

Abanico Veterinario. January-December 2019; 9:1-21. <http://dx.doi.org/10.21929/abavet2019.924>

Original article. Received: 06/02/2019. Accepted: 28/10/2019. Published: 05/11/2019.

Review: Function and regression of the corpus luteum during the estrous cycle

Revisión: Función y regresión del cuerpo lúteo durante el ciclo estral de la vaca

Aréchiga-Flores Carlos*, Cortés-Vidauri Zimri, Hernández-Briano Pedro,
Flores-Flores Gilberto Rochín-Berumen Fabiola, Ruiz-Fernández Eduardo

¹ Academic Unit of Veterinary Medicine and Zootechnics, Autonomous University of Zacatecas, Zacatecas, Mexico. *Responsible and correspondent author: Aréchiga-Flores Carlos. Academic Unit of Veterinary Medicine and Zootechnics of the Autonomous University of Zacatecas; Juarez Garden No. 147, Col. Centro, Zacatecas, Zacatecas, Mexico, CP 98000. arechiga.uaz@gmail.com, mvzzcv@hotmail.com, phbriano@gmail.com, doktorflores@yahoo.com.mx, fabiolauaz@outlook.com, halcon58@hotmail.com

ABSTRACT

The corpus luteum (CL) is an ovarian structure that produces progesterone to maintain pregnancy, begins its growth from the third day of the beginning of estrus growing until the eighteenth day. If the CL is fertilized, the formation of the embryo will produce the interferon τ (IFN- τ) substance responsible for maternal recognition of pregnancy (RMG) in cattle during their entire pregnancy. When CL is not fertilized, the uterine endometrium secretes prostaglandins F2 α (PGF2 α) causing lysis of the corpus luteum. The serum levels of progesterone decrease generating hypothalamus unlocking and gonadotropin-releasing hormone (GnRH) secretion to activate the hypothalamic-pituitary-gonadal axis that develops new follicles 48 to 72 h later and initiates a new estrus. This bibliographic review details the physiological mechanisms involved in the formation of the corpus luteum during the estrous cycle of cattle in the function and regression of the corpus luteum during the estrous cycle of cows.

Key words: bovine, corpus luteum, progesterone, prostaglandins, luteolysis.

RESUMEN

El cuerpo lúteo (CL) es una estructura ovárica que produce progesterona para mantener la gestación, inicia su crecimiento a partir del tercer día de iniciado el estro creciendo hasta el décimo octavo día. Si, el CL es fertilizado la formación del embrión producirá el interferón τ (IFN- τ) sustancia responsable del reconocimiento materno de la gestación (RMG) en los bovinos durante toda su gestación. Al no ser fertilizado el CL el endometrio uterino secreta prostaglandinas F2 α (PGF2 α) causando la lisis del cuerpo lúteo. Los niveles séricos de la progesterona disminuyen generando desbloqueo del hipotálamo y secreción de la hormona liberadora de gonadotropinas (GnRH) para activar el eje hipotalámico-hipofisiario-gonadal que desarrolla folículos nuevos de 48 a 72 h posteriores e inicia un nuevo estro. La presente revisión bibliográfica detalla los mecanismos fisiológicos involucrados en la formación del cuerpo lúteo durante el ciclo estral de los bovinos.

Palabras clave: bovinos, cuerpo lúteo, progesterona, prostaglandinas, luteolisis.

INTRODUCTION

In cows, CL develops from theca and granulosa cells, both components of the ovulatory follicle that house the oocyte. From these structures small and large cells are formed to form the CL that produces the hormone progesterone (P4), but in non-pregnant females it undergoes regression at the end of the estrous cycle (Niswender *et al.*, 1985). (Cortés-Vidauri *et al.*, 2018). Progesterone exerts a negative feedback on the hypothalamus and pituitary gland to reduce the secretion of gonadotropins (hormones FSH and LH), and prevent subsequent ovulations (Stevenson and Britt, 1972; Ireland and Roche, 1982; Wiltbank *et al.*, 2002); and the possible participation of other factors is not ruled out (Gosselin *et al.*, 2000).

Regression of the corpus luteum decreases progesterone secretion to levels prior to the formation of CL. The cow presents another zeal with ovulation and a new opportunity to mate and conceive (Hansel *et al.*, 1973; Juengel *et al.*, 1993; Miyamoto *et al.*, 2009). The prostaglandin F2 α (PGF2 α) produced in the uterine endometrium performs the regression of the CL by decreasing the blood flow to the ovary, decreases the cyclic adenosine monophosphate (cAMP), known as the second messenger and the steroidogenic action; It causes a decrease in the number of hormonal receptors for luteinizing hormone as well as the presence and action of nitric oxide. Currently there is information related to the regression of the CL generated by different groups of researchers, but it is dispersed. Therefore, the present literature review aims to analyze and discuss, succinctly, the role of CL, as well as the participation of PGF2 α in its functional and structural regression.

CORPUS LUTEUM

The corpus luteum (CL) is a transient progesterone-producing gland, in the cow it is formed from the ovulatory follicle-forming cells (theca and granulosa). This hormone regulates the duration of the estrous cycle and suppresses ovulation, thereby reducing cyclic function (Rodgers *et al.*, 1988). But in pregnant females it maintains pregnancy, providing the embryo with the uterine conditions suitable for its development and that of the mammary gland (Niswender *et al.*, 2000).

The CL is composed of steroidogenic parenchymal cells secreting progesterone and non-parenchymal cells; endothelial vascular cells, lymphocyte and macrophage fibroblasts (O'Shea *et al.*, 1989; Lei *et al.*, 1991; Reynolds and Redmer, 1999). The majority of steroidogenic cells are located adjacent to the capillaries (Zheng *et al.*, 1993). Angiogenesis is composed of condensed blood vasculature and develops under the influence of angiogenic factors, stimulated by vascular endothelial growth factor A and basic fibroblastic growth factor, among others (Connolly, 1991; Ferrara and Davis-Smyth, 1997; Reynolds and Redmer, 1999; Berisha and Schams, 2005). These factors and their receptors have high gene expression during the development of CL, but it is reduced in the middle part of the luteal phase (Berisha *et al.*, 2000; 2008). In the CL there are 2 cell

types: 1) large luteal cells (CLG), originating from granular cells of the ovarian follicle), and 2) small luteal cells (CLP), originating from theca cells. Internal ovarian follicle that ovulates after estrus and forms a transitional structure called the hemorrhagic body (CH). The corpus luteum is subsequently formed with both cell types, which synthesize progesterone (P4); hormone responsible for pregnancy.

CLGs have receptors for the FSH hormone and CLP; they have receptors for the hormone LH. Therefore, the hormone progesterone (P4) is synthesized by the influence of luteinizing hormone (LH); but progesterone is also stimulated by its own secretion of autocrine and paracrine bio-regulators (Skarzynski and Okuda, 1999; Duras *et al.*, 2005). In addition, it stimulates the production of prostaglandins (F2 α and E2) and oxytocin at the beginning of the cycle, but inhibits the secretion of prostaglandin F2 α in the middle part (Skarzynski and Okuda, 1999; Okuda *et al.*, 2004). Therefore, intraluteal progesterone promotes CL survival by stimulating its own secretion (Juengel *et al.*, 1993; Rueda *et al.*, 1997a, b; Okuda *et al.*, 2004).

CL in the cow produces vasoactive factors to regulate blood flow, such as the production of progesterone, nitric oxide (NO) (Skarzynski *et al.*, 2000a, b; Zerani *et al.*, 2007; Kowalczyk-Zieba *et al.*, 2014), endothelin-1 (Girsh *et al.*, 1995; 1996a, b; Miyamoto *et al.*, 1997), angiotensin-II (Hayashi *et al.*, 2000) and prostaglandin F2 α (Shemesh and Hansel, 1975a, b; Miyamoto *et al.*, 1993). But in cattle, progesterone secretion increases as angiogenesis and luteal cell proliferation occur during the first 6 days after ovulation. The increase can range from 1 ng/ml three days after ovulation, to 3 ng/ml at 6 days post-ovulation; reaching the highest blood concentration from 10 to 14 days. Subsequently, there is a reduction in progesterone after day 16, until the level it had at the beginning of the cycle caused by prostaglandin F2 α , the hormone responsible for its regression (Skarzynski *et al.*, 2003a; b).

SYNTHESIS OF PROGESTERONE

Progesterone (P4) is synthesized from cholesterol, the luteal cell obtains them from the blood circulation linked to low-density lipoproteins (LDLP) and high density (HDLP) (Grumer and Carroll, 1988; Carroll *et al.*, 1992). If necessary, the luteal cell synthesizes cholesterol from the acetate that is stored inside the cell as a cholesterol ester, by the action of the acyl CoA cholesterol acyl transferase. The neutral cholesterol esterase enzyme transforms the cholesterol ester into cholesterol when required (Grumer and Carroll, 1988).

