during puberty, there are usually 300,000 available for eventual ovulation. In fact, they will only ovulate between 400 and 500 throughout the lifespan. Then, through the female reproductive life, between the periods of puberty and menopause, about 250,000 follicles will be destined to die, reaching less than 1000 during perimenopause (**Figure 1**).

Sex steroids—estrogens and progesterone: Estrogens are steroid hormones produced by the granulosa follicle, the corpus luteum, and the placenta (if there is pregnancy). Its synthesis comes from cholesterol molecules. Progesterone is synthetized by corpus luteum and placenta, if there is pregnancy.

Of the estrogens, the most potent is estradiol. The actions they develop are:

- *Female genital apparatus*: they stimulate the growth and development of the female sexual organs and the proliferation of the endometrium during the sexual cycle.
- *Breast*: they favor the growth of the mammary ducts and are, in part, responsible for the development of the mammary gland during puberty.
- *Bone*: they regulate the osteoclastic activity and stimulate the osteoblastic activity, in such a way that they are essential to maintain adequate bone mineralization.

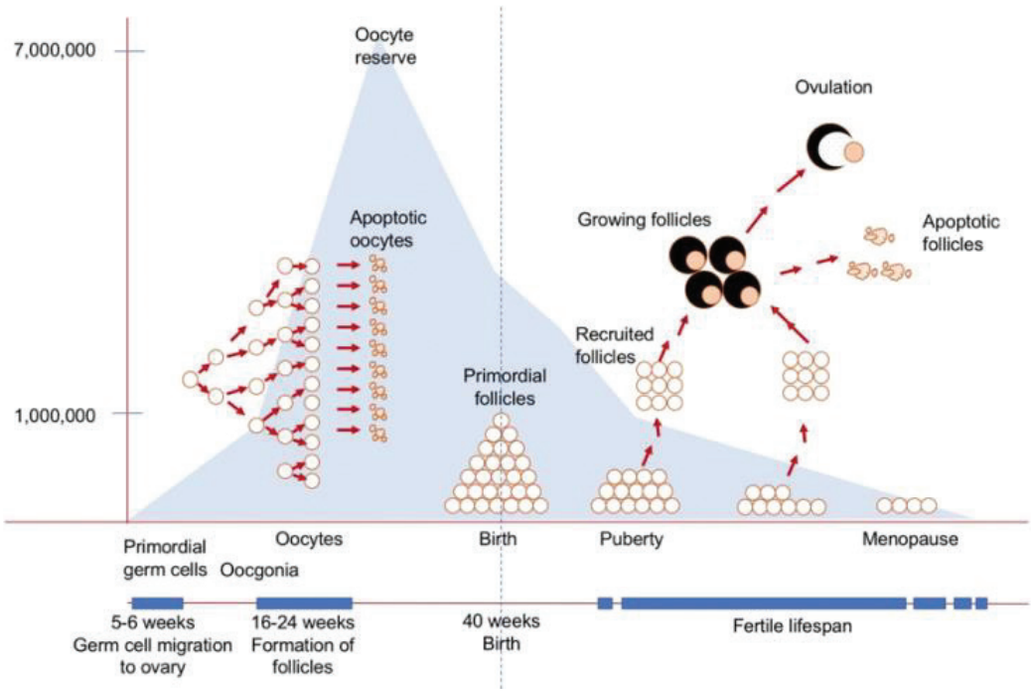


Figure 1. The number of oocytes in any woman comes defined at the moment of birth and slow down inevitably during her life during her life from 1 to 2 million at the moment of birth at 300,000 to go decreasing through her life 25,000 at 37–38 years and near 500 during the postmenopause.

- *Cardiometabolic*: estrogen relaxes the smooth muscle of arterioles, increases HDL cholesterol, and lowers LDL cholesterol, which has been associated with the lower incidence of cardiovascular disease that women have in relation to men, especially before menopause.

Progesterone is also a steroid hormone. It is responsible for the progestational changes of the endometrium. On the breasts, progesterone stimulates the development of the lobes, being its action complementary to that of the estrogens. Progesterone is thermogenic and contributes to the increase in basal temperature experienced by some women after ovulation.

3. Follicular phase

Follicular phase begins the very first day of menstruation. The development of ovarian follicles, named folliculogenesis, begins at the last days of menstrual cycle before the release of mature follicle during ovulation (**Figure 2**).

When a pregnancy did not occur, the release of inhibin A and sex steroids are reduced by the end of the functional period of the corpus luteum. Both falls contribute to reduce the release of FSH by feedback at the central level, which is dependent on pulsatility of hypothalamic GnRH. This is how FSH increases during the last days of the menstrual cycle (**Figures 3** and **4**) [2].

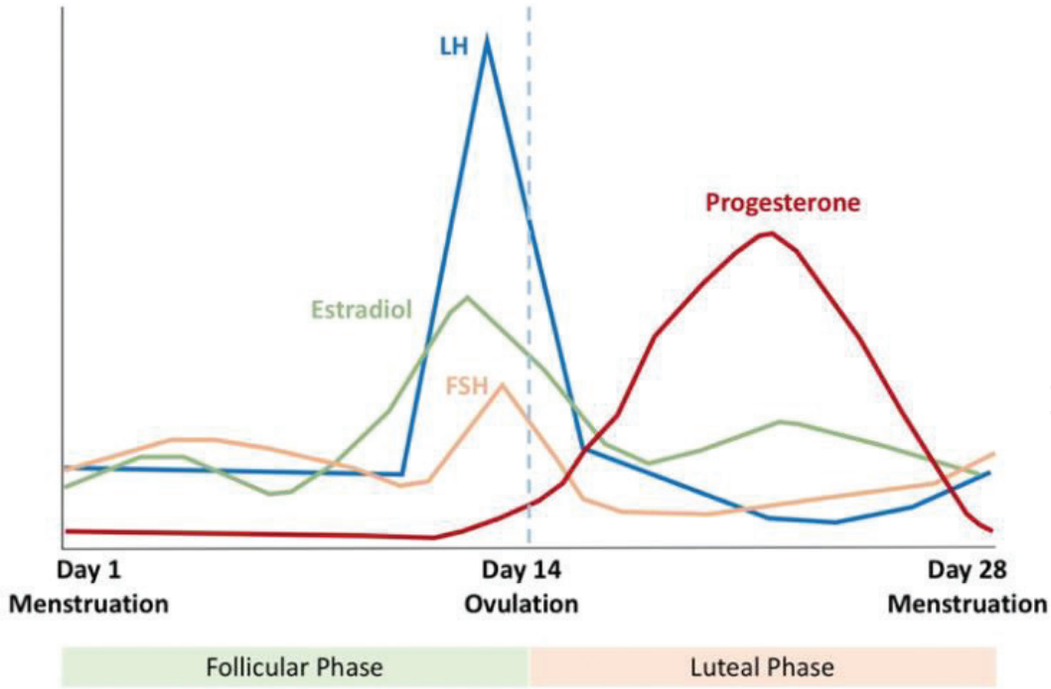


Figure 2. The menstrual cycle has two phases, follicular phase and luteal phase. The follicular phase begins with menstruation. The follicle stimulating hormone (FSH) increases released by the anterior pituitary gland and stimulates follicular growth and estradiol production. The 17 beta-estradiol produced by the follicles exerts negative feedback on the FSH. Estradiol continues to increase due to the growth of the dominant follicle. The LH increases sharply to trigger ovulation. Immediately after ovulation, the luteal phase begins. The corpus luteum produces progesterone and 17 beta-estradiol concentrations of progesterone and estradiol decrease, menstruation begins a new cycle, unless a pregnancy has been established.

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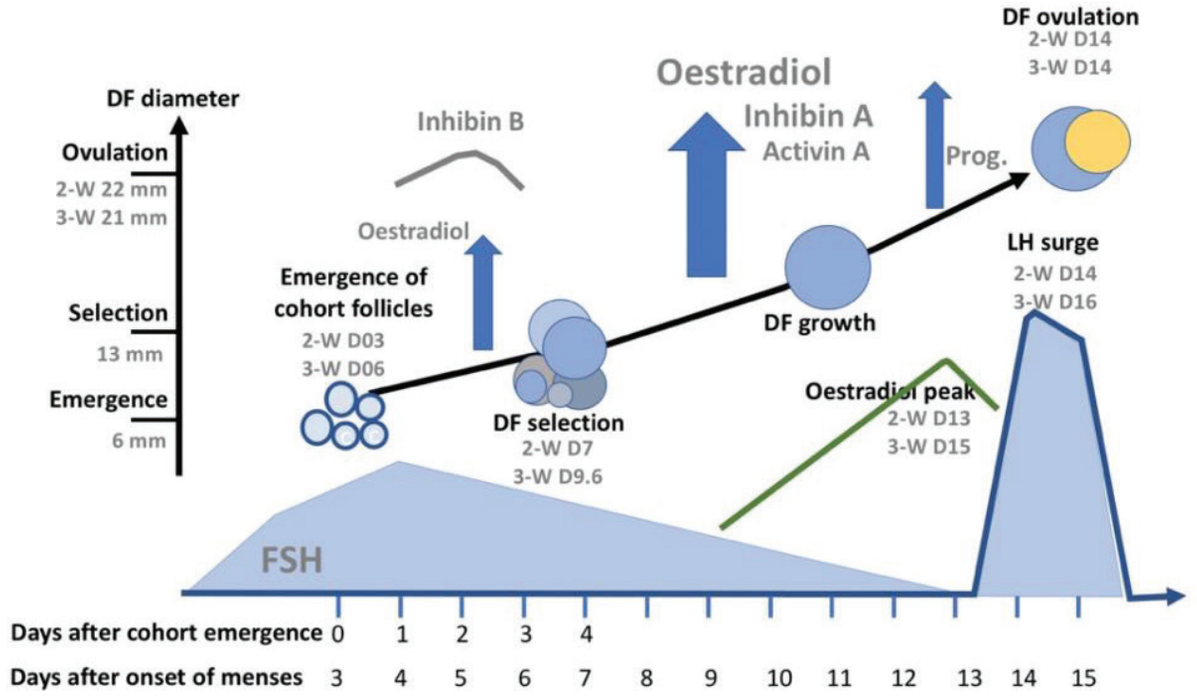


Figure 3. Dynamic scheme of follicular activity and the changes in gonadotropins, steroids, and inhibins during follicular phase of menstrual cycle.

