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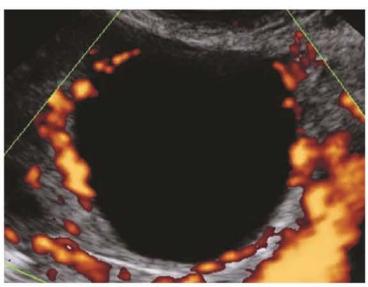
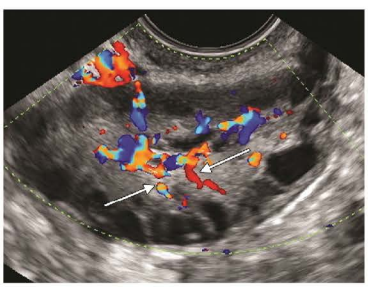
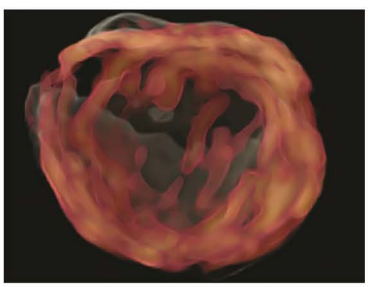

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CHAPTER 3

Endocrinology of Luteal Phase in Unstimulated Cycle

Rashmika Gandhi, Sunita Tandulwadkar

FOLLICULAR LUTEINIZATION

The onset of luteinization in granulosa-thecal cells is triggered by luteinizing hormone (LH) derived from the pituitary. This activation initiates a signal transduction pathway that relies on protein kinase A (PKA), along with a potential pathway connecting the LH receptor (LHr) to alterations in intracellular Ca2þ and diacylglycerol (IP3) generated through the activation of phospholipase C. The synthesis of estradiol shows a progressive increase originating from the dominant follicle, ultimately leading to the LH surge. Normal women exhibit a slight elevation in progesterone levels before the LH surge, indicative of the rising amplitude and frequency of LH pulses preceding the surge. In humans, a 24- to 36-hour LH surge is adequate to trigger the resumption of oocyte meiosis, disconnection of gap junctions between granulosa cells and the oocyte's plasma membrane, luteinization of granulosa cells, ovulation, and the initial phase of corpus luteum (CL) development. The LH surge also inhibits cell proliferation, likely influenced by changes in cyclins and other genes.[1-3] The surge-associated LH signaling enhances steroid biosynthesis, triggering the resumption of meiosis, ovulation, and subsequent luteinization in both theca and granulosa cells. In the latter stages of follicular maturation, LH, acting through the LHr on preovulatory granulosa cells, assumes the role traditionally played by FSH. Following the LH surge, plasma concentrations of progesterone (P) and 17a-hydroxyprogesterone (17aOHP) increase, marking the onset of luteinization in both granulosa and theca cells. The rapid elevation of P levels after the LH surge suggests that the necessary enzymes and proteins for P synthesis are either already present in the cells or are rapidly induced. The absence of the complete enzymatic machinery in human granulosa cells before the LH surge indicates that luteinization of thecal cells may serve as a potential immediate source for this rapid increase in P synthesis.[4] At this time, several morphologic and molecular changes take place in the granulosa cells.

CLASSIC PROGESTERONE RECEPTORS AND OVARIAN FUNCTION

The physiological effects of P are predominantly mediated through interaction with progesterone receptors (PR). Two classic isoforms of PR exist, namely PR-A and PR-B, with PR-A playing a crucial role in normal ovarian and uterine function, while PR-B is essential for mammary development.[5] LH serves as the primary signal for the rupture of preovulatory ovarian follicles and induces a transient expression of PR mRNA.

ENDOCRINE AUTOCRINE/ PARACRINE REGULATION OF THE CORPUS LUTEUM

Regulation of the corpus luteum involves both endocrine and autocrine/paracrine mechanisms. The CL comprises steroidogenic cells (theca and granulosa lutein) and nonsteroidogenic cells (endothelial, immune, and fibroblast), all crucial for steroid synthesis and secretion.[6] Pituitary-derived LH plays a key role in this process, utilizing the cyclic adenosine monophosphate (cAMP) second messenger signaling system to regulate genes essential for hormone synthesis and luteal development. In conception cycles, trophoblastic human chorionic gonadotropin (hCG) production prevents CL regression. While LH is essential for primate CL development and maintenance, luteal regression occurs in the menstrual cycle due to reduced responsiveness of the aging CL to LH. Elevated hCG concentrations in fertile cycles overcome this regression.[7] Additionally, various molecules, including growth factors, hormones, nitric oxide, cytokines, insulin-like growth factor 1 (IGF-1), and IGF-binding proteins, modulate the in vitro effects of LH/hCG on human luteal cell steroidogenesis.[8]