To start steroid synthesis, cholesterol must penetrate the mitochondria and transform into pregnenolone. In response to a steroidogenic stimulus, the acute steroid regulatory protein (STAR) transports cholesterol into the mitochondria and the fragmenting enzyme of the cytochrome P450 side chain transforms it into pregnenolone (Stocco and Ascoli, 1993; Stocco, 1997; 2001). Finally, in the smooth endoplasmic reticulum, pregnenolone

is transformed into low progesterone, the action of the enzyme 3β -hydroxy steroid dehydrogenase (Holt, 1989; Rabiee *et al.*, 1999; Niswender, 2002).

Progesterone can promote its own secretion in the luteal cell or act on its white organ (Niswender and Nett, 1994; Niswender *et al.*, 1994). LH simultaneously increases the expression of the coding genes for the synthesis of the StAR protein and the fragmenting enzymes of the P450 and 3β -hydroxy-steroid dehydrogenase side chain (Kotwica *et al.*, 2004; Rekawiecki *et al.*, 2005). Other factors that promote the synthesis of progesterone through enzymes that participate in the synthesis of progesterone, are progesterone itself, norepinephrine and prostaglandin E2 (PGE2) (Kotwica *et al.*, 2002; 2004; Rekawiecki *et al.*, 2005; Freitas de Melo and Ungerfeld, 2016; Berisha *et al.*, 2018). Progesterone, in turn, also stimulates the luteal secretion of PGE2 (Kotwica *et al.*, 2004) and norepinephrine synthesis of oxytocin (Bogacki and Kotwica, 1999).

P4 exerts a negative feedback on the synthesis of GnRH produced by hypothalamic neurons; Therefore, GnRH, FSH and LH are suppressed. P4 reduces the amount of GnRH receptors for the anterior pituitary gland (adenohypophysis). On the other hand, P4 exerts a positive influence on the uterine endometrium and favors the secretion of materials into the uterine lumen; although it also inhibits the myometrium, it reduces contractions and tonicity; Even P4 promotes alveolar development in the mammary gland during pregnancy.

CL REGRESSION

During the regression of the CL, it is very important that the ovary remains the same size and the luteal cells disappear. Endogenous prostaglandin F2 α promotes the corpus luteum regression (luteolysis) at the end of the estrous cycle (Niswender *et al.*, 1976; McCracken *et al.*, 1981; Lindell *et al.*, 1982; Acosta *et al.*, 2002). The process starts from day 17 to 19 of the cycle (McCracken *et al.*, 1999). Progesterone secretion is reduced to baseline levels, negative feedback on the hypothalamus-pituitary axis disappears; consequently begins another estrous cycle, the cow presents a new opportunity to conceive.

Prostaglandin F2 α is produced in the uterine endometrium, due to the estradiol-oxytocin interaction (Hansel *et al.*, 1975; Ham *et al.*, 1975; Hansel and Blair, 1996; Burns *et al.*, 1997). Estradiol increases the secretion of prostaglandin F2 α and stimulates the synthesis of receptors for oxytocin in the endometrium; Oxytocin acts on the uterine endometrium, stimulating the secretion of prostaglandin F2 α in pulsatile form. Prostaglandin F2 α of uterine origin stimulates the secretion of F2 α in luteal cells, in a process of self-amplification to complete luteolysis (Kumagai *et al.*, 2014).

The action of prostaglandin F2 α on the corpus luteum is both functional and structural; both reactive oxygen species (ROS), which include nitric oxide (NO), superoxide and the anion hyperoxide of O₂ metabolism, participate (Juengel *et al.*, 1993; Pate, 1994; Rueda *et al.*, 1997a, b; Meidan *et al.*, 1999). Reactive species are compounds with an oxygen

molecule, carrying an unpaired electron (Aruoma, 1999; Aruoma *et al.*, 1999; Young and Woodside, 2001). Unstable chemical entities, reactive and ephemeral life, with the ability to combine with most of the molecules that are part of the cellular structure; carbohydrates, lipids, proteins and nucleic acids (Attaran *et al.*, 2000; Szczpanska *et al.*, 2003; Van Langendonck *et al.*, 2002).

PGF stimulates ON synthesis in CL endothelial cells, stimulating intraluteal production of PGF (Acosta *et al.*, 2009; Lee *et al.*, 2009; Lao *et al.*, 2009; Lee *et al.*, 2009; Skarzynski *et al.*, 2003a; b; Lee *et al.*, 2010). PGF 2α binds to its receptors in the plasma membrane of luteal cells, the formation of the PGF 2α and receptor complex; they open the Ca ++ channels, allowing their entry into the intracellular space, initiating the processes of apoptosis in luteal cells. CL is a vascularized organ with abundant endothelial cells that produce nitric oxide (ON), inhibiting the synthesis and secretion of progesterone (Lei *et al.*, 1991; Lao *et al.*, 2009; Lee *et al.*, 2009) (Korzekwa *et al.*, 2004, 2006; 2007; 2014; Skarzynski and Okuda, 2000); as well as the apoptosis of the luteal cells (Korzekwa *et al.*, 2006; 2014).

The binding of the prostaglandin F 2α -receptor complex stimulates the synthesis of protein kinase type C (PK-C), which simultaneously inhibits the synthesis of P4. Functionally the corpus luteum reduces the secretion of progesterone, in its structure the degradation of the luteal tissue, apoptosis and necrosis is generated; until its volume decreases and disappears (Niswender *et al.*, 1976; McCracken *et al.*, 1999; Acosta *et al.*, 2002; Stocco *et al.*, 2007). Functional luteolysis is performed 12 h after the injection of PGF 2α , and 12 h later the structural luteolysis is performed (Neuvias *et al.*, 2004a; b; Mishra *et al.*, 2018).

CL FUNCTIONAL REGRESSION

ON prevents the synthesis and secretion of progesterone by inhibiting the expression of the StAR protein, as well as the fragmenting enzymes of the cytochrome P450scc and 3- β HSD side chain (Sessa *et al.*, 1994; Sawada and Carlson, 1996; Skarzynski and Okuda, 2000; Korzekwa *et al.*, 2004, 2006; 2007; 2014; Girsh *et al.*, 1995; 1996a, b; Skarzynski *et al.*, 2003a; b; Rekawiecki *et al.*, 2005). Consequently, cholesterol cannot enter the mitochondria and the available cholesterol within it will not be transformed into pregnenolone, and will not become progesterone. The level of progesterone decreases to a baseline concentration and the negative feedback on the hypothalamus-pituitary axis will be removed, another zeal will be presented and a new opportunity of pairing and conceive.

CL STRUCTURAL REGRESSION

The structural regression of CL is performed by apoptosis and physiological necrosis of steroidogenic luteal cells (Juengel *et al.*, 1993; Rueda *et al.*, 1995, 1997a; b; Tilly, 1996; Korzekwa *et al.*, 2006; Park *et al.* 2017).

Apoptosis

Apoptosis is the programmed cell death in a physiological model, where the cell designs and executes its own death. It is performed through genetically encoded cell collapse with cellular shrinkage; protein disintegration, chromatin condensation and DNA degradation; in addition to cell fragmentation and formation of apoptotic bodies. Finally, neighboring cells such as fibroblasts or epithelial cells, phagocytize apoptotic bodies without triggering an inflammatory reaction (Compton, 1992).

La apoptosis se realiza por medio de las caspasas (Clarke, 1990; Clark y Lampert 1990; Tilly, 1996; Carambula *et al.*, 2002); las cuales se han considerado como sus ejecutoras que participan como iniciadoras y ejecutoras del proceso (Cohen, 1997). La lutéolisis se lleva a cabo en las células lúteas esteroidogénicas (SLC) y en las células lúteas endoteliales (LEC) (Juengel *et al.*, 1993; Rueda *et al.*, 1995; 1997a,b). Su actividad la llevan a cabo principalmente a través de una vía extrínseca, por un dominio de muerte o receptor, y por vía intrínseca de tipo mitocondrial.