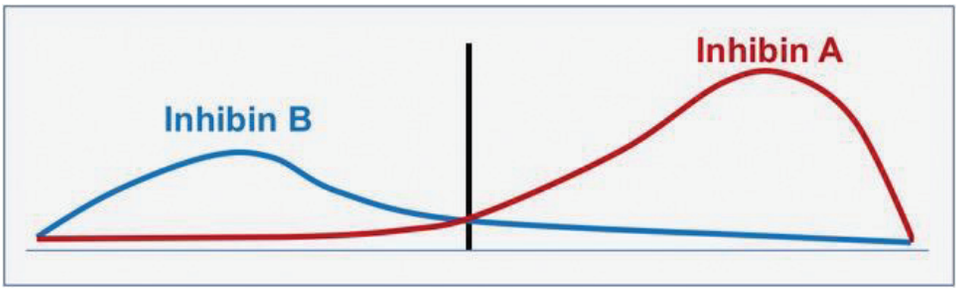


Figure 4. The level of inhibin changes through menstrual cycle. Inhibin B dominates follicular phase during the cycle while inhibin A dominates luteal phase.

The progressive elevation of FSH allows many follicles to be recruited simultaneously. Nevertheless, only some persist, in such a way that an approximate 99% of the cycles, only a dominant follicle will be destined to ovulate, during the next menstrual cycle.

The remaining 1% has codominance, that is two dominant follicles, which eventually can generate a double ovulation at the risk of a multiple pregnancy.

In women from 19 to 42 years, follicular phase has an average duration of 14.6 days, however, to be precise on each woman in what step of the cycle she is very difficult because of the following reasons:

- Duration of menstrual cycle is very changing, even among young women of similar ages, with variations described from 25 to 34 days.

- Changes that normally occur during the fertile lifespan, between the menarche to menopause. Some women may have long and irregular cycles, many times associated to abundant uterine bleeding, at the first 2 years after to menarche and 4–6 years that precede menopause.
- Besides there is a wide range of presentation for both phases of the cycle, the follicular phase may last from 10 to 23 days and luteal phases could last between 7 and 19 days. Only 10% of women with a cycle of 28 days shows follicular and luteal phase of 14 days. The variability depends more on follicular phase, which vary ±3–7 days with time, depending on the estrogen take off (ETO), at the beginning of the middle follicular phase on each cycle, which is the main explanation for the duration of cycles.
- Finally, despite of normal length in their cycles, 7% of women of 25–39 years may show anovulation, even though is more frequent to observe shorter cycles or longer ones, especially in early postmenarche and premenopause (60% between 10 and 14 years and 34% older than 50 years) as seen in **Figure 5**.
- Other environmental, ethnic, or even socioeconomic factors may affect the duration of the cycle and bleeding.

At the development of dominant follicle (DF), three steps have been described namely, **recruiting, selection,** and **dominance** (**Figure 6**). Recruiting stage is developed during the days 1–4 of menstrual cycle.

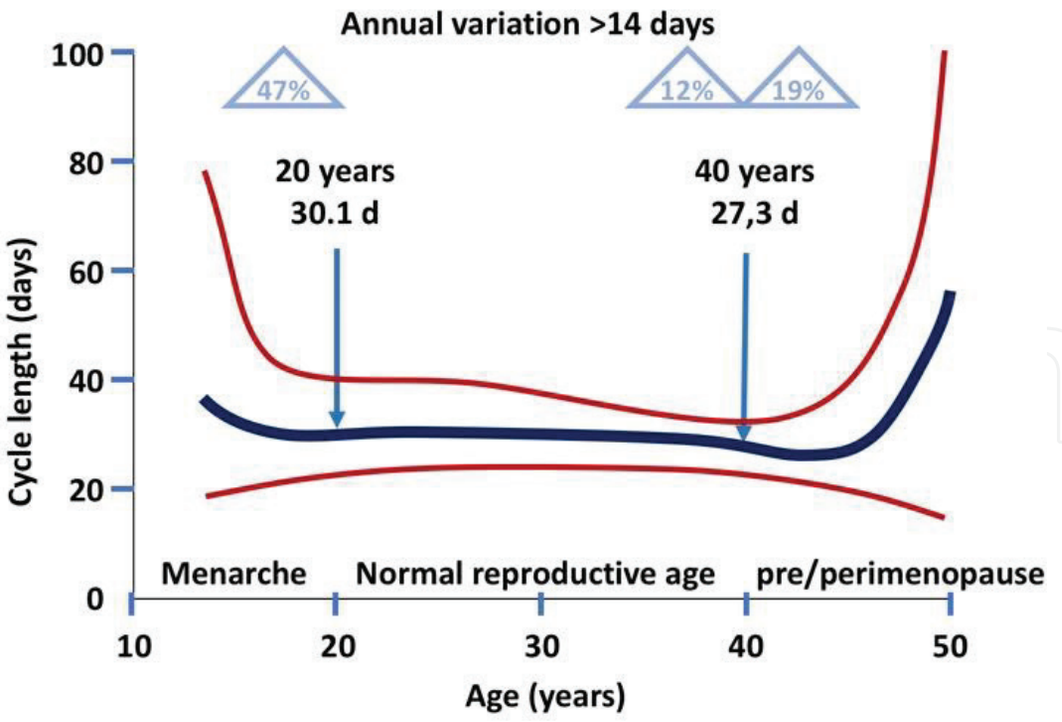


Figure 5. Menstrual cycle lasting variation according to age. Graphic shows the average lasting of the cycle and the range (percentiles 95 and 5) yrs. = years, d = days. Triangles indicate the group of age in the percentage of women with more than14 days of variation of a cycle during a year. From Mihm et al. [3].

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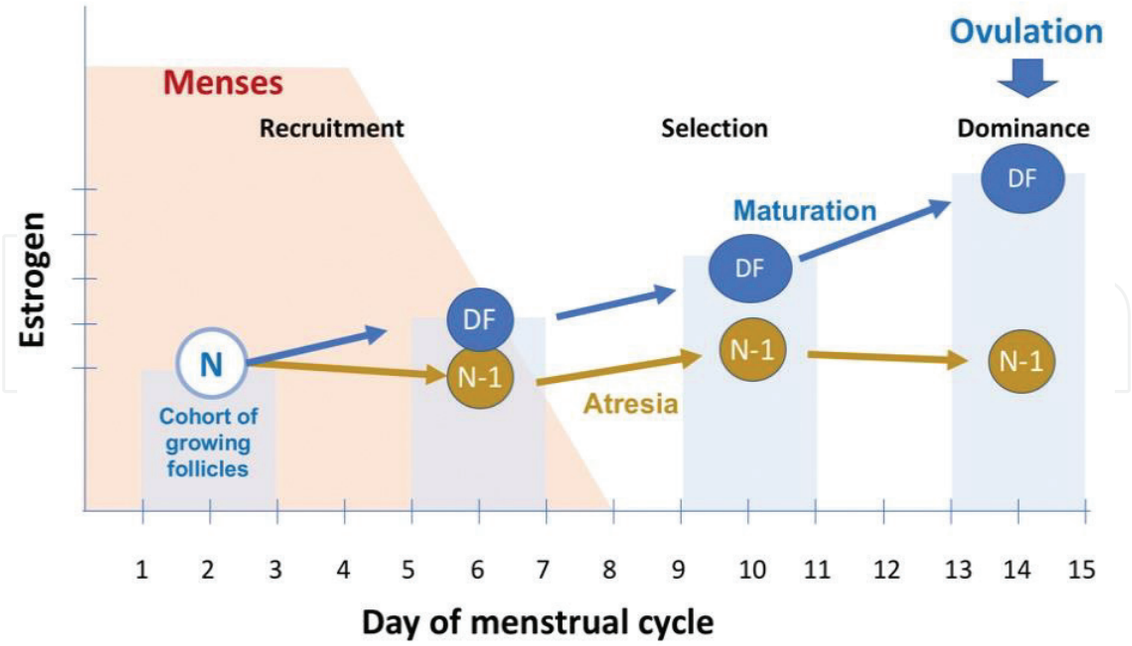


Figure 6. Time lapse of recruiting, selection, and ovulation of dominant follicle (DF) with the beginning of atresia in the other follicles of the group. Adapted from Hodgen [4].

During the follicular phase, FSH is responsible for recruitment among those follicles that remain available. Between days 5 and 7 of the cycle, follicular selection normally occurs, to allow only one follicle, the dominant follicle (FD) to ovulate and the rest to experience atresia. Anti-müllerian hormone (AMH), which is secreted in the granular layer, also participates in the selection of FD. On day 8 of the cycle, the FD promotes its own growth, suppressing the maturation of the other ovarian follicles.

During the follicular phase, estradiol plasma levels are higher along with the growth of the number of granulosa cells and the growth of the DF. FSH receptors are found exclusively in the cell membrane of granulosa cells. The increase in FSH during the late luteal phase induces its own FSH receptors and eventually increases the secretion of estradiol by the granulosa cells by transforming androstenedione, which diffuses from the theca cells (**Figure 7**).

It is important to point out that the increase in the numbers of receptors of FSH is due to an increase in the population of granulosa cells and not to an increase of the concentration of receptors of FSH on them. Each granulosa cell has 1500 receptors of FSH at secondary stage of follicular development, and the number of receptors of FSH stays constant during the rest of DF growing.

The increase in estradiol secretion also upregulates their own receptors, increasing the total of estradiol receptors (ER) in the granulosa cells. On the other hand, in the presence of estradiol, FSH stimulates the formation of LH receptors in the same cells, which allows the secretion of small amounts of progesterone and 17-hydroxyprogesterone (17 OHP) that would exert positive feedback on the pituitary gland. Already sensitized by the increase of estrogen, thus allowing the release of luteinizing hormone (LH) and achieve its peak. FSH also stimulates many steroidogenic enzymes such as aromatase and 3β-hydroxysteroid dehydrogenase (3β-HSD).

