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Review

Biology of the Corpus luteum

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Abstract

Corpus luteum (CL) is a small, transient endocrine gland formed following ovulation from the secretory cells of the ovarian follicles. The main function of CL is the production of progesterone, a hormone which regulates various reproductive functions. Progesterone plays a key role in the regulation of the length of estrous cycle and in the implantation of the blastocysts. Preovulatory surge of luteinizing hormone (LH) is crucial for the luteinization of follicular cells and CL maintenance, but there are also other factors which support the CL development and its functioning. In the absence of pregnancy, CL will cease to produce progesterone and induce itself degradation known as luteolysis. This review is designed to provide a short overview of the events during the life span of corpus luteum (CL) and to make an insight in the synthesis and secretion of its main product – progesterone. The major biologic mechanisms involved in CL development, function, and regression will also be discussed.

INTRODUCTION

Corpus luteum (CL) is a transient endocrine gland, established by residual follicular wall cells (granulosa and theca cells) following ovulation. During each ovarian cycle, up to 20 primordial follicles are activated in order to start the maturation process, but in humans usually only one reaches full maturity and ovulates, while remainders regress (Figure 1). The main secretory product of CL is progesterone, which is required for the establishment and maintenance of pregnancy. Additionally, progesterone serves as a negative feedback mechanism to the hypothalamus to suppress further follicular development (Figure 2). The inadequate progesterone production is the major cause of infertility and embryonic loss, since progesterone is essential for both endometrial growth and embryo survival. In the absence of implantation, or at the end of the pregnancy CL will cease to produce progesterone and its tissue mass will decrease in size, accompanied by loss of cellular integrity. This process allows the start of a new ovarian cycle *(1)*.

Although the term »corpus luteum« was introduced in 1681 by Marcello Malpighi in a letter to Jacobo Spon, the first description and drawings of the CL was made by Regnier de Graaf (1641–1673) who notified »globular bodies« in ovaries of pregnant rabbits *(2)*. The correct physiological function of the CL was not reported until 1901, when it was proven that mated rabbits did not maintain their pregnancies if all of their CL were destroyed *(3)*.

In mammals four types of CL can be distinguished, based on their lifespan and steroidogenic activity: CL of the pregnancy is the only one which is present in all species, CL of the cycle which is not present in induced ovulators (rabbits, ferets, cats etc.), CL of the lactation, present

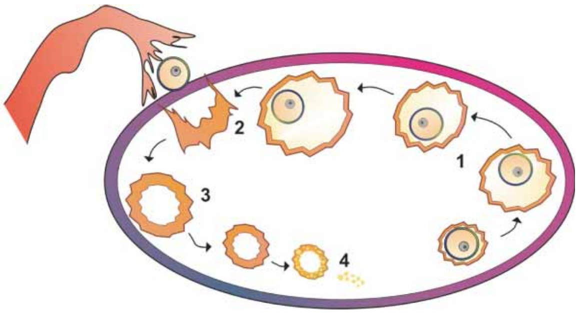

Figure 1. *The ovarian cycle in humans is divided into 3 phases: (1) Follicular phase characterized with activation of up to 20 primordial follicles in order to begin the maturation process, but usually only one reaches full maturity, (2) Ovulatory phase in which the cumulus-oocite complex is released from ovulating follicle, and (3) Luteal phase when CL develops from follicular wall and produces hormones (prevalently progesterone). If fertilization does not occur and an ovum does not implant into the uterine wall, CL degenerates and forms the corpus albicans (4). In case that implantation does occur, the developing placenta secretes chorionic gonadotrophin which prevents degeneration of the corpus luteum and prolongs secretion of progesterone. In humans, placenta is sufficiently developed after 5–6 weeks and then becomes the main organ of progesterone secretion.*

only in species which ovulate after partiturion and CL of the pseudopregnancy which does not exist in primates *(4)*. Only in rodents all four types of CL can be detected. Extrapolating findings regarding the type of CL between species come with difficulties, for example, there are clear differences in luteal cell compartmentalization and dependence on pituitary LH for steroidogenesis (Sanders and Stouffer, 1996) that distinguish primates (macaques and women) from most domestic animals (e.g.