Extrinsic via

The extrinsic via is executed by a wide variety of factors involved in apoptosis (Friedman *et al.*, 2000; Petroff *et al.*, 2001; Taniguchi *et al.*, 2002; Okuda *et al.*, 2004; Korzekwa *et al.*, 2006; Hojo *et al.*, 2010; 2016) as the tumor necrosis factor α (TNF), interferon- γ (IFNG), FAS ligand (FASL) and nitric oxide (NO) (Friedman *et al.*, 2000; Petroff *et al.*, 2001; Nakamura and Sakamoto, 2001; Taniguchi *et al.*, 2002; Korzekwa *et al.*, 2006; Hojo *et al.*, 2010; 2016). These factors have also been found to participate in the vascular regression of CL; for example, the type 1 TNF receptor (TNFR1); as well as the related protein called Fas (CD95) and its ligand (Fas ligand); they have intracellular death domains that recruit adapter proteins such as the death domain associated with the TNF receptor (TRADD) and the death domain associated with Fas (FADD); also, cysteine proteases such as caspases. The binding of the death ligand with its corresponding receptor leads to the formation of a binding site for the adapter protein, as a consequence a ligand-receptor-adapter complex known as DISC (signaling complex that induces death) is formed. This assembles and activates pro-caspase 8, with the subsequent constitution of caspase-8, an active form of the enzyme that will constitute the initiating caspase and establishing the caspase cascade. In the cow's CL, TNF is located (Sakamoto *et al.*, 2011), and induces interferon- γ and Fas in the apoptosis process, by increasing the activation of caspase-3 (Taniguchi *et al.*, 2002); which is finally the effector molecule (Nagata, 1997; Muzio *et al.*, 1998).

Intrinsic via

The intrinsic pathway begins within the cell through internal stimuli such as hypoxia; Caspase is activated during apoptosis at the mitochondrion level, which stimulates the

union of pro-apoptosis caspase with mitochondria, and inhibits the association of anti-apoptosis Bcl-2. This leads to the filtration of cytochrome-c from the mitochondria into the cytosol, which promotes the formation of apoptosome and triggers the activation of the Caspase effector (Scaffidi *et al.*, 1998). In the Bcl family there are two groups; pro-apoptotic proteins, such as Bax and anti-apoptotic, such as Bcl-2. Its function as noted, is related to the release of cytochrome-c, for the formation of apoptosome, and to activate caspase. Pro and anti-apoptotics release and slow the release of cytochrome-c from the mitochondria into the cytoplasm, respectively. Based on the above, the activation of the deadly pathway involves the release of cytochrome-c within the cytosol, which in turn promotes the formation of apoptosome and activation of the effector caspase-3, with subsequent DNA fragmentation (Thorneberry and Lazebnik, 1998), in the final step of apoptosis (Scaffidi *et al.*, 1998).

The participation of ON is done through the stimulation of Bax proapoptotic expression, with no effect on the expression of Fas and Bcl-2 RNA (Korzekwa *et al.*, 2006). Consequently, the ratio of Bcl-2 to bax decreases, ratio of Bcl-2 mRNA and Bax mRNA in bovine CL, decreases in luteolysis; In addition, in these cells in vitro, ON stimulates the expression and activity of caspase-3 (Skarzynski *et al.*, 2005; Korzekwa *et al.*, 2006). ON also increases the production of intraluteal PGF2 α and reduces the expression of mRNA superoxide dismutase (SOD) and its protein in 24-hour culture of bovine LECs (Lee *et al.*, 2010). The increase in intraluteal PGF constitutes an amplification system, where a small stimulus triggers a series of reactions that increase the cellular response; in this way it increases its function, and the reduction of SOD to increase intraluteal super oxide. The reduction of SOD at 24 h could increase the intraluteal accumulation of SO for the promotion of structural luteolysis (Nakamura and Sakumoto, 2001; Buttke and Sandstrom, 1994; Rothstein *et al.*, 1994; Suhara *et al.*, 1998). SOD catalyzes the dismutation of superoxide to H₂O₂ and oxygen, and as a consequence keeps it below the level of superoxide (Fridovich, 1995).

Necroptosis

Apoptosis can be performed by a mechanism independent of caspases, as an alternate route for cell death or necroptosis and is carried out by receptors that interact with protein kinase (RIPK) such as 1 (RIPK1) and 3 (RIPK3) (Festjens *et al.*, 2007; Hitomi *et al.*, 2008; Degterev *et al.*, 2008; Degterev *et al.*, 2008; Declercq *et al.*, 2009; Cho *et al.*, 2009; He *et al.*, 2009; Zhang *et al.*, 2009; Christofferson and Yuan, 2010; Vandenabeele *et al.*, 2010). RIPK1 binds to the membrane of TNFR1 and FAS; Apoptosis inducing ligand receptors TNF1 (TRAILR1) and 2 (TRAILR2), to trigger the necroptotic pathway of members of the TNF receptor super family (Holler *et al.*, 2000). RIPK3 is a necessary modulator for necroptosis, but particularly TNFR1 and FAS. (Taniguchi *et al.*, 2002; Cho *et al.*, 2009; He *et al.*, 2009; Zhang *et al.*, 2009; Vanlangerakker *et al.*, 2012). (Zhang *et al.*, 2009; Vanlangerakker *et al.*, 2012; Moujalled *et al.*, 2013). Necroptosis-dependent RIPKs

participate in bovine structural luteolysis (Christofferson and Yuan, 2010; Vandenabeele *et al.*, 2010).

BLOOD IRRIGATION

Prostaglandin F2 α participates in vasodilation and in the vasoconstriction of CL (Wiltbank *et al.*, 1995; Díaz *et al.*, 2002); in spontaneous luteolysis and application of exogenous F2 α prostaglandin, an increase in blood flow continues in the periphery of the corpus luteum (Acosta *et al.*, 2002; Miyamoto *et al.*, 2005; Ginther *et al.*, 2007; Miyamoto and Shirasuna, 2009; Shirasuna *et al.*, 2012). This is due to the ON which has vasodilator capacity and directly inhibits the secretion of progesterone, inducing apoptosis of the luteal cells (Skarzynski *et al.*, 2003a, b; Shirasuna *et al.*, 2008a, b, c; Shirasuna *et al.*, 2012). The effect of prostaglandin on the secretion of ON and the acute increase in blood flow at the periphery of the corpus luteum has been considered the first physiological indicator of luteolysis (Shirasuna *et al.*, 2008a, b, c; 2010; 2012). The influence of prostaglandin F2 α on nitric oxide has been proven by its effect on intermediates.

The application of prostaglandin F2 α stimulates the endothelial expression of nitric oxide synthase (enzyme responsible for transforming L-arginine into nitric oxide) in the corpus luteum, 30 minutes after its application, with the corresponding increase in luteal blood flow (Shirasuna *et al.*, 2008a, b, c). On the other hand, the effect of nitric oxide on blood flow has been demonstrated through its promotion and inhibition. The supplier of nitric oxide (S-nitroso-N-acetyl-D, L-pellicilamine) in the corpus luteum, induces an acute increase in blood flow and shortens the estrous cycle. In addition, the injection of nitric oxide synthase inhibitor (L-NG-nitroarginine methyl ester) into the corpus luteum completely suppresses the acute increase in blood flow caused by prostaglandin F2 α , and delays the onset of luteolysis (Shirasuna *et al.*, 2008b).

Prostaglandin F2 α , after its vasodilator effect, limits the supply of oxygen and nutrients to the corpus luteum to culminate luteolysis by inhibiting angiogenesis, angiolytic and vasoconstriction (Guilbault *et al.*, 1984; Acosta *et al.*, 2002). Thirty minutes after the injection of prostaglandin F2 α in the middle part of the cycle; down regulation of RNAm expression of vascular endothelial growth factor and basic trophoblastic growth factor has been observed; as well as the protein expression of vascular endothelial growth factor A (Berisha *et al.*, 2008; Shirasuna *et al.*, 2010). With this, prostaglandin F2 α inhibits the development of thin and subsequently thick blood vessels (Hojo *et al.*, 2009).

Prostaglandin F2 α stimulates the biosynthesis of endothelin-1 (EDN1) and the expression of its RNAm; as well as angiotensin II (Ang II) and the expression of the angiotensin-converting enzyme, both *in vivo* and *in vitro* (Girsh *et al.*, 1996b; Miyamoto *et al.*, 1997; Hayashi and Miyamoto, 1999). These are potent vasoconstrictors that operate in response to prostaglandin F2 α to reduce blood supply, and therefore decrease the

availability of oxygen and nutrients to the corpus luteum during luteolysis (Girsh *et al.*, 1996a; Miyamoto *et al.*, 1997; Hayashi and Miyamoto, 1999). EDN1 and Ang II have also been found to inhibit progesterone secretion in the corpus luteum *in vitro* (Stirling *et al.*, 1990; Girsh *et al.*, 1996a; Miyamoto *et al.*, 1997), which places them as factors that they participate in functional luteolysis.