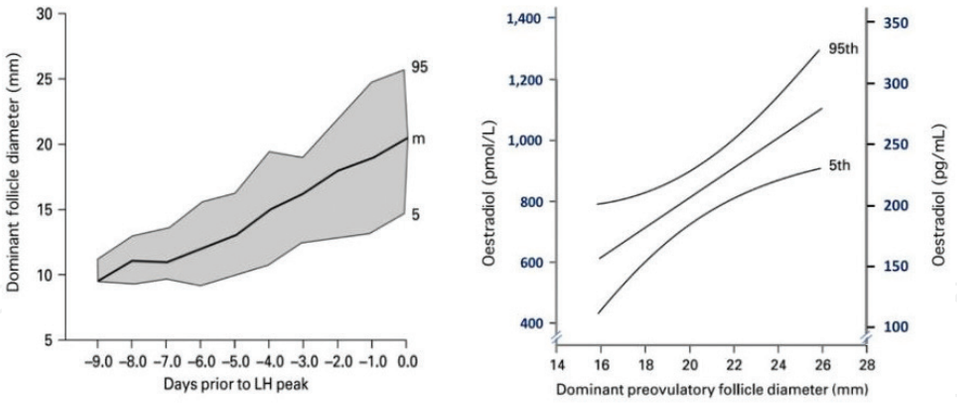


Figure 7. Diameter of dominant follicle (DF) days prior to LH peak and plasma concentration of estradiol per follicle diameter (curved lines are 95th and 5th percentiles). Adapted from Macklon and Fauser [5].

There are other signaling pathways that impact the differentiation of theca cells, not only LH but also insulin-like 3 (INSL3) that appear to modulate LH-mediated androgen biosynthesis and increased follicle cell apoptosis and luteal regression, bone morphogenetic proteins (BMPs) produced by granulosa cells, and/or oocytes who antagonized the effects of LH and INSL3, the circadian clock genes, androgens, and estrogens and (2) theca-associated vascular, immune and fibroblast cells, as well as the cytokines and matrix factors that play key roles in follicle growth [6].

At **Table 1**, production rates are presented for sexual steroids during follicular phase, luteal phase at the moment of ovulation.

Differently from granulose cells, LH receptors are localized at theca cells during all of the stages of menstrual cycle. LH receptors stimulates granuloma's cells. LH stimulates the production of androstenedione and at a lesser level the production of testosterone at the theca cells.

Androstenedione is then transported to the cells of granulosa where it is aromatized, and finally, it becomes estradiol 17-β-hydroxysteroid dehydrogenase type I. This is known as the

Sex steroids*	**Early follicular**	**Preovulatory**	**Mid-luteal**
Progesterone (mg)	1	4	25
17α-Hydroxyprogesterone (mg)	0.5	4	4
17α-Hydroxyprogesterone (mg)	7	7	7
Androstenedione (mg)	2.6	4.7	3.4
Testosterone (μg)	144	171	126
Estrone (μg)	50	350	250
Estradiol (μg)	36	380	250

*Values are expressed in milligrams or micrograms per 24 hours.
From Baird and Fraser [7].

Table 1. Production rate of sex steroids in women at different stages of the menstrual cycle.

hypothesis of two cells and two gonadotropins of the regulation of synthesis on the ovary (**Figure 8**).

The normal follicular phase has been divided in two stages: (a) early and (b) middle and (c) late, to allow a better comprehension of the endocrine events that will be finally responsible of ovulation.

Early follicular phase (days 1–4): it begins with the first day of menstruation. Follicular recruitment occurs due to the elevation of FSH, as a consequence of the decrease in estradiol, progesterone, and inhibin A released by the corpus luteum of the previous cycle, allowing the number of LH receptors to increase in the cells of the teak and the granulosa. The plasma levels of estradiol tend to remain low at this stage (**Figure 1**).

Medium follicular phase (days 5–7): as the recruitment and growth of follicles induced by FSH progress, estradiol increases slowly in a progressive manner thanks to the increased activity of CYP19, an FSH-dependent aromatase that is present in granulosa cells. The follicle that achieves the highest number of FSH receptors may aromatize more estradiol and become the dominant follicle. The other follicles, with fewer receptors for FSH, suffer atresia. For estrogen synthesis, it is necessary for the thecal cells to produce androgens, under the stimulus of LH, and for these to diffuse to the granulosa cells. Simultaneously, two glycoproteins, activin and inhibin, are produced in the theca and granulose, with local actions. Inhibin B exerts a negative hypophyseal feedback effect, where it potentiates the effect of estradiol and inhibits the synthesis and release of FSH [9, 10]. This would be a mechanism to achieve dominance giving an advantage to the follicle that has greater

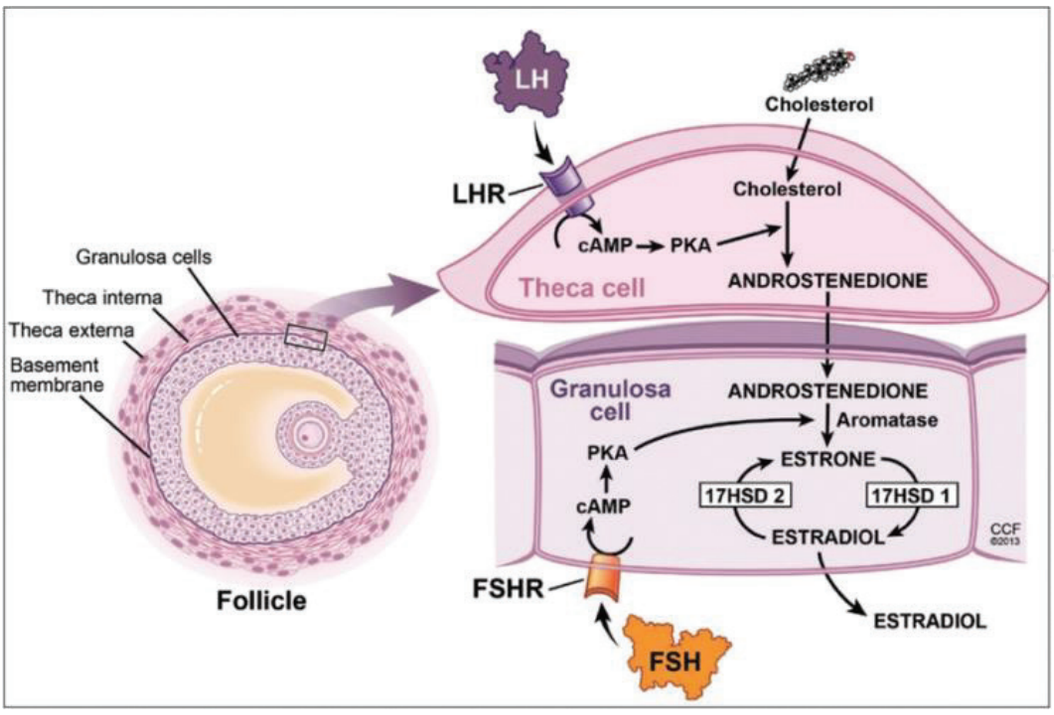


Figure 8. Two cells and two gonadotropins, on the regulation and the synthesis of estrogens at the ovary. From: Doshi and Agarwal [8].

development. The estrogen take-off (ETO) marks the successful establishment of the dominance of a follicle.

The FD develops its internal theca and increases receptivity to LH, which stimulates the production of androgens by degrading molecules of cholesterol to progesterone and from this to dehydroepiandrosterone, androstenedione, and testosterone.

At the end of this phase, the granulosa-theca complex of the FD has almost complete functionality to enter the late follicular phase.

Late follicular phase (days 8–12): this period is characterized by the elevation of estrogens that come from the DF, reaching its maximum values between 40 and 50 hours, before an elevation of FSH that precedes the ovulatory peak of LH. This preovulatory follicle reaches an average diameter of 15–20 mm.

3.1. Follicular phase and fertility

The moment of greatest likelihood of successful fertilization is intercourse on the day before ovulation. However, the potentially fertile period, which depends on sperm survival, can extend from 5 days before ovulation. Those pregnancies that have been obtained after day 14, are associated with later ovulation, a normal variability in the duration of the follicular phase depending on the time of the ETO.

It is believed that cycles of 30–31 days and 5 days of bleeding would have a higher probability of pregnancy [11], perhaps due to better quality of the DF, good function of the corpus luteum and optimal endometrial receptivity. The moment of the fertile window is quite variable. It has been reported that a significant number of women with regular menstrual cycles can be in their fertile window before day 10 or after day 17, of their menstrual cycle [12]. However, it seems that the possibility of pregnancy is low when the cycles are short, less than 25 days [13].

In clinical practice, to determine the fertility potential of a given cycle, indirect methods are used, which require observing at least one of the three primary signs of fertility (basal body temperature, cervical mucus and position of the cervix), known as methods based on symptoms.

There are kits to detect the increase in LH, which occurs 24–36 hours before ovulation named ovulation predictor kits (OPK). Those urine-based ovulation test kits are available in versions standard OPKs, digital OPKs or advanced digital OPKs, but some saliva-based ovulation tests are available also.

Computerized devices that interpret basal body temperature, urinary test results, or changes in saliva are called fertility monitors, and there are different types: urine-based fertility monitors, perspiration-based fertility monitors and saliva-based fertility monitors.

In the monitoring of assisted fertility procedures, effective follicular follow-up with ultrasonography is preferred.

In infertility treatments, ovulation inducers are used that increase endogenous levels of FSH or eleven therapeutically by administering FSH parenterally, which manages to rescue

multiple follicles from atresia. So, this patient has a higher risk of multiple ovulation. It is interesting to note that when rescuing follicles from atresia, the follicular endowment remains the same, so that follicles will not be depleted in an accelerated manner.

3.2. Follicle types

At born, woman count with primordial follicles (PF), each surrounded by one layer of cells of granulosa and are detained at the pro phase of the first meiotic division.

During adolescence, the woman has antral follicles that depend on FSH. On average, this follicle takes 14 days to mature to preovulatory FD. They are derived from a recruitment process that is independent of FSH and is mainly regulated by the anti-müllerian hormone (AMH), which is produced by the granulosa cells of the follicles in early development and inhibits the transition from the primordial to the primary follicular stage [14]. AMH levels can be measured in serum and used to measure the follicular reserve (**Figures 9 and 10**).

Primordial follicles (PF) are independent of FSH. Their average life is 60–65 days, then they are transformed in to preantral follicles (PAF), also independent of FSH, and are surrounded by many layers of granulosa's cells and also by theca cells. In this process, many primordial follicles suffer atresia (**Figure 11**).

Due to the presence of 5α-reductase, the early preantral and antral follicles produce more androstenedione and testosterone compared to the estrogen rate. 5α-reductase is the enzyme responsible for converting testosterone to dihydrotestosterone (DHT). Once testosterone has been reduced by 5α, DHT cannot be aromatized.