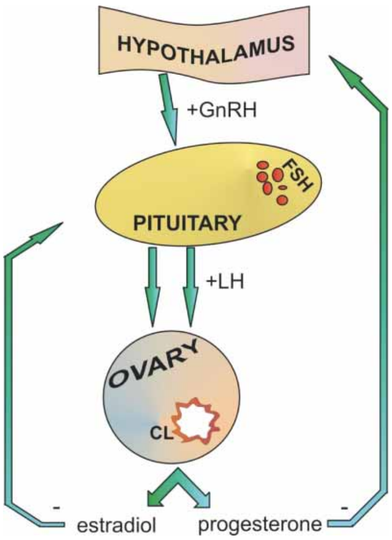

Figure 2. *Scheme of feedback mechanisms that control CL function. Together with estradiol, progesterone suppresses pituitary gonadotrophin release during the luteal phase of the cycle. Increasing concentrations of progesterone following ovulation gradually reduce the frequency of the GnRH/LH pulses and increase their amplitude. During this phase, FSH is synthesized and stored ready for release when the corpus luteum fails.*

cows and sheep) and rodents *(5)*. There are also morphologic and temporal variations in the process of corpus luteum development and maintenance among species, such as strict time point of follicular cell differentiation into luteal cells, as well as the size and role of the theca lutal cells *(5)*. Corpus luteum of the cycle has the shortest lifespan of any tissue structure in the mammalian body. In women, its function ceases after two weeks, while in rodents this period is even shorter. The end of CL function is followed by its transformation into inactive corpus albicans (CA). The association of various types of immune cells with the CL during its development and regression indicates that the immune system is involved in CL maintenance and function.

Corpus luteum is formed following ovulation, but the real stimulus for luteinization represents the preovulatory LH surge from hypophysis. Even in case when ovulation does not occur, granulosa cells will differentiate and form CL, while oocyte will be trapped within the non-ovulating structure *(6, 7)*. Also, the progesterone production can occur even if ovulation fails, so the mechanism of luteinization does not depend on the rupture of the follicle. Conversely, oocyte release from the follicle is not a guarantee of normal development and function of CL *(8, 9)*.

Development of the corpus luteum

Mature preovulatory follicle which proceeds to the CL, contains oocyte surrounded with granulosa cells (so called cumulus oophorus), immersed in the follicular fluid and surrounded with the follicular wall. In the follicular wall, which is formated from granulosa cells, until ovulation there are no other structures than cellular (capillaries, blood cells and nerve processes). The follicular basal lamina separates granulosa cells from the surrounding stromal theca layers in antral follicles *(10, 11)*. *P*reovulatory decrease of gap junctions induces the cumulus oocyte complex (COC) detachment from the follicular wall which makes COC free-floating structure within the antrum.

Preovulatory surge of Luteinizing Hormone (LH) from the pituitary gland induces the activation of LH receptor (LH-R) on the follicular cells and initiates ovulation. Simultaneously, LH induces the transformation of ovulated follicle cells into the CL, a process known as luteinization. The consequences of LH surge include preturbances in intracellular signaling, gene regulation and remodeling of tissue structures within booth cell populations of the distinct ovarian compartments *(12–14)*. Following expulsion of the ovum, the granulosa cell layer is thrown into follicular antrum, which contains follicular fluid and blood elements. At the same time the basement membrane that divides the avascular follicular wall (granulosa cells) from theca layer degrades. These processes facilitate the invasion of numerous cell types: theca cells, fibroblasts, and especially, endothelial cells into the incipient CL. *(15, 16)*. Remodeling associated with luteinization also includes changes in extracellular matrix adhesion molecules such as integrin $\alpha5$, which is not present on human follicular granulosa cells, but is acquired during luteinization *(17)*. Collagen type IV, ligand of integrin α2, increases in granulosa cells at ovulation, and persists through luteinization *(18)*. Integrin α6β1 is also present in early corpora lutea and interacts with laminin and CD9, both involved in cell adhesion and migration *(19)*. The temporal and differentiation--dependent expression of adhesion molecules confirms their involvement in initiation and implies their role in induction of CLs occurrence.