Circulating concentrations of progesterone are determined by a balance between primary production of P4, by the CL; and the metabolism of P4, by the liver. The volume of the luteal tissue, the number and functionality of the large luteal cells are the main factors that determine the production of the hormone progesterone (Gregson *et al.*, 2016). The metabolic rate of P4 is usually determined by hepatic blood flow and can be very important, especially in dairy cows, to determine the circulating concentrations of progesterone (P4).

By performing artificial time insemination (IATF), it has been possible to increase the concentrations of P4, by increasing the number of CLs, inducing the appearance of an accessory CL, or by supplementing exogenous sources of the P4 hormone. Controlling the diet can also modify P4 concentrations; however, there are still no practical strategies that allow altering P4 in the diet at the field level and in a practical way. By raising P4 before artificial fixed-time insemination (IATF), double ovulations are generally reduced and fertility of fixed-time insemination is increased. By raising P4 at the time of AI, it generates slight increases in circulating P4, possibly due to an inadequate luteal regression that could compromise fertility in response to AI. By raising P4 after AI, circulating levels of P4 are critical for embryonic growth and the establishment and maintenance of pregnancy. Several studies have attempted to increase fertility by increasing circulating levels of P4 after IATF. There is a meta-analysis that indicates a slight increase in fertility (3 to 3.5 %), mainly in first-birth cows (Wiltbank *et al.*, 2014). Future research should focus on manipulating P4 in the cow to ensure greater success in reproductive function.

CONCLUSION

The ovarian corpus luteum is an ephemeral life gland that produces the hormone progesterone. Progesterone exerts negative feedback on the hypothalamus and pituitary gland to reduce gonadotropin secretion to avoid ovulations. In cows that do not conceive PGF2 α , it regresses, which reduces the secretion of progesterone to levels that were recorded before its formation. The regression of the corpus luteum is functional and structural. In the functional regression the synthesis and secretion of progesterone is prevented, but the structural regression is carried out by means of apoptosis and necroptosis of the steroidogenic luteal cells. PGF2 α participates in the irrigation of the corpus luteum by providing nutrients.

Therefore, in future research, the manipulation of circulating prostaglandins should be concentrated to ensure greater reproductive success, mainly when fixed or predetermined insemination programs are applied in bovine females.

CITED LITERATURE

ACOSTA E, Peña Ó, Naftolin F, Avila J, Palumbo A. 2009. Angiotensin II induces apoptosis in human mural granulosa-lutein cells, but not in cumulus cells. *Fertility and Sterility*. 91(5):1984-1989. <https://doi.org/10.1016/j.fertnstert.2008.04.026>

ACOSTA TJ, Bah MM, Korzekwa A, Woclawek-Potocka I, Markiewicz W, Jaroczewski JJ, Okuda K, Sharzynski DJ. 2009. Acute changes in circulating concentrations of progesterone and nitric oxide and partial pressure of oxygen during prostaglandin F_{2α}-induced luteolysis in cattle. *Journal of Reproduction and Development*. 55(2):149-155. <https://doi.org/10.1262/jrd.20133>

ACOSTA TJ, Yoshizawa N, Ohtani M, Miyamoto A. 2002. Local changes in blood flow within the early and midcycle corpus luteum after prostaglandin F_{2α} injection in the cow. *Biology of Reproduction*. 66(3):651-658. <https://doi.org/10.1095/biolreprod66.3.651>

ARUOMA OI. 1999. Antioxidant actions of plant foods: use of oxidative DNA damage as a tool for studying antioxidant efficacy. *Free Radical Research*. 30(6):419-427. <https://doi.org/10.1080/10715769900300461>

ARUOMA OI, Spencer JPE, Mahmood N. 1999. Protection against oxidative damage and cell death by the natural antioxidant ergothioneine. *Food and Chemical Toxicology*. 37(11):1043-1053. [https://doi.org/10.1016/S0278-6915\(99\)00098-8](https://doi.org/10.1016/S0278-6915(99)00098-8)

ATTARAN M, Pasqualotto E, Falcone T, Goldberg JM, Miller KF, Agarwal A, Sharma RK. 2000. The effect of follicular fluid reactive oxygen species on the outcome of in vitro fertilization. *International Journal of Fertility and Women's Medicine*. 45(5):314-320. (PMID:11092702).

BERISHA B, Schams D. 2005. Ovarian function in ruminants. *Domestic Animal Endocrinology*. 29(2):305-317. <https://doi.org/10.1016/j.domaniend.2005.02.035>

BERISHA B, Schams D, Kosman M, Amselgruber W, Einspanier R. 2000. Expression and tissue concentration of vascular endothelial growth factor, its receptors, and localization in the bovine corpus luteum during estrous cycle and pregnancy. *Biology of Reproduction*. 63(4):1106-1114. <https://doi.org/10.1095/biolreprod63.4.1106>

BERISHA B, Schams D, Rodler D, Sinowat, F, Pfaffl MW. 2018. Changes in the expression of prostaglandin family members in bovine corpus luteum during the oestrous cycle and pregnancy. *Molecular Reproduction and Development*. 85(7):622-634. <https://doi.org/10.1002/mrd.22999>

BERISHA B, Steffl M, Welter H, Kliem H, Meyer HH, Schams D, Amselgruber W. 2008. Effect of the luteinising hormone surge on regulation of vascular endothelial growth factor and extracellular matrix-degrading proteinases and their inhibitors in bovine follicles. *Reproduction, Fertility and Development*. 20(2):258-268. <https://doi.org/10.1071/RD07125>

- BOGACKI M, Kotwica J. 1999. Influence of noradrenaline on progesterone synthesis and posttranslational processing of oxytocin synthesis in the bovine corpus luteum. *Theriogenology*. 52(1):91-102. [https://doi.org/10.1016/S0093-91X\(99\)00112-0](https://doi.org/10.1016/S0093-91X(99)00112-0)
- BURNS PD, Spitzer JC, Henricks DM. 1997. Effect of dietary energy restriction on follicular development and luteal function in nonlactating beef cows. *Journal of Animal Science*. 75(4):1078-1086. <https://doi.org/10.2527/1997.7541078x>
- BUTTKE TM, Sandstrom PA. 1994. Oxidative stress as a mediator of apoptosis. *Immunology Today*. 15(1):7-10. [https://doi.org/10.1016/0167-5699\(94\)90018-3](https://doi.org/10.1016/0167-5699(94)90018-3)
- CARAMBULA SF, Matikainen T, Lynch MP, Flavell RA, Dias Gonçalves PB, Tilly JL, Rueda BR. 2002. Caspase-3 is a pivotal mediator of apoptosis during regression of the ovarian corpus luteum. *Endocrinology*. 143(4):1495-1501. <https://doi.org/10.1210/endo.143.4.8726>
- CARROLL DJ, Grummer RR, Mao FC. 1992. Progesterone production by cultured luteal cells in the presence of bovine low-and high-density lipoproteins purified by heparin affinity chromatography. *Journal of Animal Science*. 70(8):2516-2526. <https://doi.org/10.2527/1992.7082516x>
- CHO Y, Challa S, Moquin D, Genga R, Ray TD, Guildford M, Chan FKM. 2009. Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. *Cell*. 137(6):1112-1123. <https://doi.org/10.1016/j.cell.2009.05.037>
- CHRISTOFFERSON DE, Yuan J. 2010. Necroptosis as an alternative form of programmed cell death. *Current Opinion in Cell Biology*. 22(2):263-268. <https://doi.org/10.1016/j.ceb.2009.12.003>
- CLARK DM, Lampert IA. 1990. Apoptosis is a common histopathological finding in myelodysplasia: the correlate of ineffective haematopoiesis. *Leukemia & Lymphoma*. 2(6):415-418. <https://doi.org/10.3109/10428199009069295>
- CLARKE PG. 1990. Developmental cell death: morphological diversity and multiple mechanisms. *Anatomy and Embriology*. 181(3):195-213. <https://doi.org/10.1007/BF00174615>
- COHEN GM. 1997. Caspases: the executioners of apoptosis. *Biochemistry Journal*. 326(1):1-16. DOI: 10.1042/bj3260001
- COMPTON MM. 1992. A biochemical hallmark of apoptosis: internucleosomal degradation of the genome. *Cancer and Metastasis Reviews*. 11(2):105-119. <https://doi.org/10.1007/BF00048058>
- CONNOLLY DT. 1991. Vascular permeability factor: a unique regulator of blood vessel function. *Journal of Cellular Biochemistry*. 47(3):219-223. <https://doi.org/10.1002/jcb.240470306>
- CORTÉS-VIDAURI Z, Aréchiga-Flores C, Rincón-Delgado M, Rochín-Berumen F, López-Carlos M, Flores-Flores G. 2018. Revisión: El Ciclo Reproductivo de la Yegua. *Abanico Veterinario*. 8(3):14-41. ISSN-e 2007-428X, ISSN 2448-6132. <http://dx.doi.org/10.21929/abavet2018.83.1>
- DECLERCQ W, Berghe TV, Vandenabeele P. 2009. RIP kinases at the crossroads of cell death and survival. *Cell*. 138(2):229-232. <https://doi.org/10.1016/j.cell.2009.07.006>