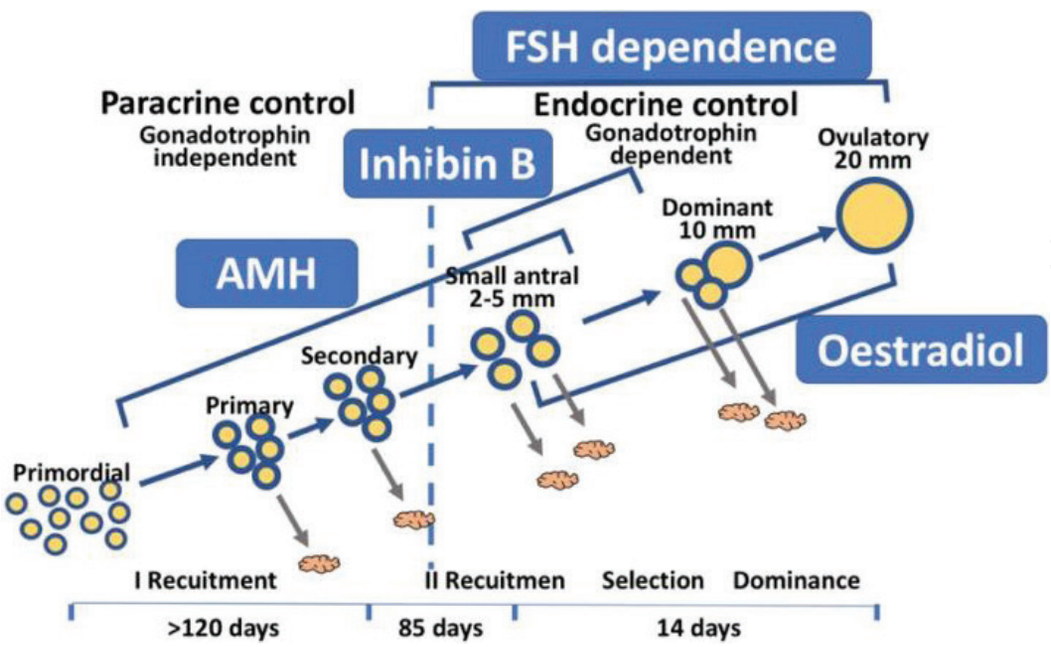


Figure 9. AMH is involved in the paracrine control of recruitment in the first stage, when the process is still independent of gonadotropins. AMH can not only reflect the number of early antral follicles in the process of development, but also those in earlier stages. Adapted from Ref. [1].

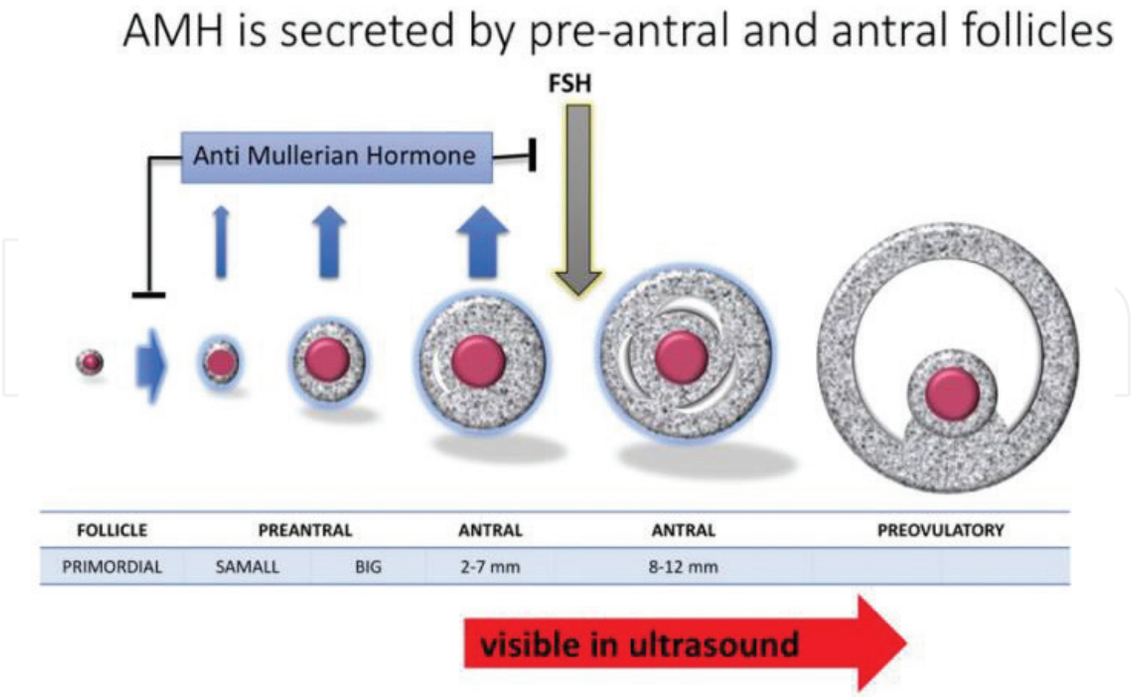


Figure 10. Clinical witnesses of the follicular development in stage pre- and postdependence of FSH: AMH and ultrasound, respectively. Adapted from Ref. [15].

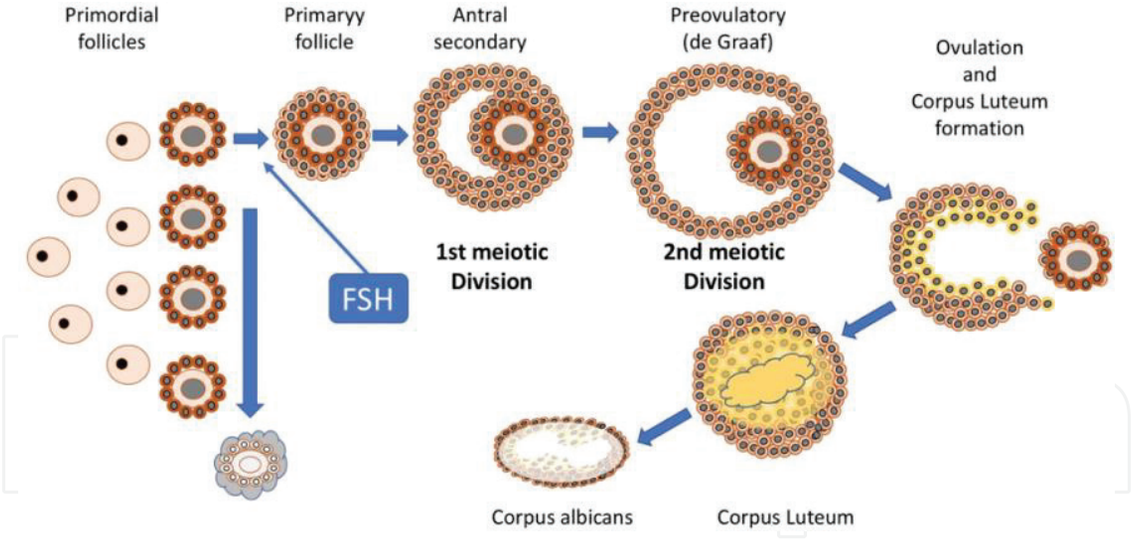


Figure 11. Follicular dynamics and illustration of folliculogenesis process.

With the increase in age in women, the involution of granulosa cells decreases the levels of inhibin production. Because of this, when a woman approaches menopause her FSH levels become higher, a sign that her ovarian reserve has decreased. On the other hand, the peri-menopausal follicles are of the worst quality, half have chromosomal alterations.

As mentioned, the development of the preantral follicle is independent of FSH, so any follicle that grows beyond this point will require an interaction.

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Secretion of gonadotropin is regulated by the releasing hormone of gonadotropin (GnRH), steroidal hormones, and diverse peptides released by dominant follicle.

Among substances that can be found al follicular liquid there are steroids, pituitary hormones, plasmatic proteins, proteoglycans, and ovarian factors nonsteroidal, which regulate the micro environment of the ovary and the steroidogenesis of the granulosa.

Factors of growing such as the insulin growth factors 1 and 2 (IGF1, IGF2) and the epidermal growth factor (EGF) would have an important role at the development and maturity of oocytes. Concentration of ovarian steroids is higher at follicular liquid compared to plasmatic concentrations.

There are two population of antral follicles: **big follicles**, which measure more than 6 mm diameter, and **little follicles**, less than 8 mm. In big follicles, concentrations of FSH are higher. Estrogen and progesterone are higher as well, while prolactin concentration is lower. Inside little follicles, prolactin and androgen levels are higher in comparison to big antral follicles.

In addition, as mentioned, FSH increases during the early follicular phase and then begins to decrease until the ovulation phase, except in the short preovulatory peak. In contrast, LH is low in the early follicular phase and begins to increase in the middle follicular phase due to positive feedback of increasing levels of estrogen.

To achieve positive feedback of LH release, plasma estradiol should be greater than 200 pg/ml, for at least 48 hours. The gonadotropins are secreted in a pulsatile manner in the anterior pituitary, with a frequency and widening of pulses that change according to the phase of the menstrual cycle (**Figure 12**).