STEROID BIOSYNTHESIS BY THECA AND LUTEINIZED GRANULOSA CELLS

The human CL is characterized by diverse cell types with distinct morphologic, endocrine, and biochemical phenotypes.[9] Throughout the luteal phase, these cells undergo changes in number, morphology, function, and secretory capabilities. Approximately 30% of CL cells are steroidogenic, with small luteal cells believed to originate from the theca-interna and large luteal cells from the granulosa cell lineage. Granulosa-lutein cells, responsible for both P and estradiol (E2) production, exhibit a greater basal P production and express aromatase for E2 synthesis. Theca-lutein cells, on the other hand, demonstrate a substantial increase in steroid production in response to hCG stimulation and express 17a-hydroxylase/17/20 lyase activity (P450c17). These cells produce androgen precursors, which are then aromatized by granulosa-lutein cells, and serve as the site for 17a-hydroxyprogesterone (17a-OHP) synthesis.

NONSTEROIDOGENIC LUTEAL CELLS

During the transition from the ovulatory follicle to a fully functional CL, there is a pronounced phase of proliferation among vascular endothelial cells, leading to the development of a robust capillary network. Endothelial cells constitute approximately 30–40% of mature CL cells. The luteal vasculature is crucial for transporting gonadotropins, plasma lipoproteins (a source of cholesterol for progesterone production), and facilitating the removal of secretory products, primarily steroid hormones, from luteal cells. The regulation of luteal vasculature is pivotal for controlling luteal function. Vascular endothelial growth factor (VEGF) mRNA and protein are localized in the granulosa-lutein cells of the CL. Inhibiting VEGF in vivo during the luteal phase in nonhuman primates hinders luteal angiogenesis and suppresses progesterone secretion.[10] In the past decade, an angiogenic factor known as endocrine gland-vascular endothelial growth factor (EG-VEGF), exhibiting a certain degree of specificity to the ovary, has been identified in human granulosa-lutein cells. Unlike VEGF mRNA,

the mRNA levels of EG-VEGF increase in the mid and late CL stages. The presence of EG-VEGF is believed to empower the CL to respond to hCG, particularly in the early stages of pregnancy.[11] The significance of vasculature to CL function is evident in the modified parameters of blood flow observed in conditions such as luteinized unruptured follicle (LUF) and luteal phase defects.[12] Immune cells, including macrophages and T lymphocytes, are found within luteal tissue. Macrophages and endothelial cells form close connections with other luteal cells, enabling the regulation of luteal cells through paracrine mechanisms. The capability of macrophages to release interleukin (IL)-1b and tumor necrosis factor-α (TNF-α) is noteworthy, as both cytokines can influence luteal steroidogenesis. In vitro studies suggest that these cytokines reduce the LH/hCG-stimulated progesterone production in cultured human granulosa-lutein cells.[13] IL-1 and TNF-α are primarily secreted by activated luteal monocytes, macrophages, as well as T and B cells. The midluteal and late luteal phases of the corpus luteum are characterized by the presence of activated macrophages.[13] In normal physiological conditions, these cytokines likely contribute to functional and structural luteolysis, facilitating the initiation of a new menstrual cycle. However, the unregulated activation of these mechanisms could lead to dysfunction in the corpus luteum.

CHOLESTEROL TRANSPORT TO AND WITHIN LUTEAL STEROIDOGENIC CELLS

Obtaining the cholesterol precursor is the initial hurdle for steroid-producing cells, including luteal cells. While luteal steroidogenic cells have the capacity to synthesize cholesterol de novo, this pathway is of minor significance, as indicated by the low levels of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the key enzyme in this cholesterol pathway.[14] Steroidogenic luteal cells in humans acquire cholesterol carried by lipoproteins, particularly low-density lipoprotein (LDL), through endocytosis, maintaining reserves of esterified cholesterol. Additionally, high-density lipoproteins (HDL) may contribute cholesterol precursors for steroidogenesis via the SR-B1 receptors, facilitating the selective uptake of HDL cholesterol esters. Upon gonadotropin stimulation, cholesterol from various sources, including intracellular cholesterol esters stored in lipid droplets (which are hydrolyzed), is transported to the inner membrane of the mitochondria to serve as a substrate for pregnenolone (P5) production. The movement of cholesterol from the outer mitochondrial membrane to the inner membrane, where the cytochrome P450scc complex is situated, is believed to be the rate-limiting step in P synthesis. This sterol translocation in response to tropic hormones, including LH and hCG, is reliant on the essential role of steroidogenic acute regulatory (StAR) protein.[15,16]