DEGTEREV A, Hitomi J, Germscheid M, Ch'en IL, Korkina O, Teng X, Abbott D, Cuny GD, Yuan C, Wagner G, Hedrick SM, Gerber SA, Lugovskoy A, Yuan J. 2008. Identification of RIP1 kinase as a specific cellular target of necrostatins. *Nature Chemical Biology*. 4(5):313-321 <https://doi.org/10.1038/nchembio.83>

DÍAZ FJ, Anderson LE, Wu YL, Rabot A, Tsai SJ, Wiltbank MC. 2002. Regulation of progesterone and prostaglandin F₂ α production in the CL. *Molecular and Cellular Endocrinology*. 191(1): 65-80. [https://doi.org/10.1016/S0303-7207\(02\)00056-4](https://doi.org/10.1016/S0303-7207(02)00056-4)

DURAS M, Mlynarczyk J, Kotwica J. 2005. Non-genomic effect of steroids on oxytocin-stimulated intracellular mobilization of calcium and on prostaglandin F₂ α and E₂ secretion from bovine endometrial cells. *Prostaglandins and Other Lipid Mediators*. 76(1-4):105-116. <https://doi.org/10.1016/j.prostaglandins.2005.02.001>

FERRARA N, Davis-Smyth T. 1997. The biology of vascular endothelial growth factor. *Endocrine Reviews*. 18(1):4-25. <https://doi.org/10.1210/edrv.18.1.0287>

FESTJENS N, Berghe TV, Cornelis S, Vandenabeele P. 2007. RIP1, a kinase on the crossroads of a cell's decision to live or die. *Cell Death and Differentiation*. 14(3):400-410. <https://doi.org/10.1038/sj.cdd.4402085>

FREITAS-DE-MELO A, Ungerfeld R. 2016. Progesterona y respuesta de estrés: mecanismos de acción y sus repercusiones en rumiantes domésticos. Revisión. *Revista Mexicana de Ciencias Pecuarias*. 7(2):185-199. Versión On-line ISSN 2448-6698. Versión impresa ISSN 2007-1124. http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S2007-11242016000200185&lng=es&nrm=iso

FRIDOVICH I. 1995. Superoxide radical and superoxide dismutases. *Annual Review of Biochemistry*. 64(1):97-112. <https://doi.org/10.1146/annurev.bi.64.070195.000525>

FRIEDMAN A, Weiss S, Levy N, Meidan R. 2000. Role of tumor necrosis factor α and its type I receptor in luteal regression: induction of programmed cell death in bovine corpus luteum-derived endothelial cells. *Biology of Reproduction*. 63(6):1905-1912. <https://doi.org/10.1095/biolreprod63.6.1905>.

GINTHER OJ, Silva LA, Araujo RR, Beg MA. 2007. Temporal associations among pulses of 13, 14-dihydro-15-keto-PGF₂ α , luteal blood flow, and luteolysis in cattle. *Biology of Reproduction*. 76(3):506-513. <https://doi.org/10.1095/biolreprod.106.057653>

GIRSH E, Greber Y, Meidan R. 1995. Luteotrophic and luteolytic interactions between bovine small and large luteal-like cells and endothelial cells. *Biology of Reproduction*. 52(4):954-962. <https://doi.org/10.1095/biolreprod52.4.954>

GIRSH E, Milvae RA, Wang W, Meidan R. 1996a. Effect of endothelin-1 on bovine luteal cell function: role in prostaglandin F₂ α -induced antisteroidogenic action. *Endocrinology*. 137(4):1306-1312. <https://doi.org/10.1210/en.137.4.1306>

GIRSH E, Wang W, Mamluk R, Arditi F, Friedman A, Milvae RA, Meidan R. 1996b. Regulation of endothelin-1 expression in the bovine corpus luteum: elevation by prostaglandin F₂ α . *Endocrinology*. 137(12):5191-5196. <https://doi.org/10.1210/endo.137.12.8940334>

GOSSELIN N, Price CA, Roy R, Carriere PD. 2000. Decreased LH pulsatility during initiation of gonadotropin superovulation treatment in the cow: evidence for negative feedback other than estradiol and progesterone. *Theriogenology*. 54(4): 507-521. [https://doi.org/10.1016/S0093-691X\(00\)00366-6](https://doi.org/10.1016/S0093-691X(00)00366-6)

GREGSON E, Webb R, Sheldrick EL, Campbell BK, Man GE, Liddell S, Sinclair KD. 2016. Molecular determinants of a competent bovine corpus luteum: first vs final wave dominant follicles. *Reproduction*. REP-15-0415 Online ISSN: 1741-7899. Print ISSN: 1470-1626.

GRUMMER RR, Carroll DJ. 1988. A Review of lipoprotein cholesterol metabolism: importance to ovarian function. *Journal of Animal Science*. 66(12):3160-3173. <https://doi.org/10.2527/jas1988.66123160x>

GRUMER RR, Carroll DJ. 1991. Effects of dietary fat on metabolic disorders and reproductive performance of dairy cattle. *Journal of Animal Science*. 69(9):3838-3852. <https://doi.org/10.2527/1991.6993838x>

GUILBAULT LA, Thatcher WW, Foster DB, Caton D. 1984. Relationship of 15-Keto-1 β , 14-Dihydro-Prostaglandin F $_{2\alpha}$ concentrations in peripheral plasma with local uterine production of F series prostaglandins and changes in uterine blood flow during the early postpartum period of cattle. *Biology of Reproduction*. 31(5):870-878. <https://doi.org/10.1095/biolreprod31.5.870>.

HAM EA, Cirillo VJ, Zanetti ME, Kuehl FA. 1975. Estrogen-directed synthesis of specific prostaglandins in uterus. *Proceedings of the National Academy of Sciences*. 72(4):1420-1424. <https://doi.org/10.1073/pnas.72.4.1420>

HANSEL W, Concannon PW, Lukaszewska J. 1973. Corpora lutea of the large domestic animals. *Biology of Reproduction*. 8(2):222-245. ISSN 0006-3363; EISSN 1529-7268

HANSEL W. 1975. "Luteal regression in domestic animals". En: *Annales de Biologie Animale Biochimie Biophysique*. 15(2):147-160. EDP Sciences. ISSN: 0003-388X.

HANSEL W, Blair RM. 1996. Bovine corpus luteum: a historic overview and implications for future research. *Theriogenology*. 45(7):1267-1294. [https://doi.org/10.1016/0093691X\(96\)00098-2](https://doi.org/10.1016/0093691X(96)00098-2)

HAYASHI K, Acosta TJ, Berisha B, Kobayashi S, Ohhtani M, Schams D, Miyamoto A. 2003. Changes in prostaglandin secretion by the regressing bovine corpus luteum. *Prostaglandin Other Lipid Mediators*. 70:339-349. [https://doi.org/10.1016/S0090-6980\(02\)00148-X](https://doi.org/10.1016/S0090-6980(02)00148-X)

HAYASHI K, Miyamoto A. 1999. Angiotensin II interacts with prostaglandin F $_{2\alpha}$ and endothelin-1 as a local luteolytic factor in the bovine corpus luteum in vitro. *Biology of Reproduction*. 60(5):1104-1109. <https://doi.org/10.1095/biolreprod60.5.1104>

HAYASHI K, Miyamoto A, Berisha B, Kosmann MR, Okuda K., Schams D. 2000. Regulation of angiotensin II production and angiotensin receptors in microvascular endothelial cells from bovine corpus luteum. *Biology of Reproduction*. 62(1):162-167. <https://doi.org/10.1095/biolreprod62.1.162>

HE S, Wang L, Miao L, Wang T, Du F, Zhao L, Wang X. 2009. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF- α . *Cell*. 137(6):1100-1111. <https://doi.org/10.1016/j.cell.2009.05.021>