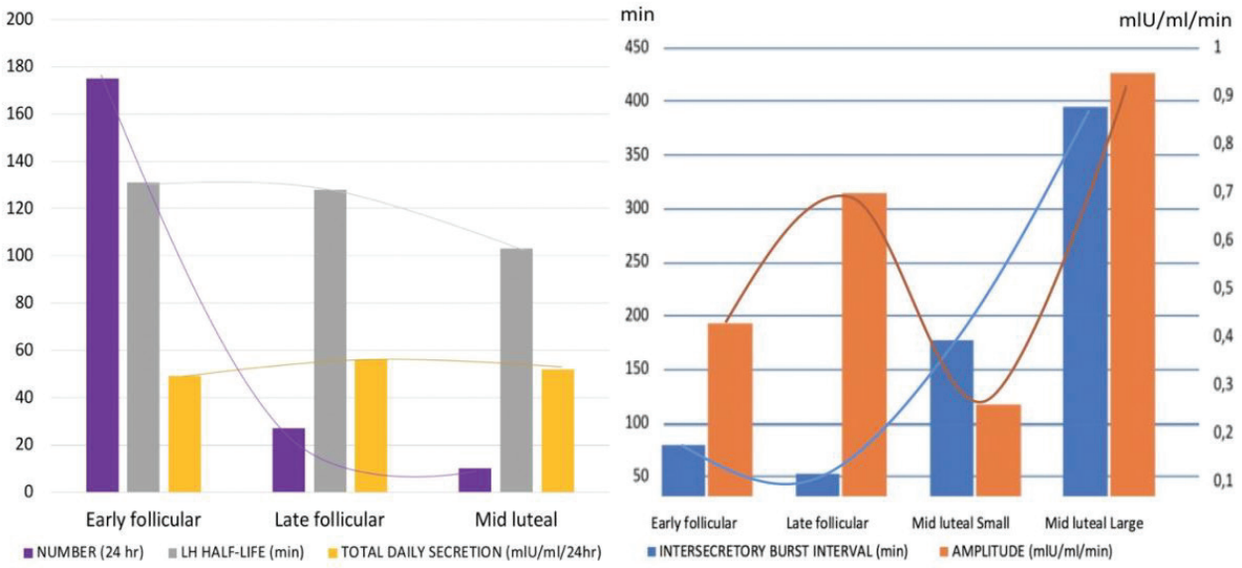


Figure 12. Pulses of LH throughout a normal cycle. Number of pulses per 24 h decreases, but total daily secretion and LH half-life are stable. The intersecretory burst interval becomes longer as the cycle progresses, being very long in the luteal phase, whereas the pulse amplitude of LH shows a dichotomous behavior, with small and high waves. Adapted from data of Sollenberger et al. [16].

During early follicular phase, secretion of LH occurs to a frequency of pulse from 60 to 90 minutes with a widening of pulse constant but variations on number of pulses intersecretory burst interval and pulse amplitude [16]. During late follicular phase, previous to ovulation, frequency of pulse increases and widening may be beginning to increase. Most of women have widening of pulse of LH beginning to increase after ovulation.

Once menstruation is produced, levels of FSH begin to decrease due to negative retro alimentation on inhibin B produced by developing follicle.

4. Ovulation

Hatching occurs 10–12 hours after peak of LH (**Figure 8**). Augmentation of LH is generated by significative raising of estradiol, with levels between 200 and 450 pg/mL, produced at the preovulatory follicle.

The critical concentration of estradiol needed to initiate positive feedback requires that the dominant follicle reach a size >15 mm in diameter. The increase in LH occurs 34–36 hours before ovulation and is a very reliable predictor of ovulation (**Figure 9**). This increase in LH is responsible for the luteinization of granulosa cells that stimulates the synthesis of progesterone and also estradiol. In addition, the LH increase resumes the second meiotic division and the chromosomal reduction in the oocyte with the release of the first polar corpuscle.

Estradiol levels decrease abruptly immediately before peak of LH. This can be due to regulation to down of LH from its own receptor or due to direct inhibition of estradiol synthesis because of progesterone.

Progesterone also participates in the stimulation of the increase in FSH in the middle of the cycle (**Figure 13**).

This increase in FSH would produce the release of oocytes from their follicular junctions, to stimulate the plasminogen activator and increase the LH receptors in the granulosa. The exact mechanism responsible for the post ovulatory fall is unknown.

Decrease in LH would occur as the consequence of the loss of positive retro alimentation of estrogens the inhibitory retro alimentation of progesterone (**Figure 14**).

It takes 36 hours from the peak of estrogen until ovulation occurs. The time to ovulation measured from the peak of LH is 12 hours; considering the time of detection in urine, ovulation will take place at 24 hours since LH is measured in the urine. The hormone hCG is similar to LH and can be used as an exogenous hormone to trigger ovulation, which will occur 36 hours after administration.

During the ovulatory period, progesterone and prostaglandins are secreted inside the follicle, as well as proteolytic enzymes. This results in digestion and rupture of the follicular wall allowing hatching, commonly called ovulation [18].

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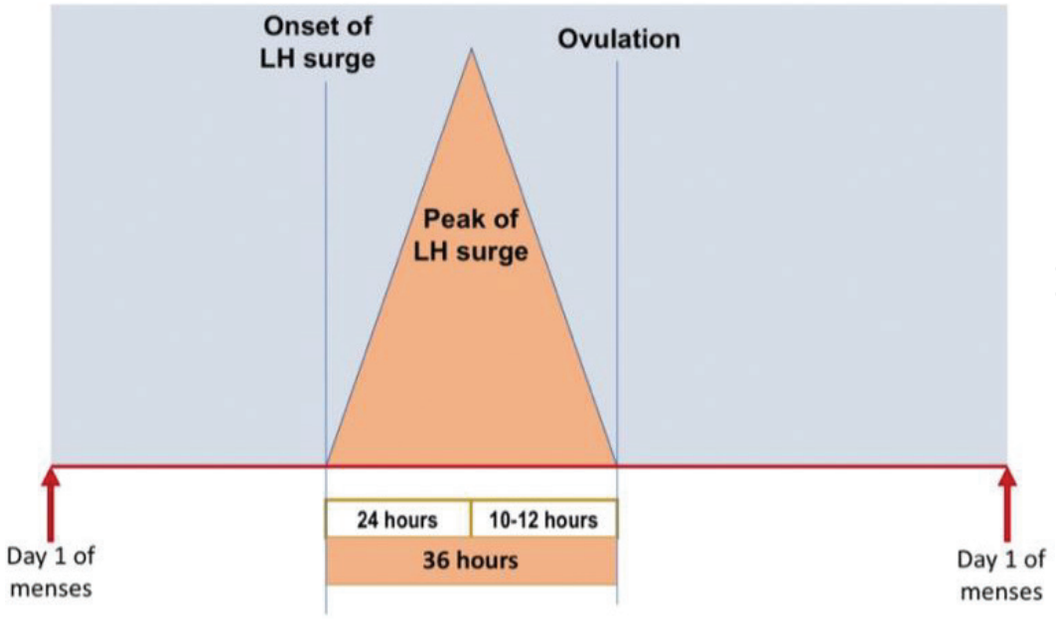


Figure 13. Increase of LH precedes ovulation in 36 hours. Peak, on the other side, precedes ovulation in 10–12 hours.

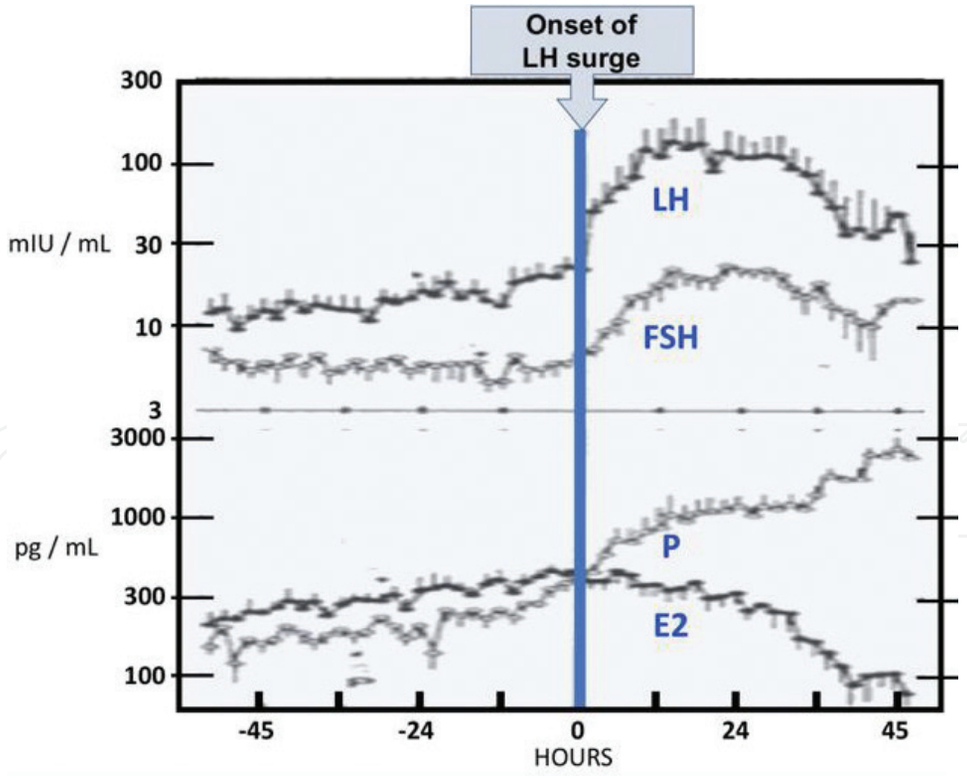


Figure 14. Changes in ovarian gonadotropins and steroids in the middle of the cycle, just before ovulation. The beginning of the increase of LH is at time. 0 time. Abs: E2, estrogen; P, progesterone. Adapted from Hoff et al. [17].

Proteolytic enzymes and prostaglandins are activated in response to LH and progesterone and digest collagen in the follicular wall, which leads to an explosive release of the cumulus-oocyte complex. Prostaglandins can also stimulate the release of oocytes, stimulating the smooth muscle within the ovary.

The point of the dominant follicle closest to the ovarian surface where the rupture occurs is called a "stigma."

All the mechanisms are still not elucidated. The concentrations of prostaglandins E and F and hydroxyeicosatetraenoic acid (HETE) reach a maximum level at the follicular level just before ovulation.

Prostaglandins stimulate proteolytic enzymes, whereas HETE stimulates angiogenesis and hyperemia. The use of high doses of prostaglandin inhibitors could hinder the follicular rupture, causing what is known as luteinized unruptured follicle syndrome, and can be observed in fertile and infertile women.

Consequently, it should be recommended to women in search of pregnancy and especially that with fertility problems, avoid the intake of inhibitors of prostaglandin synthesis, and inhibitors of cyclooxygenase (COX), in fact, are being investigated as an alternative to morning after pill in emergency contraception [19, 20].