LUTEAL PROGESTERONE SYNTHESIS

In primate ovarian physiology, three pivotal endocrine events support progesterone secretion:

1. *LH surge:* This surge serves as the signal for follicular rupture and the luteinization of theca and granulosa cells.
2. *LH pulses during luteal phase:* LH pulses during the luteal phase are crucial for the development and function of the CL.
3. *hCG secretion in early pregnancy:* hCG secretion by the embryo's trophoblast sustains CL function in early pregnancy.[17]

The biosynthesis of progesterone requires only two enzymatic steps: (1) The conversion of cholesterol to pregnenolone (P5), catalyzed by P450scc located on the inner mitochondrial membrane, and (2) its subsequent conversion to progesterone, catalyzed by 3β-HSD present in the smooth endoplasmic reticulum. Before the LH surge, StAR is virtually absent from human granulosa cells, rendering them unable to synthesize progesterone from cholesterol precursors.[18] On the contrary, StAR is present in high levels in the periovulatory human theca cells. These cells have the capability to synthesize androgens from cholesterol.[19] Therefore, the abrupt elevation in progesterone levels during the LH surge implies that the luteinizing theca cells might be the origin of progesterone. Moreover, the restricted vascular network of the human periovulatory granulosa cells could impede their access to cholesterol (low-density lipoprotein) through the vasculature. The formation of an insufficient vascular network in the corpus luteum is hypothesized to have substantial implications for steroid secretion in the later stages of the luteal phase. The expression of StAR transcripts and proteins is most prominent in the early and midluteal phases of the corpus luteum.

LUTEAL ESTRADIOL BIOSYNTHESIS

Small luteal cells are believed to be the primary source of luteal androgens,[20] while large luteal cells are considered the main site for luteal estrogen synthesis.[21] This suggests the preservation of the two-cell model of estrogen biosynthesis, initially proposed for follicular estrogen synthesis, in the primate corpus luteum. The enzyme P450c17, responsible for androgen synthesis, is in cells near the periphery of the gland along the vascular tract.[22] Although the two-cell system for estrogen production persists after luteinization of the follicle, the role of FSH in stimulating androgen aromatization is not conserved.[23] LH and IGF-1 appear to substitute for FSH, sustaining estradiol production by luteal cells in culture.[24]

A new model of follicular wave dynamics in the monovular mammalian ovary has been proposed, distinguishing between major and minor waves. Major waves lead to the development of the ovulatory follicle, while minor waves involve follicles that express P450arom and reach a diameter smaller than 5 mm. This raises the possibility that serum estradiol levels during the luteal phase may partly stem from luteal-phase follicle waves rather than exclusively from luteal tissue. The role of luteal estradiol secretion remains uncertain, as it was initially hypothesized to be involved in luteolysis in primates, where the luteolytic process is independent of uterine prostaglandin. However, the recent discovery of both types of estrogen receptors in the human corpus luteum supports a local role of estradiol in luteal function.[25]

LUTEOLYSIS

In a nonfertile cycle, the CL of primates undergoes a process of regression known as luteolysis. This process involves the loss of both functional and structural integrity of the gland.[26] The functional regression of the corpus luteum during luteolysis is characterized by a decrease in P production, while the structural regression occurs subsequently and is associated with various forms of cell death. The molecular events underlying luteal regression and how they are prevented by exposure to hCG remain unclear. A key feature of functional luteal regression is the reduced production of P, accompanied by a decline in the expression of the *StAR* gene and protein. This decrease

in StAR expression precedes a decline in the expression of other steroidogenic enzymes, highlighting the critical role of StAR in luteal P production. Administration of hCG during the late human luteal phase restores StAR levels to those found in the midluteal phase corpus luteum, as well as plasma P and E2 levels. Various molecules, including prostaglandin F2-α (PGF2-α), TNF-α, interleukin-1β (IL-1β), endothelin, monocyte chemoattractant (MCP-1), estrogens, and reactive oxygen species, have been implicated in the luteolytic process.[27] The available data suggest that apoptosis is a characteristic feature of human luteal regression. Luteal cells showing a positive apoptotic signal and the number of luteal cells positive for inducible nitric oxide synthase (iNOS) increase within the human corpus luteum during luteal regression.[28] However, the percentages of luteal cells with apoptotic signals are relatively low, ranging from 5 to 7%, raising uncertainty about apoptosis being the sole mechanism responsible for luteal cell death. Other forms of cell death, including autophagy and necrosis, also seem to play a role in luteal regression.[29,30] The unscheduled activation of these mechanisms may contribute to luteal phase defects.