- HITOMI J, Christofferson DE, Ng A., Yao J, Degterev A, Xavier RJ, Yuan J. 2008. Identification of a molecular signaling network that regulates a cellular necrotic cell death pathway. *Cell*. 135(7):1311-1323. <https://doi.org/10.1016/j.cell.2008.10.044>
- HOJO T, Al-Zi'Abi MO, Skarzynski DJ, Acosta TJ, Okuda K. 2009. Changes in the vasculature of bovine corpus luteum during the estrous cycle and prostaglandin F2 α -induced luteolysis. *Journal of Reproduction and Development*. 55(5):512-517. <https://doi.org/10.1262/jrd.20257>
- HOJO T, Oda A, Lee SH, Acosta TJ, Okuda K. 2010. Effects of tumor necrosis factor α and Interferon on the viability and mRNA expression of TNF receptor type I in endothelial cells from the bovine corpus luteum. *Journal of Reproduction and Development*. 56(5):515-519. <https://doi.org/10.1262/jrd.10-056T>
- HOJO T, Siemieniuch MJ, Lukasik K, Piotrowska-Tomala KK, Jonczyk AW, Okuda K, Skarzynski DJ. 2016. Programmed necrosis-a new mechanism of steroidogenic luteal cell death and elimination during luteolysis in cows. *Scientific Reports*. 6:38211. <https://doi.org/10.1038/srep38211>
- HOLLER N, Zaru R, Micheau O, Thome M, Attinger A, Valitutti S, Bodmer JL, Schneider P, Seed B, Tschopp J. 2000. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. *Nature Immunology*. 1(6):489-495. <https://doi.org/10.1038/82732>
- HOLT JA. 1989. Regulation of progesterone production in the rabbit corpus luteum. *Biology of Reproduction*. 40(2):201-208. <https://doi.org/10.1095/biolreprod40.2.201>
- IRELAND JJ, Roche JF. 1982. Effect of progesterone on basal LH and episodic LH and FSH secretion in heifers. *Reproduction*. 64(2): 295-302. <https://doi.org/10.1530/jrf.0.0640295>
- JUENGEL JL, Garverick HA, Johnson AL, Youngquist RS, Smith MF. 1993. Apoptosis during luteal regression in cattle. *Endocrinology*. 132(1):249-254. <https://doi.org/10.1210/en.132.1.249>
- KINDAHL H, Edqvist LE, Larsson K, Malmqvist A. 1982. Influence of prostaglandins on ovarian function post partum. *Current Topics in Veterinary Medicine and Animal Science*. <http://www.nal.usda.gov/>
- KORZEKWA AJ, Jaroszewski JJ, Bogacki M, Deptula KM, Maslanka TS, Acosta TJ, Okuda K, Skarzynski DJ. 2004. Effects of prostaglandin F2 α and nitric oxide on the secretory function of bovine luteal cells. *Journal of Reproduction and Development*. 50(4):411-417. <https://doi.org/10.1262/jrd.50.411>
- KORZEKWA AJ, Lukasik K, Pilawski W, Piotrowska-Tomala KK, Jaroszewski JJ, Yoshioka S, Okuda K, Skarzynski DJ. 2014. Influence of prostaglandin F2 α analogues on the secretory function of bovine luteal cells and ovarian arterial contractility in vitro. *The Veterinary Journal*. 199(1):131-137. <https://doi.org/10.1016/j.tvjl.2013.09.021>
- KORZEKWA AJ, Murankami S, Woclawek-Potocka I, Bah MM, Pilawski W, Okuda K, Skarzynski DJ. 2006. Nitric oxide induces apoptosis in bovine luteal cells. *Journal of Reproduction and Development*. 52(3):353-361. <https://doi.org/10.1262/jrd.17092>
- KORZEKWA A, Woclawek-Potocka I, Okuda K., Acosta TJ, Skarzynski DJ. 2007. Nitric oxide in bovine corpus luteum: possible mechanisms of action in luteolysis. *Animal Science Journal*. 78(3):233-242. <https://doi.org/10.1111/j.1740-0929.2007.00430.x>

- KOTWICA J, Bogacki M, Rekawiecki R. 2002. Neural regulation of the bovine corpus luteum. *Domestic Animal Endocrinology*. 23(1-2):299-308. [https://doi.org/10.1016/S0739-7240\(02\)00165-0](https://doi.org/10.1016/S0739-7240(02)00165-0)
- KOTWICA J, Rekawiecki R, Duras M. 2004. Stimulatory influence of progesterone on its own synthesis in bovine corpus luteum. *Bulletin-Veterinary Institute in Pulawy*. 48(2):139-146. ISSN 2450-7393. eISSN 2450-8608
- KOWALCZYK-ZIEBA I, Boruszezewska D, Sinderewicz E, Skarzynski DJ, Woclawek-Potocka I. 2014. Influence of lysophosphatidic acid on nitric oxide-induced luteolysis in steroidogenic luteal cells in cows. *Biology of Reproduction*. 90(1):p17, 1-11. <https://doi.org/10.1095/biolreprod.113.113357>
- KUMAGAI A, Yoshioka S, Sakumoto R, Okuda K. 2014. Auto - amplification system for prostaglandin F2 α in bovine corpus luteum. *Molecular Reproduction and Development*. 81(7):646-654. <https://doi.org/10.1002/mrd.22332>
- LAO F, Li W, Han D, Liu Y, Zhao Y, Chen C. 2009. Fullerene derivatives protect endothelial cells against NO-induced damage. *Nanotechnology*. 20(22):225103. <https://doi.org/10.1088/0957-4484/20/22/225103>
- LEE S, Acosta TJ, Nakagawa Y, Okuda K. 2010. Role of nitric oxide in the regulation of superoxide dismutase and prostaglandin F2 α production in bovine luteal endothelial cells. *Journal of Reproduction and Development*. 56(4):454-459. <https://doi.org/10.1262/jrd.10-013K>
- LEE SH, Acosta TJ, Yoshioka S, Okuda K. 2009. Prostaglandin F2 α regulates nitric oxide generating system in bovine luteal endothelial cells. *Journal of Reproduction and Development*. 55(4):418-424. <https://doi.org/10.1262/jrd.20205>
- LEI ZM, Chegini N, Rao CV. 1991. Quantitative cell composition of human and bovine corpora lutea from various reproductive states. *Biology of Reproduction*. 44(6):1148-1156. <https://doi.org/10.1095/biolreprod44.6.1148>
- LINDELL JO, Kindahl H, Jansson L, Edqvist LE. 1982. Post-partum release of prostaglandin F2 α and uterine involution in the cow. *Theriogenology*. 17(3):237-245. [https://doi.org/10.1016/0093-691X\(82\)90085-1](https://doi.org/10.1016/0093-691X(82)90085-1)
- MCCANN SM, Mastronardi C, de Laurentis A, Tettori V. 2005. Nitric oxide theory of aging revisited. *Annals of New York Academy Sciences*. 1057:64-84. <https://doi.org/10.1196/annals.1356.064>
- MCCRACKEN JA. 1981. The identification of prostaglandin F2 α as a uterine luteolytic hormone and the hormonal control of its synthesis. *Acta Vet Scand suppl*. 77:71-88. NII Article ID (NAID) 10026621725
- MCCRACKEN JA, Custer EE, Lamsa JC. 1999. Luteolysis: a neuroendocrine mediated event. *Physiological Reviews*. 79(2):263-323. <https://doi.org/10.1152/physrev.1999.79.2.263>
- MEIDAN R, Milvae RA, Weiss S, Levy N, Friedman A. 1999. Intraovarian regulation of luteolysis. *Journal of Reproduction and Fertility suppl*. 54:217-228. (PMID:10692857).
- MISHRA GK, Patra MK, Sheikh PA, Teeli AS, Kharayat NS, Karikalan M, Bag S, Singh SK, Das GK, Narayanan K, Kumar H. 2018. Functional characterization of corpus luteum and its association with peripheral progesterone profile at different stages of estrous cycle in the buffalo. *Journal of Animal Research*. 8(3):507-512. <http://dx.doi.org/10.30954/2277-940X.06.2018.28>