For ovulation to occur, a series of complex molecular mechanisms that commence after the gonadotrophin surge must be given. These include intracellular signaling, gene regulation, and remodeling of tissue structure in each of the distinct ovarian compartments, which can be summarized in (a) ovulatory mediators that exert effects through the cumulus cell complex, (b) convergence of ovulatory signals through the cumulus complex co-ordinates the mechanistic processes that control oocyte maturation and ovulation, and (c) other multiple inputs, including

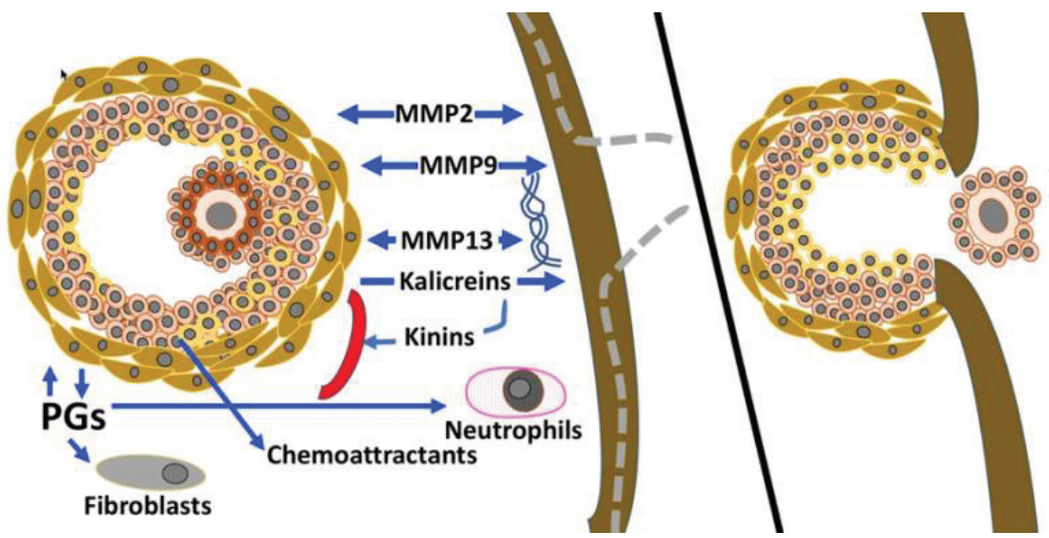


Figure 15. Proposed mechanisms at follicular rupture. LH stimulates the expression of genes in granulosa cells (PR, PGS-2) that control the activation of matrix metalloproteinases (MMPs), leading to the breakdown and remodeling of extracellular matrices and the surface epithelium to allow rupture of the follicle and extrusion of the oocyte (ovulation). Modified from Richards et al. [22].

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endocrine hormones, immune and metabolic signals, as well as intrafollicular paracrine factors from the theca, mural and cumulus granulosa cells, and the oocyte itself. Therefore, healthy and meiotically competent oocytes and the coordination and synchronization of endocrine, paracrine, immune, and metabolic signals acting mainly through the cumulus compartment exert control on oocyte maturation, developmental, and ovulation process [21].

Mechanisms suggested implied in follicle rupture [22] are shown in **Figure 15**.

5. Luteal phase

This phase lasts 14 days in most women after ovulation. The granulosa cells that are not released with the oocyte acquire a vacuolated appearance and a characteristic yellow color due to the concentration of a carotenoid called lutein and the incorporation of fat drops. No other function has been described for lutein than being a powerful antioxidant.

The luteinized cells combine with the newly formed theca-lutein cells together with the surrounding stroma; thus, originates the transitory endocrine organ that secretes progesterone, known as the corpus luteum, whose main function is to prepare the endometrium, already proliferated by the action of follicular phase estrogens, for the implantation of the fertilized egg.

The endometrium expresses adhesion molecules that make it receptive to the blastocyst and between days 7 and 9 from ovulation, a period of maximum efficiency known as the window of implantation is established; after day 9, implantation is not possible, which is why it is called the refractory phase.

Eight or nine days after ovulation, at the time when implantation is expected, maximum vascularization is reached, the basal lamina dissolves, and the capillaries invade the granulosa cell layers in response to the secretion of angiogenic factors, both from the granulosa and from the theca cells, in harmony with the maximum levels of plasma progesterone and estradiol.

The survival of the corpus luteum depends on the continuous stimulation of LH, but estradiol metabolites, acting via paracrine-autocrine pathways, affect angiogenesis or LH-mediated events also [23].

The function of the corpus luteum decreases at the end of the luteal phase unless chorionic gonadotropin appears due to an eventual pregnancy. If pregnancy does not occur, the corpus luteum undergoes luteolysis. Under the action of estradiol and prostaglandins, it forms a scar tissue called *corpus albicans* [24].

As noted, estrogen levels increase and decrease twice during the menstrual cycle, increase during the middle follicular phase, and then decrease rapidly after ovulation, followed by a further increase during the middle luteal phase, in parallel with the increase in serum levels of progesterone and 17α-hydroxyprogesterone, all falling at the end of the menstrual cycle (**Figure 1**).

The mechanism of how the corpus luteum regulates steroid secretion is not known exactly. It may be determined in part by the pattern of LH secretion, changes in its receptor, or variations

in the levels of enzymes that regulate the production of steroid hormones. The amount of granulosa cells formed during the follicular phase and the levels of LDL cholesterol that surround it may also play a role in the regulation of steroid synthesis by the corpus luteum.

There are at least two types of luteal cells, large and small.

Both produce progesterone but with differences. Large cells come from granulosa, are more active in steroidogenesis, produce large amounts of progesterone, and although they have numerous LH receptors, they do not elevate progesterone secretion in response to LH or cAMP. Instead, they possess receptors for PGF2a and respond to this hormone with activation of at least two second messengers. Activation of protein kinase C (PKC) decreases progesterone's secretion.

As a result of the binding of PGF2a to its receptor, the concentration of free intracellular calcium increases, which seems to be related to the induction of apoptosis and cell death.

The large cells are influenced by other autocrine and paracrine factors, such as inhibin, relaxin, and oxytocin (**Figure 16**). The small cells are derived from the theca, contain receptors for LH, and respond to LH or cAMP by increasing the secretion of progesterone by 5–15 times [25, 26].

The synthesis of progesterone by the corpus luteum is essential for the establishment and maintenance of pregnancy.

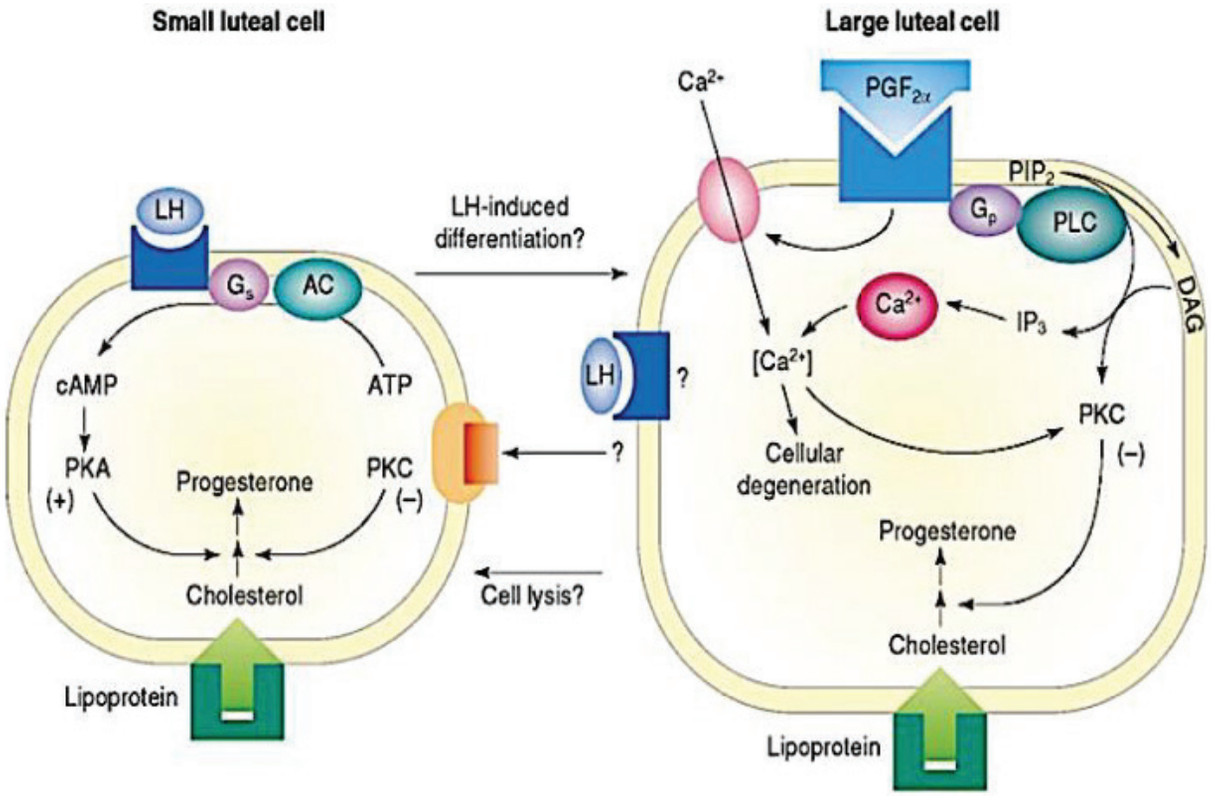


Figure 16. Regulation of small luteal cells (left) and large (right). In small luteal cells, the binding of LH to its receptor activates the second messenger protein kinase A (PKA) pathway, which stimulates the synthesis of progesterone. In large cells, the LH that binds to its receptor does not increase the intracellular concentrations of cAMP nor the synthesis of progesterone, but the binding of PGF2a to its receptor activates PKC, which inhibits the synthesis of progesterone and causes an influx of calcium that leads to cell degeneration. AC: adenylate cyclase, DAG: diacylglycerol, IP3: inositol 1,4,5-trisphosphate, PIP2: phosphatidylinositol 4,5-bisphosphate, and PLC: phospholipase C. From Niswender [25].

In addition to luteinization, that is, the conversion of an ovulatory follicle into the corpus luteum and luteal regression to allow a new cycle, there are also mechanisms of luteal maintenance and rescue to sustain pregnancy.

Humans preferably use circulating LDL cholesterol for steroidogenesis although the corpus luteum has the ability to synthesize its own cholesterol, in smaller amounts [27].

Inside the cells, lipid steroid precursors are found as free cholesterol. There is also esterified cholesterol that accumulates within the rough endoplasmic reticulum and as cytoplasmic lipid droplets or lipoprotein particles. These fatty acid esters of cholesterol cannot replace free cholesterol as a structural ingredient of the plasma membrane nor serve as direct substrates for the production of steroids. They are hydrolyzed by a neutral cholesterol ester hydrolase (NCEH), also known as hormone-sensitive lipase, because their activity is tightly regulated in steroidogenic tissues by FSH, LH, and hCG.