CORPUS LUTEUM RESCUE IN A FERTILE CYCLE

During the conception cycle, the trophoblast's production of hCG prevents the regression of the CL. Compelling evidence supporting the rescue role of hCG is demonstrated by the administration of a β-hCG vaccine to women, which inactivates endogenous hCG and leads to a decline in P levels and the onset of menstruation.[31] The hormonal profiles of conception and nonconception cycles differ during the early luteal phase. Conception cycles exhibit significantly higher levels of LH and E2 on days 4 and 5 after the LH peak in urine. However, serum levels of FSH, P, and relaxin are not significantly different during this period. These variations may indicate changes in signaling within the hypothalamic-pituitary-ovarian axis that commence in the periovulatory period of nonconception cycles.[32] Serum hCG becomes detectable around the time of implantation (day 8 after ovulation) and progressively increases up to the first 12 weeks of pregnancy. Vaginal ultrasound measurements show a rapid increase in CL volume during early human pregnancy, without a simultaneous rise in 17a-hydroxyprogesterone (17aOHP), P, or E2. However, the serum level of 17aOHP during the first 6 weeks of pregnancy is considered a reliable marker of luteal steroidogenesis because this steroid is not synthesized by the trophoblast, which lacks expression of P450c17. A positive correlation is observed between CL volume and serum concentrations of relaxin and hCG, suggesting that the growth of the CL in early pregnancy is mainly derived from the proliferation of nonsteroid-secreting cells.[33] Limited data are available on the molecular changes underlying the functional and structural alterations in the CL during pregnancy. Administration of exponentially increasing doses of LH or hCG extends the lifespan of the CL. Moreover, hCG administration during the late luteal phase restores the abundance of StAR mRNA and protein levels to those found in midluteal phase CL, along with an increase in plasma P levels. Additionally, hCG administration promotes the expansion of the vascular network in the theca and granulosa cell layers, with intense staining detected in the cytoplasm of steroidogenic cells.

The molecular changes underlying the functional and structural alterations in the CL during pregnancy are not extensively documented. However, studies have shown

that the administration of exponentially increasing doses of LH or hCG can extend the lifespan of the CL.[7] Specifically, when hCG is administered during the late luteal phase, it restores the abundance of StAR mRNA and protein levels to those observed in the midluteal phase CL. This is accompanied by an increase in plasma P levels. Moreover, hCG administration induces the expansion of the vascular network within the theca and granulosa cell layers, and intense staining is detected in the cytoplasm of steroidogenic cells. These findings suggest that hCG plays a crucial role in maintaining the functional and structural integrity of the CL during pregnancy by influencing molecular factors such as StAR expression and vascular development.[13]

LABORATORY ASSESSMENT OF THE LUTEAL PHASE

The confirmation of ovulation has often relied on determining the P levels in the midluteal phase. There is variability in the cut-point values used to establish ovulation, ranging from 4 to 10 ng/mL in different settings. The considerable amplitude of pulsatile progesterone secretion during the late luteal phase, driven by large-amplitude LH pulses, poses a challenge to the accuracy of a single determination of this steroid. Alternatively, an increased daily excretion of pregnanediol, compared to the early menstrual cycle levels, is often considered as evidence that a woman has undergone ovulation. This method provides an alternative approach to assessing ovulation by looking at changes in pregnanediol excretion over time.

ULTRASONOGRAPHIC AND DOPPLER EVALUATION OF THE CORPUS LUTEUM

Ultrasonographic identification of the CL following ovulation is initially reported to occur in only 50–80% of natural menstrual cycles, as determined by transabdominal ultrasonography.[34] Two morphological types of CL can be observed after ovulation: those with and without a central fluid-filled cavity (CFFC). The majority of CLs contain a CFFC, and the incidence of CLs with a CFFC is highest immediately after ovulation, subsequently declining over time. The presence of a CFFC is associated with the leakage of blood into the follicular lumen following follicular rupture, and its ultrasonographic detection should be interpreted as a normal physiologic event during the menstrual cycle.[35]

A decrease in echogenicity during luteinization indicates increased vascularization of luteal tissue and a corresponding decrease in tissue density. In contrast, the increased echogenicity observed during luteolysis could be attributed to decreased vascularization and the replacement of luteal tissue with fibrous connective tissue.