- MIYAMOTO A, Kobayashi S, Arata S, Ohtani M, Fukui Y, Schams D. 1997. Prostaglandin F2 α promotes the inhibitory action of endothelin-1 on the bovine luteal function in vitro. *Journal of Endocrinology*. 152(2):R7-R11. <https://doi.org/10.1677/joe.0.152R007>
- MIYAMOTO A, Lützow Hv, Schams D. 1993. Acute actions of prostaglandin F2 α , E2, and 12 in microdialyzed bovine corpus luteum in vitro. *Biology of Reproduction*. 49(2):423-430. <https://doi.org/10.1095/biolreprod49.2.423>
- MIYAMOTO A, Shirasuna K. 2009. Luteolysis in the cow: a novel concept of vasoactive molecules. *Animal Reproduction*. 6(1):47-59. ISSN 1806-9614.
- MIYAMOTO A, Shirasuna K, Sasahara K. 2009. Local regulation of corpus luteum development and regression in the cow: impact of angiogenic and vasoactive factors. *Domestic Animal Endocrinology*. 37(3): 159-169. <https://doi.org/10.1016/j.domaniend.2009.04.005>
- MIYAMOTO A, Shirasuna K, Wijayagunawardane MPB, Watanabe S, Hayashi M, Yamamoto D, Matsui M, Acosta TJ. 2005. Blood flow: a key regulatory component of corpus luteum function in the cow. *Domestic Animal Endocrinology*. 29(2):329-339. <https://doi.org/10.1016/j.domaniend.2005.03.011>
- MONCADA S. 1991. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacological Reviews*. 43:109-142. NII Article ID (NAID) 10009922604
- MOUJALLED DM, Cook WD, Okamoto T, Murphy J, Lawlor KE, Vince JE, Daux & Vaux DL. 2013. TNF can activate RIPK3 and caused programmed necrosis in the absence of RIPK1. *Cell Death Diseases*. 4:e465. PMID: 23328672
- MUZIO M, Stockwell BR, Stennicke HR, Salvesen GS, Dixit VM. 1998. An induced proximity model for caspase-8 activation. *Journal of Biological Chemistry*. 273(5):2926-2930. DOI: 10.1074/jbc.273.5.2926
- NAGATA S. 1997. Apoptosis by death factor. *Cell*. 88(3):355-365. [https://doi.org/10.1016/S0092-8674\(00\)81874-7](https://doi.org/10.1016/S0092-8674(00)81874-7)
- NAKAMURA T, Sakamoto K. 2001. Reactive oxygen species up-regulates cyclooxygenase-2, p53, and Bax mRNA expression in bovine luteal cells. *Biochemical and Biophysical Research Communications*. 284(1):203-210. <https://doi.org/10.1006/bbrc.2001.4927>
- NEUVIANS TP, Berisha B, Schams D. 2004a. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) expression during induced luteolysis in the bovine corpus luteum. *Molecular Reproduction and Development*. 67:389–395. <https://doi.org/10.1002/mrd.20032>
- NEUVIANS TP, Schams D, Berisha B, Pfaffl MW. 2004b. Involvement of pro-inflammatory cytokines, mediators of inflammation, and basic fibroblast growth factor in prostaglandin F2 α -induced luteolysis in bovine corpus luteum. *Biology of Reproduction*. 70(2):473–480. <https://doi.org/10.1095/biolreprod.103.016154>
- NISWENDER GD. 2002. Molecular control of luteal secretion of progesterone. *Reproduction*. 123(3):333-339. ISSN: 1741-7899

NISWENDER GD, Juengel JL, McGuire WJ, Belfiore CJ, Wiltbank MC. 1994. Luteal function: the estrous cycle and early pregnancy. *Biology of Reproduction*. 50(2):239-247. <https://doi.org/10.1095/biolreprod50.2.239>

NISWENDER GD, Juengel JL, Silva PJ, Rollyson MK, McIntush EW. 2000. Mechanisms controlling the function and life span of the corpus luteum. *Physiological Reviews*. 80 (1):1-29. <https://doi.org/10.1152/physrev.2000.80.1.1>

NISWENDER GD., Nett TM. 1994. "Corpus luteum and its control in infraprimates species". En: Knobil E. and Neill JD. *The Physiology of Reproduction*. 781–816 p. Raven Press, New York, NY. NII Article ID (NAID) 10024940098

NISWENDER GD, Reimers TJ, Diekmann MA., Nett, TM. 1976. Blood flow: a mediator of ovarian function. *Biology of Reproduction*. 14(1):64-81. <https://doi.org/10.1095/biolreprod14.1.64>

NISWENDER GD, Schwall RH, Fitz TA, Farin CE, Sawyer HR. 1985. Regulation of luteal function in domestic ruminants: new concepts. En Proceedings of the 1984 Laurentian Hormone Conference. *Recent Progress in Hormone Research*. 41:101-151. <https://doi.org/10.1016/B978-0-12-571141-8.50007-X>

OKUDA K, Korzekwa A, Shibaya M, Murakami S, Nishimura R, Tsubouchi M, Woclawek-Potocka I, Skarzynski DJ. 2004. Progesterone is a suppressor of apoptosis in bovine luteal cells. *Biology of Reproduction*. 771:2065-2071. <https://doi.org/10.1095/biolreprod.104.028076>

O'SHEA JD, Rodgers RJ, D'Occhio MJ. 1989. Cellular composition of the cyclic corpus luteum of the cow. *Journal of Reproduction and Fertility*. 85(2):483-487. <https://doi.org/10.1530/jrf.0.0850483>

PARK SJ, Kim JH, Kim TS, Lee SR, Park JW, Lee S, Kim JM, Lee DS. 2017. Peroxiredoxin 2 regulates PGF2 α -induced corpus luteum regression in mice by inhibiting ROS-dependent JNK activation. *Free Radical Biology and Medicine*. 108:44-55. <https://doi.org/10.1016/j.freeradbiomed.2017.03.013>

PATE JL. 1994. Cellular components involved in luteolysis. *Journal of Animal Science*. 72(7):1884-1890. <https://doi.org/10.2527/1994.7271884x>

PENNY LA, Armstrong D, Bramley TA, Webb R, Collins RA., Watson ED. 1999. Immune cells and cytokine production in the bovine corpus luteum throughout the oestrous cycle and after induced luteolysis. *Journal of Reproduction and Fertility*. 115(1):87-96. <https://doi.org/10.1530/jrf.0.1150087>

PETROFF MG, Petroff BK, Plate JL. 2001. Mechanisms of cytokine-induced death of cultured bovine luteal cells. *Reproduction*. 121(5):753-760. Online ISSN: 1741-7899. Print ISSN: 1470-1626.

RABIEE AR, Lean IJ, Gooden JM, Miller BG. 1999. Relationships among metabolites influencing ovarian function in the dairy cow. *Journal of Dairy Science*. 82(1):39-44. [https://doi.org/10.3168/jds.S0022-0302\(99\)75206-9](https://doi.org/10.3168/jds.S0022-0302(99)75206-9)

REKAWIECKI R, Nowik M, Kotwica J. 2005. Stimulatory effect of LH, PGE2 and progesterone on StAR protein, cytochrome P540 cholesterol side chain cleavage and 3 β -hydroxysteroid dehydrogenase gene expression in bovine luteal cells. *Prostaglandins and Other Lipid Mediators*. 78(1-4):169-184. <https://doi.org/10.1016/j.prostaglandins.2005.06.009>

REYNOLDS LP, Redmer DA. 1999. Growth and development of the corpus luteum. *Journal of Reproduction and Fertility suppl.* 54:181-191. PMID: 10692854. <https://europepmc.org/oai.cgi?verb=ListRecords&from=2007-1001&metadataPrefix=pmc>

RODGERS RJ, Mitchell MD, Simpson ER. 1988. Secretion of progesterone and prostaglandins by cells of bovine corpora lutea from three stages of the luteal phase. *Journal of Endocrinology.* 118(1):121-126. <https://doi.org/10.1677/joe.0.1180121>

ROTHSTEIN JD, Bristol LA, Hosler B, Brown RH, Kuncel RW. 1994. Chronic inhibition of superoxide dismutase produces apoptotic death of spinal neurons. *Proceedings of the National Academy of Sciences USA.* 91(10):4155-4159. <https://doi.org/10.1073/pnas.91.10.4155>

RUEDA BR, Hamernik DL, Hoyer PB, Tilly JL. 1997a. "Potential regulators of physiological cell death in the corpus luteum". En: *Cell Death in Reproductive Physiology* 161-181 p. Springer, New York, NY. https://doi.org/10.1007/978-1-4612-1944-6_14

RUEDA BR, Tilly KI, Botros IW, Jolly PD, Hansen TR, Hoyer PB, Tilly JL. 1997b. Increased bax and interleukin-1 β -converting enzyme messenger ribonucleic acid levels coincide with apoptosis in the bovine corpus luteum during structural regression. *Biology of Reproduction.* 56(1):186-193. <https://doi.org/10.1095/biolreprod56.1.186>

RUEDA BR, Tilly KI, Hansen TR, Hoyer PB, Tilly JL. 1995. Expression of superoxide dismutase, catalase and glutathione peroxidase in the bovine corpus luteum: evidence supporting a role for oxidative stress in luteolysis. *Endocrine.* 3(3):227-232. <https://doi.org/10.1007/BF02994448>