Progesterone secretion and estradiol during luteal phase is tightly connected with the pulses of secretion of LH (**Figure 12**). The frequency and widening of secretion of LH during follicular phase regulates the function of the posterior luteal phase and is concordant with the function of LH during luteal phase.

The frequency and widening of the pulses of secretion of pituitary LH affect the secretion of progesterone and estradiol during the luteal phase (**Figure 12**).

The half-life of the corpus luteum can be reduced with the continuous administration of LH during any of the phases, follicular or luteal, as if the LH concentration is lower or its pulses are reduced.

The luteal phase can suffer shortening also if the levels of FSH are inadequate or low, during the follicular phase, conditioning the development of a smaller corpus luteum.

The function of the corpus luteum begins to decrease 9–11 days after ovulation. The mechanism by which the corpus luteum undergoes involution (luteolysis) is partially elucidated. Prostaglandin F2α would have a luteolytic action, through the synthesis of endothelin-1 that inhibits steroidogenesis and stimulates the release of a growth factor, the tumor necrosis factor alpha (TNFα) oxytocin, and vasopressin and would produce a luteotropic effect through an autocrine/paracrine mechanism.

The ability of LH to negatively regulate its own receptor may also play a role at the end of the luteal phase; thereby, the involution of the corpus luteum must be caused by a decrease in the sensitivity of the LH receptors, rather than by a pulsatile secretion of it. Finally, the matrix metalloproteinases would also play a role in luteolysis and, therefore, in the fall of progesterone levels.

6. Menstruation

In the absence of pregnancy, the levels of progesterone and estradiol begin to decrease as a result of the corpus luteum decreasing. The fall of progesterone increases in degree of coiling

and the constriction of the spiraled arterioles. This finally produces tissue ischemia due to decreased blood flow from the superficial, spongy, and compact endometrial layers. After the fall of serum concentrations of ovarian steroids, matrix metalloproteinases play a key role in the onset of menstrual bleeding in the human endometrium, by inducing the degradation of the extracellular matrix of this mucosa [28]. Endometrial prostaglandins cause contractions of the uterine smooth muscle and detachment of degraded tissue.

The release of prostaglandins may appear due to instability of the lysosomal membranes in the endometrial cells. The magnitude of this effect is such that inhibitors of prostaglandin synthesis can be used as a therapy in women with excessive uterine bleeding. Menstrual flow is composed of detachment of endometrial tissue, red blood cells, inflammatory exudates, and proteolytic enzymes.

Two days after the start of menstruation and while the shedding of the endometrium still occurs, the estrogen produced by the new growing follicles begins to stimulate the regeneration of the superficial layers of the endometrium. The estrogen secreted by the growing follicles causes a long constriction of the vessel facilitating the formation of a veil over the denuded endometrial vessels.

The average duration of menstruation is 4–6 days, but the normal range can be 2–8 days. As mentioned above, the average amount of bleeding loss is 30 ml and more than 80 ml is considered abnormal. A few years ago, a classification has been generalized to describe the abnormalities of bleeding suggested by the International Federation of Gynecology and Obstetrics [29].

6.1. Types of endometrium at echographies

The characteristics of the endometrium in gynecological ultrasound change depending on the period of the menstrual cycle, presenting different thicknesses according to the stage of the menstrual cycle (**Figure 17**).

Endometrium type 0, postmenstrual: it is characterized because only a fine refractive line can be seen. It is the endometrium typical of postmenopause, postpartum, or after a uterine scraping. Most postmenopausal women are between 3 and 5 mm thick, but it is normal up to 8 mm if there has been no unexpected bleeding.

Endometrium type 1, preovulatory: trilaminar endometrium, refers to the observation of three refractive lines. This stage corresponds to the proliferative or estrogenic phase. In an early follicular stage, the size of the endometrium is between 3 and 4 mm thick, while in the stage close to ovulation, it can reach 9–11 mm.

Endometrium type 2, postovulatory: in this stage, the progesterone matures the already proliferated endometrium, especially in its glandular and vascular structures, thickening the endometrium. The ultrasound image becomes whiter to the extent that it contains more water and glycogen. This layer of refringency represents most of the endometrium toward the end of the luteal phase.

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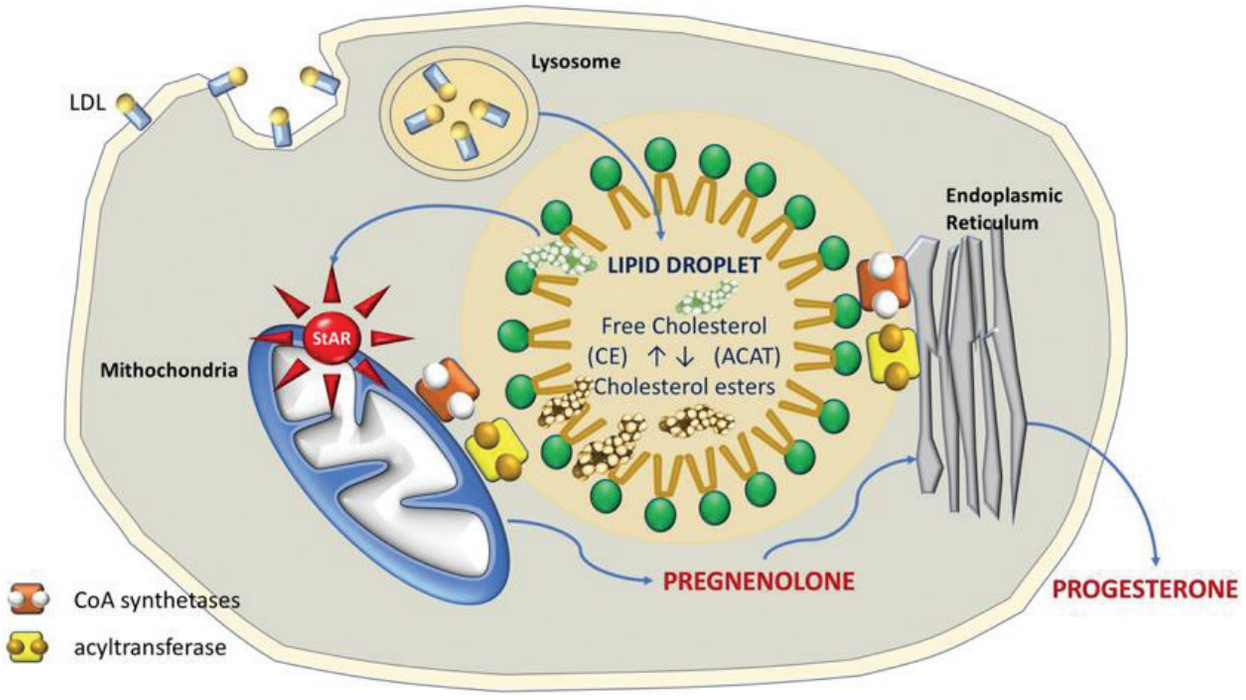


Figure 17. The main substrate for human steroidogenesis is LDL cholesterol: it is incorporated by endocytosis and stored as free cholesterol or as ester. Esterified cholesterol is hydrolyzed cholesterol esterases (CE) and transported as free cholesterol to the mitochondria. It passes from the outer mitochondrial membrane to the internal membrane, with the concurrence of the steroidogenic acute regulatory protein (StAR), peripheral type benzodiazepine receptors and endozepine. In mitochondria, cholesterol is converted to pregnenolone by cytochrome P450scc, which is transported out of the mitochondria and converted to progesterone by 3b-hydroxysteroid dehydrogenase, D5, D4 isomerase (3b-HSD), which is present in the smooth endoplasmic reticulum (The cell nucleus is not shown.)

Endometrium type 3, premenstrual: in this stage, there is only one large refractive line and corresponds to the late secretory phase.

6.2. Endocrine regulation of the menstrual cycle

When the gonadal axis has reached maturity, the neurons of the preoptic area and the infundibular and arcuate nuclei in the hypothalamus secrete GnRh in a pulsatile fashion, every 60–90 minutes, to the pituitary portal system.

Frequency and amplitude are essential to produce and maintain the effect on the gonadotropic cells of the anterior part of the pituitary gland, which consists of releasing both LH and FSH. The secreted amounts of each will depend not only on the pulsatility of GnRH, but also on the positive and negative feedbacks mechanisms of sex steroids.

In general, estrogen sensitizes and counter-regulates FSH, at both levels, the hypothalamus and the adenohypophysis, selectively modulated by other factors such as inhibins A and B. LH is sensitive to positive feedback, while there are estrogens in the late follicular phase and in the luteal phase, but the feedback becomes negative when estrogen levels fall at the end of the cycle.

Recent evidence indicates that the administration of progesterone in the late well-estrogenized follicular phase does not prevent the LH surge, which is of great importance because it would have no interference with ovulation [30, 31].

Relatively, low levels of estradiol, in early follicular and luteal phases, decrease kisspeptin expression, which reduces the amplitude of GnRH pulses [32]. On the other hand, progesterone would increase the dynorphin expression, which in turn reduces that of kisspeptin. These changes have been associated with the lower frequency of GnRH pulses in the luteal phase.

Other modulators that stimulate the pulsatile secretion of GnRH are glutamate and norepinephrine, while GABA and endogenous opioids inhibit it.

Neurokinin B and dynorphin neuropeptides act in an auto-synaptic fashion in the arcuate/infundibular nucleus, so that an increase in the expression of neurokinin B (NKB) stimulates the secretion of and, therefore, of GnRH, while an increase in dynorphin (Dyn) expression decreases kisspeptin secretion by inhibiting the pulsatility of GnRH. This system is known as KNDy [33].

At the beginning of the menstrual cycle, estradiol levels are low and FSH levels are slightly elevated. This ratio manages to recruit follicles and as that happens, not only estradiol increases but also inhibin A, due to the empowerment of FD, which generates a continuous decrease in FSH in the follicular phase.

The concentrations of FSH reach the maximum levels on the day when the FD is defined, followed by a slow decrease during the follicular phase, from day 5 to 13, reaching a nadir and then a peak just before ovulation (**Figure 14**). There comes a time when estradiol levels are such that they trigger the peak of FSH and LH, producing ovulation.