ULTRASONOGRAPHIC AND DOPPLER EVALUATION OF THE LUTEAL PHASE ENDOMETRIUM

There is currently no reliable diagnostic method to evaluate endometrial receptivity, although various techniques have been proposed, including histologic assessment of endometrial biopsy,[36] evaluation of endometrial protein expression,[37] and ultrasound examination of the endometrium.[38]

Different ultrasound parameters have been suggested to assess endometrial receptivity, such as endometrial thickness, endometrial echogenic pattern, and endometrial volume.[39-41]

Endometrial Thickness and Pattern

Ultrasonographically, the endometrium appears as a thin, simple, hyperechogenic single stripe immediately after menses.

The stratum functionalis and basalis layers offer distinct views compared to the endometrial development during the mid–late follicular phase. In the periovulatory period, a pronounced triple-line echo-textural pattern, reflecting the separation between the stratum basalis and functionalis layers, is observed in association with rising estrogen (E2) levels. This triple-line pattern disappears after ovulation. A more homogeneous and hyperechogenic endometrium is observed as endometrial glands expand under the influence of luteal progesterone (P) production in the secretory phase.[42]

Endometrial Blood Flow

Doppler study of uterine arteries reflects blood flow to both the endometrium and myometrium. Blood flow to the endometrium originates from the radial artery, which divides after passing through the myometrial–endometrial junction to form basal arteries supplying the basal portion of the endometrium and spiral arteries continuing up toward the endometrium. Blood flow in the uterine vessels, assessed by color Doppler ultrasound, is typically expressed as downstream impedance to flow.

CONCLUSION

In conclusion, the CL in humans is a crucial temporary endocrine gland that produces significant amounts of steroid hormones, particularly progesterone, influencing menstrual cyclicity, endometrial receptivity, and early pregnancy maintenance. Regulation of the CL involves intricate endocrine, autocrine, and paracrine mechanisms, with luteolysis marking the regression of the CL in nonfertile cycles. The CL's rescue in a fertile cycle, facilitated by trophoblastic hCG production during conception, prevents regression, and sustains P levels. Various molecular events, including StAR expression and vascular development, contribute to the dynamic changes in the CL during pregnancy. Understanding the intricate mechanisms of CL development, function, and regression is essential for comprehending reproductive cycle dynamics and addressing potential issues related to fertility and luteal phase defects.

KEY LEARNING POINTS

The human corpus luteum (CL), a temporary endocrine gland originating from the ovulated follicle, serves as a significant source of steroid hormones, producing up to 40 mg of progesterone (P) daily. Unlike other species, the CL in many primates, including humans, exhibits a distinctive secretion pattern involving substantial amounts of androgens and estradiol (E2) alongside P. This secretion profile plays a critical role in shaping menstrual cyclicity, influencing endometrial receptivity for successful implantation, and is vital for the maintenance of early pregnancy. Therefore, gaining insights into the inherent endocrine, autocrine/paracrine, and molecular mechanisms governing P production during follicular cell luteinization, CL development, function, and rescue is crucial for comprehending the dynamics of a fertile reproductive cycle.

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Sunita Tandulwadkar is a distinguished figure in the realm of Obstetrics and Gynecology, IVF, and Endoscopy, renowned for her exceptional contributions and numerous awards. Hailing from India, Dr Tandulwadkar's journey began with a strong passion for women's health and reproductive medicine, shaping her illustrious career.

She currently holds the esteemed position of Head, Department of Obstetrics and Gynecology, Ruby Hall Clinic, Pune, Maharashtra, India, and is also the Chief of Ruby Hall IVF and Endoscopy Centre and also the Director of DY Patil IVF and Endoscocpy Centre, Pune, where she leads groundbreaking advancements. Currently, she is the President Elect FOGSI (2025–2026) and President Elect ISAR (2026–2027).

Dr Tandulwadkar is a pioneer in endoscopy in India, advocating minimally invasive surgical techniques and conducting innovative research, positively impacting patients. She founded Solo Stem Cells, a Stem Cells Research and Application Center, pioneering stem cell treatments, including India's first stem cell baby at 45.

Her accolades include leadership roles in medical organizations, prestigious awards, and serving as a sought-after speaker and keynote address giver. Dr Tandulwadkar's philanthropic efforts include co-founding the Solo Research Foundation, dedicated to improving healthcare accessibility.

Her legacy embodies unwavering commitment, innovation, and compassion in healthcare, shaping Obstetrics and Gynecology, IVF, and Endoscopy fields, and inspiring countless individuals.

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