Changes in thecal microvasculature begin immediately after LH surge, starting the formation of new vessels in developing CL. The human female reproductive tract is highly dependent on Vascular endothelial grow factor (VEGF) for normal development of the CL *(20)*. This intensive blood vessel formation is often compared with angiogenesis in rapidly growing and aggressive tumors. Newly formed blood vessels enable mature CL to receive one of the greatest rates of blood flow of any tissue in the body *(21)*. The duration of this intense angiogenic phase in the CL varies among species, and is characterized by the development of a high-density capillary network, where microvascular endothelial cells are the most abundant and proliferating cells in the CL *(22)*. Additionally, the direct interaction of blood platelets with granulosa cells was demonstrated to promote progesterone production by granulosa cells. Platelets regulate spatiotemporal construction of vascular networks in the early human CL *(23)*.

During folicular development, both types of follicular cells (granulosa and theca cells) simultaneously produce the estradiol, which is a potent mitogen of granulosa cells *(24)*. However, as a consequence of LH surge, granulosa cells exit the cell cycle, exhibit altered patterns of expression of cyclin D2 and p27 and undergo terminal differentiation *(25)*. Although the division of granulosa cells is stopped (mitotic arrest) there is an evidence of residual mitosis in theca layer and fibroblasts, while endothelial cells divide in terms of forming new vessels *(22, 26)*.

During CL development, different cell types are not strictly segregated into distinct compartments as they are in the follicle. The human CL contains steroidogenic cells of two sizes; the larger and the smaller form. Larger form of cells predominates in number, while smaller cells are restricted to clusters in the periphery of the gland, associated with the vascular septa *(26)*. Following their differentiation, these steroid producing cells are often described as small lutheal or large luteal cells based on their size. Alternatively, these same cell types are described as theca-lutein or granulosa-lutein cells, based on their recognized origin. Although both cells produce progesterone, their function is regulated by different mechanisms. Large cells exhibit higher basal steroid production but are less or not responsive to addition of LH, while small luteal cells bind respond to administration of LH with pronounced increase in progesterone synthesis *(27)*. Evidence for two steroidogenic cell types in CL has been reported in primates, rodents and domestic farm animals. However, in response to lutheotropins, the steroidogenic cells of CL, regardless of their cellular origin, provide the required progesterone levels to initiate uterine quiescence and glandularisation in preparation and establishment of pregnancy *(28)*.