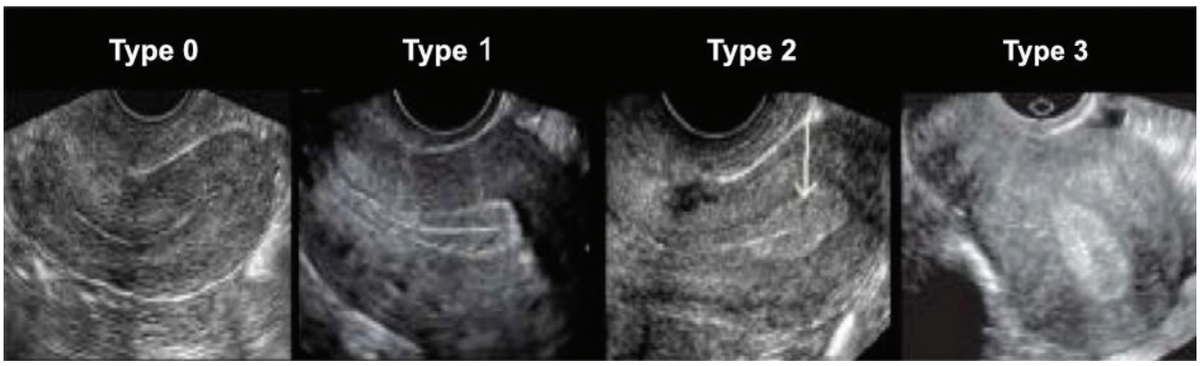


Figure 18. Types of endometrium in transvaginal ultrasound. The endometrium was classified into four types (0, 1, 2, and 3) according to the appearance of the myometrium-endometrium and endometrium-endometrium interfaces, the texture, and the thickness of the functional layer. Type 0: smooth, thin as a pencil line; type 1: trilaminar structure with an iso- or hypoechoic functional layer; type 2: also trilaminar, but the myometrium-endometrium interfaces are thicker than those of type 1; and type 3: thick and homogeneous echogenic image. The type of endometrium correlates with the day of the menstrual cycle. Ultrasound is defined on day 0 as the day of the follicle break. Type 0 is usually found on day −11, during and immediately after menstruation. Type 1 is observed during the middle follicular phase and until day +2. Types 2 and 3 are observed after the ovulatory days. The endometrium increases more thickness during the preovulatory phase (average +5.5 mm), and in the luteal phase, the average is +2.6 mm.

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As the luteal phase advance in time, inhibin A, estradiol, and progesterone fall together with the increase in activin A. FSH increases in the transition from the luteal phase to the next follicular phase, beginning 4 days before menstruation, a stage in which inhibin B increases during follicular recruitment.

The concentration of activin A secreted by the follicles increases in the second half of the luteal phase [34] (**Figure 18**), decreases at the beginning of the follicular phase, increases during the early follicular phase, and then increases during the middle follicular phase in parallel with estradiol and inhibin A (**Figure 19**).

In older women, FSH is higher, even during nadir, and the increase occurs early during the luteal phase. Recruitment of a group of follicles begins early, but the selection of DF is altered and can either advance or delay. The result is the variability of the cycle at the expense of a variable follicular phase, called "lag phase," which ends when the ETO is produced [35].

The ETO is when the estradiol overt elevation is achieved, which marks the selection of the FD. If an FD capable of ovulating was not achieved, the woman can go through a hyperestrogenic state without establishing a corpus luteum, so at the endometrial level, the cycle is hormonally monophasic. This is the pathophysiological basis that explains the monophasic hyperestrogenism that affects approximately one-third of women in perimenopause (**Figure 20**).

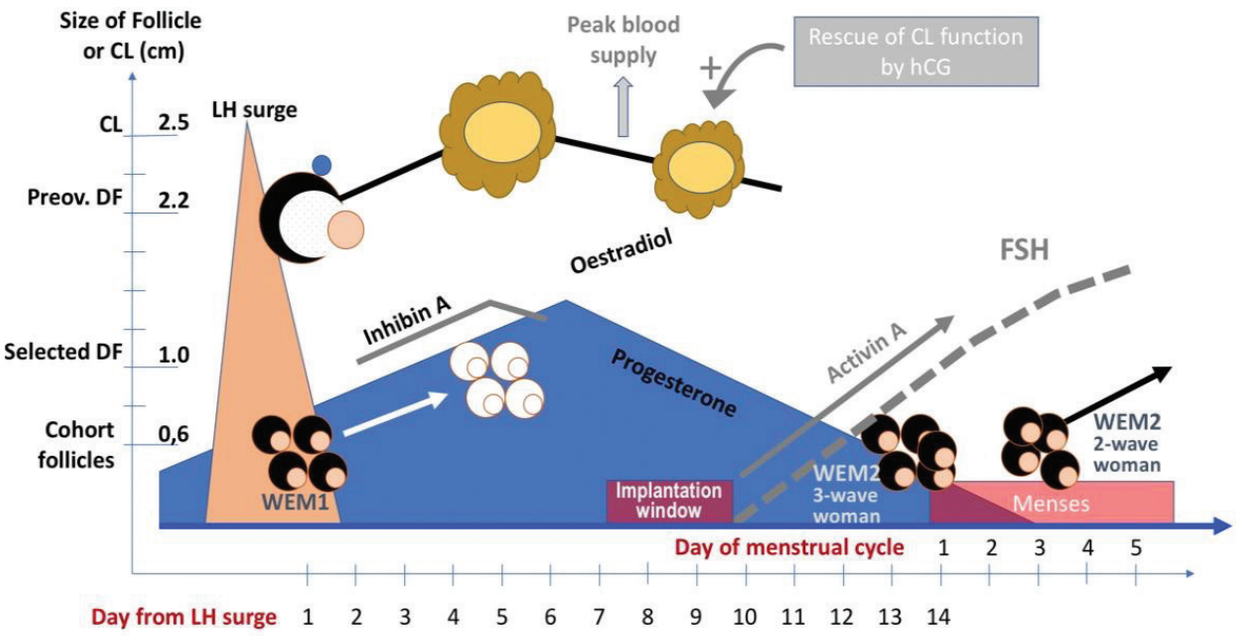


Figure 19. Scheme composed shows luteal events, follicular ones and hormonals during luteal phase of woman CL = corpus luteum; DF = dominant follicle; WEM1–3 = wave emergency 1, 2, or 3 at the cycle; the waves of follicle of light gray color indicates the low frequency of the principal waves (selection of DF) during luteal phase or early follicular ones in women of 2 or 3 waves. The estradiol rise in the follicular phase begins after the emergence of the ovulatory DF and becomes more rapid following DF selection, and occurs earlier in women with 2 versus 3 follicle waves per cycle. After ovulation, estradiol concentrations increase to the mid-luteal phase (days 7–9 after ovulation) and then decline, and this is due to luteal estradiol secretion and is unaffected by minor or major anovulatory waves. Adapted from Macklon and Fauser [5].

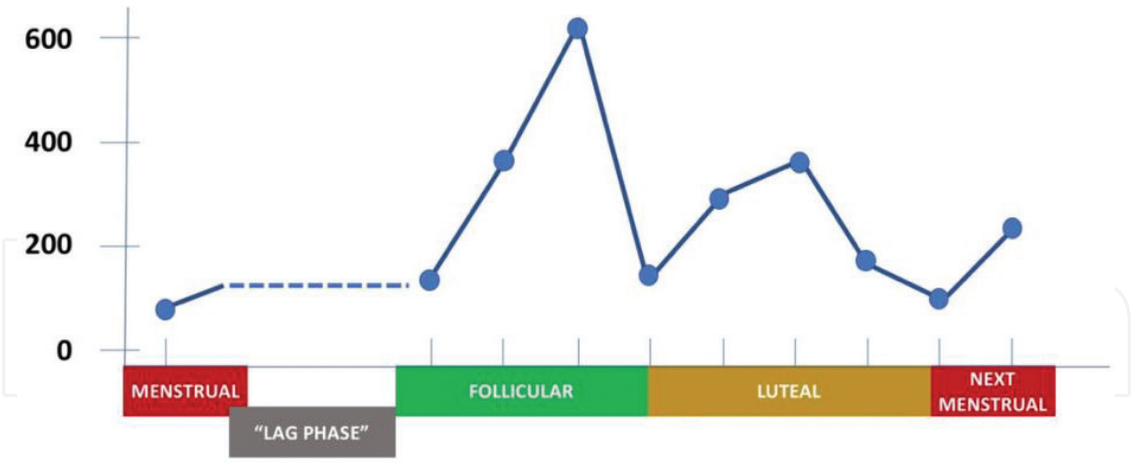


Figure 20. The variability in perimenopause depends on the lag phase, a delayed recruitment process. Adapted from Hale et al. [35].

A chronic negative energy imbalance reduces the pulsatility of LH, generates atresia of FD and, consequently, anovulation and amenorrhea. Weight loss is associated with a reduction in LH pulses, which generates functional, reversible hypothalamic amenorrhea. On the contrary, the pulsatility of LH is increased in adolescents with irregular cycles or in women with polycystic ovary syndrome, associated with anovulation also, but here the selection of DF is absent.

7. Conclusion

Human reproduction depends on the integrity of a system of intracrine and paracrine signals within the ovaries, in which those recruited follicles that have reached a level of differentiation that make them sensitive to the endocrine control of the other distant and great actor, the hypothalamus axis participate pituitary. Once a dominant follicle has been achieved, the elevations of the circulating levels of estradiol and inhibin B produced by it will modulate FSH levels and will allow, on the one hand, the atresia of the other follicles, and on the other, they will facilitate the LH surge, necessary to trigger ovulation. After hatching, the surrounding theca and granulosa cells from the follicular bed abandoned by the newly ovulated egg interact to produce a corpus luteum, which retains sufficient steroidogenic properties to produce progesterone at the concentration required to regulate the endometrium, till the implantation of a fertilized egg. If pregnancy does not occur, since the end of the luteal phase, gonadotropic changes are prepared to allow the development of a follicular recruitment phase.

Being such a complex process, dependent on so many variables and exposed to so many actions, reactions and interferences, the sequences of the menstrual cycle are remarkably predictable within not very wide ranges of variability. In general, the duration standards of each cycle, 25–35 days, coincide with the ovulation presumption criteria accepted for women with ovulatory anomalies such as in the polycystic ovarian syndrome. The detailed understanding of the mechanisms allow to improve the efficiency in the clinical management when it

is intended to give assistance to obtain a pregnancy, as well as to avoid it when the goal is contraception, or to correct bleeding anomalies that may result from ovulatory disorders with luteal insufficiency. There are still many aspects to investigate.

Conflict of interest

The authors declare no conflict of interest in relation to this publication.

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