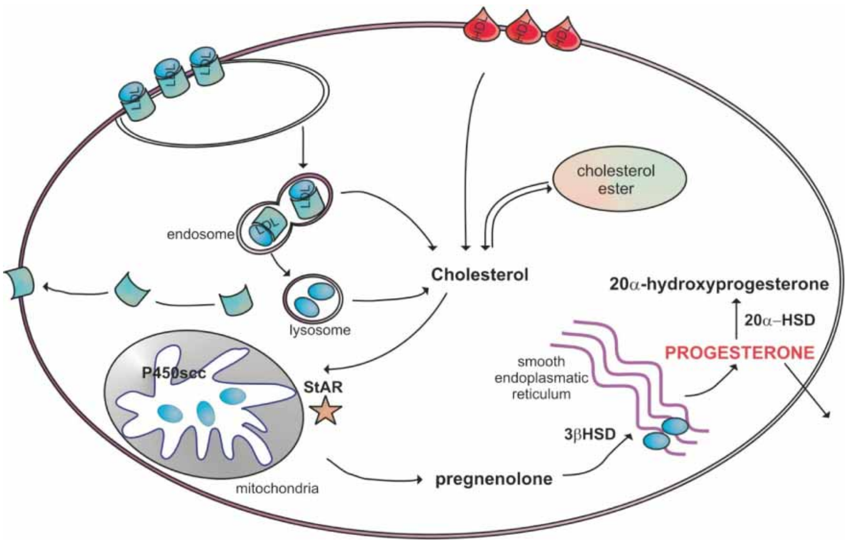

Figure 3. *Pathway for progesterone biosynthesis in a luteal cell. Three sources of cholesterol can be used as substrate for progesteron synthesis: low density lipoprotein (LDL); high density lipoprotein (HDL) and hydrolysed cholesterol esters by cholesterol esterase (CE). Free cholesterol is transported to the mitochondria with the involvement of cytoskeletal elements and sterol carrier proteins. Cholesterol is then transported from the outer to the inner mitochondrial membrane, and this process involves steroidogenic acute regulatory protein (StAR), peripheral type benzodiazepine receptors and endozepine. Cholesterol is converted to pregnenolone in mitochondria by cytochrome P450scc, and finally to progesterone by 3β-hydroxysteroid dehydrogenase, Δ5, Δ4 isomerase (3β-HSD) in the smooth endoplasmic reticulum. Ones sintesyzed, progesterone either diffuses from luteal cells or can be submited to the intraluteal inactivation by 20α-HSD enzime which is necessary for species with short ovarian cycle.*

Progesterone production

During the formation of CL differentiation into cells capable of producing progesterone at high rates is accomplished by increased expression of enzymes necessary for conversion of cholesterol to progesterone (cholesterol side--chain cleavage cytochrome *P*-450 complex (*P*-450scc) and 3β-hydroxysteroid dehydrogenase/Δ^5, Δ^4 isomerase (3β-HSD). At the same time expression of the enzymes that convert progesterone to estrogens decreases *(29)*. During its lifetime, human CL has been estimated to secrete 10–40 mg/day of progesterone *(26)*.

Cholesterol is the biosynthetic precursor of progesterone and is provided by low – or high-density lipoproteins (Figure 3). Once free cholesterol is inside the cell, it can further be used for steroidogenesis, or stored as cholesterol esters in lipid droplets (esterified with long-chain fatty acids). When needed for steroidogenesis, free cholesterol in the cytosol is bounded by Steroidogenic acute regulatory protein (StAR) and transported into the mitochondria. So far, most likely the main role in this process, together with Star, has the peripheral-type benzodiazepine receptor (PBR). Transport of the lipophilic cholesterol into the mitochondria through the aqueous phase between two membranes is the rate limiting step in hormone biosynthesis and the step most acutely influenced by second messengers *(30–33)*. On the inner mitochondrial membrane the *P*-450scc enzyme cleaves the side chain from cholesterol to form pregnenolone *(34)*. Phosphorylation of StAR by protein kinase A (PKA) stimulates cholesterol transport, whereas phosphorylation by Protein kinase C (PKC) may inhibit this process. Endozepine, the natural ligand for PBR, also appears to be involved in the regulation of the rate of cholesterol transport to the inner mitochondrial membrane and play a role in the stimulatory effects of PKA on steroidogenesis *(35)*. Increased concentrations of endozepine were detected in large luteal cells, and may explain the increased progesterone secretion from this type of cell.

Pregnenolone formatted in mitochondria has two hydrophilic residues that make it less stable in cellular membranes and more mobile through cell compartments. Pregnenolone is transported to the smooth endoplasmatic reticulum, where is then converted to progesterone by 3β-HSD. Progesterone diffuses out of the cell and into the bloodstream to be transported to target tissues. When sufficient, progesterone is converted to apparently inactive 20α-hydroxyprogesterone which has important regulatory role in certain species *(36)*. This process is induced by activation of luteal 20α-hidroxysteroid dehidrogenase (20α-HSD) situated in luteal cytosol *(36)*.

Control of Corpus Luteum

Corpus luteum is not an autonomous organ. Its function is controlled by the interaction of several tropic hormones secreted by the pituitary gland, the decidua and the placenta. After ovulation, during the luteal phase of the cycle, LH pulses stimulate the progesterone release, a process essential for normal endometrial transformation.

The critical role for LH in regulation of CL function and support of progesterone secretion in primates has been confirmed, while in rodents, the crucial role for CL development and production belongs to prolactin (PRL) *(36–38)*. Approximately one-half of all luteal phase deficiencies are the result of improper function of the gonadothropin releasing hormone (GnRH) pulse from hypothalamus *(39)*. Growth hormone (GH) is also necessary for normal luteal development, shown to increase progesterone concentrations in the serum *(40)*. Thus, it is accepted that hormonal signals from hypophisis are critical for CL development and normal course of luteal phase of ovarian (estrus) cycle. In pregnancy, prolonged function of the CL is enacted by the trophoblastic secretion of chorionic gonadotropin (hCG) and progesterone production is secured until the luteo-placental shift is completed, and the placenta is able to sustain the required level of progesterone synthesis *(34)*.

However, CL has some level of autonomy, which is established by its own progesterone production. Synthesized progesterone supports its own generation, affecting transcription of genes encoding steroidogenic enzymes in lutheal cells. Additionally, products of luteal origin *i.e.* prostaglandins (PG) I2 and E2, oxytocin, noradrenaline and Insulin like growth factor-1 (IGF-1) play a role in regulation of progesterone synthesis *(41)*. Moreover, high progesterone concentrations in luteal cells protect these cells from apoptosis, while the impairment of steroidogenesis, or reduced ability of progesterone production leads to luteal cells death *(42, 43)*. In fact, the endocrine function of luteal cells subpopulations is critical for the maintenance of CL function, including neovacularization and steroid hormones production.

Corpus Luteum regression

In the absence of pregnancy, corpus luteum self destructs. Maintenance of CL is the result of precise interaction between pituitary and embryonic gonadotropins, as well as intraluteal autocrine and paracrine signals that modulate the endocrine function of luteal cells. In the absence of uterine and embryonic signals, progesterone production decreases. The administration of gonadotropin releasing hormones (GnRH) antagonists causes a rapid decline in progesterone secretion from mature CL in primates, while in cattle and rodents this effect is less dramatic *(34)*.

Process of CL regression – Luteolysis is defined as loss of function and subsequent involution of luteal structure. Luteolytic process is characterized by a decrease in progesterone synthesis and subsequent involution of luteal structure with increased rates of different types of cell death *(41, 44)*. The expression of VEGF and molecules that promote endothelial cell survival is diminished *(45)*, resulting in degeneration of vasculature as well as steroidogenic cells. Total volume density of blood vessels decreases during early luteolysis. Nevertheless, some of the large microvessels are still maintained, most likely to assist the resorption of luteal mass, and ultimately of corpus albicans *(21)*. Whilst a temporal pattern of luteolysis is well established, molecular factors which regulate luteal regression and mechanisms of »luteal rescue« by gonadotrophins still remain partly understood *(46)*.

In contrast to prostaglandins (PG) I2 and E2, which support CL development and maintenance, the prostaglandin F2α induces a marked decrease in secretion of progesterone from the CL *in vivo* and from large luteal cells *in vitro*, which appears to be mediated via the effects of the PKC system *(47)*. Prostaglandin F2α has the main role in initiation of lutheolysis in most nonprimate species *(48)*, but there are accumulating evidence that intraluteal PGF2α may also contribute to decrease of progesterone secretion and demise of the CL in primates *(49, 50)*. The treatment with PGF2α decreases luteal concentrations of mRNA encoding receptor for LH, LDL, StAR and 3β-HSD, whereas mRNA encoding receptors for HDL and P450scc are not altered significantly *(51)*. Prostaglandin F2α treatment also reduces ovarian and luteal blood flow and induces DNA fragmentation and apoptosis resulting in cell death, apparently as a result of increased intracellular free calcium *(48)*. Endothelin 1 is also described as a factor involved in PGF2α mediated destruction of luteal tissue *(52)*.

Apoptosis plays a significant part in CL regression in animals and humans. The initiation of apoptosis is not apparent until several hours after the onset of the decline in plasma progesterone (functional luteolysis) and increases significantly during late luteal phase, indicating its role in CL regression *(53)*. The expression of TNF-α and Caspase-3 correlates to some extent with the apoptosis rate, while other apoptosis related factors (Bcl-2, Bax and NK-kB) remain relatively constant throughout the luteal phase *(54)*. Additional processes contributing CL regression include lipid peroxidation, which induces membrane damage, and the loss of gonadotropin receptors increases during luteolysis, thus resulting in the decrease of steroidogenic capacity. On the other hand, the resultant pro-oxidative status enhances COX2 protein abundance, which amplifies ovarian PGF2α secretion *(53)*. Increase in matrix metalloproteinase expression (MMP-2 and MMP-9) is an additional important component of CL structural regression *(54–56)*.

Depending on the microenvironment, TNF can stimulate cell proliferation or induce apoptosis. In ovary TNF can be implicated in follicular development and CL regression *(57, 58)*. Experiments on tumor necrosis factor receptor type I knockout mice revealed irregular estrous cycles and an inordinate amount of time in diestrus, suggesting a defect in luteal regression *(59)*.

TNFα inhibits both luteal cell progesterone and estradiol secretion in vitro *(60)*, since luteal cells and endothelial cells are capable of TNFα synthesis. However, macrophages remain the primary ovarian source of TNFα *(48)*. The number of these cells increases throughout the luteal phase to a maximum in the late-luteal phase *(61)*. HCG's Luteal »rescue« is associated with a marked reduction in the numbers of tissue macrophages *(62)*, while increase in the percentage of CD8+ T cells and decrease in anti-inflammatory cytokines leads to inflammatory and cytolytic events that take part in the final luteal regression *(53)*.

Luteal Dysfunction

During the preimplantation period, the uterus undergoes important developmental changes stimulated by progesterone; hence, disorders related to its secretion are likely to affect the pregnancy outcome. Inadequate CL progesterone production causes delayed or otherwise abnormal pattern of endometrial development which leads to disorder classically described as Luteal phase deficiency (LPD) *(63)*. In humans progesterone level in serum lower than 10 ng/mL strongly suggest the inability of successful pregnancy. Luteal phase defect is a relatively uncommon but important cause of infertility and/or habitual abortion. Approximately one-half of all LPD are due to improper function of the GnRH pulse generator, namely, following ovulation the increased serum progesterone levels oversuppress the GnRH pulse generator, resulting in improper luteal function. Many other endocrinological abnormalities such as thyroid disease, hypoparathyroidism or uncontrolled diabetes also can disturb this highly coordinated and delicately balanced hypothalamic-pituitary-ovarian axis and adversely affect the quality and duration of CL *(64)*. In this context LPD may be classified as a subtle form of ovarian dysfunction. In cases where the corpus luteum is LH-responsive, such as the hypothalamic corpus luteum insufficiency and the large luteal cell defect, treatment with GnRH or hCG is advisable. In the case of LH/hCG – unresponsibility, it is defect of small luteal cell, and progesterone substitution is suggested *(65)*. Series of case reports have recorderd microorganisms affecting the ovary, but the studies directly addressing the influence of infection on ovarian function leaves its mechanisms open to speculation. Possible mechanisms include an alteration in vascular supply of developing CL, interference with the paracrine regulation of CL maintenance, as well as direct tissue damage *(66)*.

Concluding remarks

In the field of female reproductive health the investigation of CL is necessary to address relevant questions not only in infertility issues, but also in the development of contraceptive methods. Our understaining of CL function has been greatly facilitated by the analysis of murine CL function and maintenance. Targeted mutagenesis in this model is frequently used to study the process of ovulation in which many of inflammatory factors are involved, mechanisms of CL development, which have a lot of similarities with tumorigenesis, as well as the process of luteolysis when CL clearly retains the potential for high rates of apoptosis and therefore presents an useful model for examining molecular mechanisms of apoptotic cell death.

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