SAKUMOTO R, Berisha B, Kawate N, Schams D, Okuda K. 2000. Tumor necrosis factor- α and its receptor in bovine corpus luteum throughout the estrous cycle. *Biology of Reproduction.* 62(1):192-199. <https://doi.org/10.1095/biolreprod62.1.192>

SAKUMOTO R, Verehnen M, Kenngott RA, Okuda K, Sinowatz F. 2011. Localization of gene and protein expression of tumor necrosis factor- α and tumor necrosis factor receptor types I and II in the bovine corpus luteum during the estrous cycle. *Journal of Animal Sciences.* 89:3040-3047. DOI:10.2527/jas.2010-3479

SAWADA M, Carlson JC. 1996. Intracellular regulation of progesterone secretion by the superoxide radical in the rat corpus luteum. *Endocrinology.* 137(5):1580-1584. <https://doi.org/10.1210/en.137.5.1580>

SCAFFIDI C, Fulda S, Srinivasan A, Friesen C, Li F, Tomaselli KJ, Debatin KM, Krammer PH, Peter ME. 1998. Two CD95 (APO-1/Fas) signaling pathways. *EMBO Journal.* 17:1675-1687. DOI 10.1093/emboj/17.6.1675

SCHAMS D, Berisha B. 2004. Regulation of corpus luteum function in cattle--an overview. *Reproduction in Domestic Animals.* 39(4):241-51. DOI: 10.1111/j.1439-0531.2004.00509.x

SESSA WC. 1994. The nitric oxide synthase family of proteins. *Journal of Vascular Research.* 31:131-143. DOI.org/10.1159/000159039.

SHEMESH M, Hansel W. 1975. Stimulation of prostaglandin synthesis in bovine ovarian tissues by arachidonic acid and luteinizing hormone. *Biology of Reproduction.* 13(4):448-452. <https://doi.org/10.1095/biolreprod13.4.448>

- SHEMESH M, Hansel W. 1975. Arachidonic acid and bovine corpus luteum function. *Proceedings of the Society for Experimental Biology and Medicine*. 148(1):243-246. <https://doi.org/10.3181%2F00379727-148-38514>
- SHIRASUNA K. 2010. Nitric oxide and luteal blood flow in the luteolytic cascade in the cow. *Journal of Reproduction and Development*. 56(1):9-14. <https://doi.org/10.1262/jrd.09-206E>
- SHIRASUNA K, Nitta A, Sineenard J, Shimizu T, Bollwein H, Miyamoto A. 2012. Vascular and immune regulation of corpus luteum development, maintenance, and regression in the cow. *Domestic Animal Endocrinology* 43(2):198-211. <https://doi.org/10.1016/j.domaniend.2012.03.007>
- SHIRASUNA K, Shimizu T, Sayama K, Asahi T, Sasaki M, Berisha B, Schams D, Miyamoto A. 2008a. Expression and localization of apelin and its receptor APJ in the bovine corpus luteum during the estrous cycle and prostaglandin F₂ α -induced luteolysis. *Reproduction*. 135(4):519-525. <https://doi.org/10.1530/REP-07-0409>
- SHIRASUNA K, Watanabe S, Asahi T, Wijayagunawardane MPB, Sasahara K, Jiang C, Matsui M, Sasaki M, Shimizu T, Davis JS, Miyamoto A. 2008b. Prostaglandin F₂ α increases endothelial nitric oxide synthase in the periphery of the bovine corpus luteum: the possible regulation of blood flow at an early stage of luteolysis. *Reproduction*. 135(4):527-539. <https://doi.org/10.1530/REP-07-0496>
- SHIRASUNA K, Yamamoto D, Morota K, Shimizu T, Matsui M., Miyamoto A. 2008c. Prostaglandin F₂ α stimulates endothelial nitric oxide synthase depending on the existence of bovine granulosa cells: analysis by co - culture system of endothelial cells, smooth mMuscle Cells and Granulosa Cells. *Reproduction in Domestic Animals*. 43(5):592-598. <https://doi.org/10.1111/j.1439-0531.2007.00957.x>
- SKARZYNSKI DJ, Bah MM, Deptula KM, Woclawek-Potocka I, Korzeka A, Shibaya M, Pitawski W, Okuda K. 2003a. Roles of tumor necrosis factor- α of the estrus cycle in cattle: an in vivo study. *Biology of Reproduction*. 69(6):1907-1913. <https://doi.org/10.1095/biolreprod.103.016212>
- SKARZYNSKI DJ, Jaroszewski JJ, Bah MM, Deptula KM, Barszczewska B, Gawronska B, Hansel W. 2003b. Administration of a nitric oxide synthase inhibitor counteracts prostaglandin F₂-induced luteolysis in cattle. *Biology of Reproduction*. 68(5):1674-1681. <https://doi.org/10.1095/biolreprod.102.008573>
- SKARZYNSKI DJ, Jaroszewski JJ, Okuda K. 2005. Role of tumor necrosis factor- α and nitric oxide in luteolysis in cattle. *Domestic Animal Endocrinology*. 29(2):340-346. <https://doi.org/10.1016/j.domaniend.2005.02.005>
- SKARZYNSKI DJ, Kobayashi S, Okuda K. 2000a. Influence of nitric oxide and noradrenaline on prostaglandin F₂ α -induced oxytocin secretion and intracellular calcium mobilization in cultured bovine luteal cells. *Biology of Reproduction*. 63(4):1000-1005. <https://doi.org/10.1095/biolreprod63.4.1000>
- SKARZYNSKI, DJ, Miyamoto Y, Okuda K, 2000b. Production of prostaglandin F₂ α by cultured bovine endometrial cells in response to tumor necrosis factor α : cell type specificity and intracellular mechanisms. *Biology of Reproduction*. 62(5):1116-1120. <https://doi.org/10.1095/biolreprod62.5.1116>
- SKARZYNSKI DJ, Okuda K. 1999. Sensitivity of bovine corpora lutea to prostaglandin F₂ α is dependent on progesterone, oxytocin, and prostaglandins. *Biology of Reproduction*. 60(6):1292-1298. <https://doi.org/10.1095/biolreprod60.6.1292>

SKARZYNSKI DJ, Okuda K. 2000. Different actions of noradrenaline and nitric oxide on the output of prostaglandins and progesterone in cultured bovine luteal cells. *Prostaglandins and Other Lipid Mediators*. 60(1-3):35-47. [https://doi.org/10.1016/S0090-6980\(99\)00046-5](https://doi.org/10.1016/S0090-6980(99)00046-5)

STEVENSON JS, Britt JH. 1979. Relationships among luteinizing hormone, estradiol, progesterone, glucocorticoids, milk yield, body weight and postpartum ovarian activity in Holstein cows. *Journal of Animal Science*. 48(3):570-577. <https://doi.org/10.2527/jas1979.483570x>

STIRLING D, Magness RR, Stone R, Waterman MR, Simpson ER. 1990. Angiotensin II inhibits luteinizing hormone-stimulated cholesterol side chain cleavage expression and stimulates basic fibroblast growth factor expression in bovine luteal cells in primary culture. *Journal of Biological Chemistry*. 265(1):5-8. Online ISSN 1083-351X.

STOCCO DM. 1997. A StAR search: implications in controlling steroidogenesis. *Biology of Reproduction*. 56(2):328-336. <https://doi.org/10.1095/biolreprod56.2.328>

STOCCO DM. 2001. StAR protein and the regulation of steroid hormone biosynthesis. *Annual Review of Physiology*. 63(1):193-213. <https://doi.org/10.1146/annurev.physiol.63.1.193>

STOCCO DM, Ascoli M. 1993. The use of genetic manipulation of MA-10 Leydig tumor cells to demonstrate the role of mitochondrial proteins in the acute regulation of steroidogenesis. *Endocrinology*. 132(3):959-967. <https://doi.org/10.1210/en.132.3.959>

STOCCO C, Telleria C, Gibori G. 2007. The molecular control of corpus luteum formation, function, and regression. *Endocrine Reviews*. 28(1):117-149. <https://doi.org/10.1210/er.2006-0022>

SUHARA T, Fukuo K, Sugimoto T, Morimoto S, Nakahashi T, Hata S, Shimizu M, Ogihara T. 1998. Hydrogen peroxide induces up-regulation of Fas in human endothelial cell. *Journal of Immunology*. 160(8):4042-4047. Print ISSN 0022-1767; Online ISSN 1550-6606.

SZCZEPAŃSKA, M., Koźlik, J., Skrzypczak, J., & Mikołajczyk, M. 2003. Oxidative stress may be a piece in the endometriosis puzzle. *Fertility and Sterility*. 79(6):1288-1293. [https://doi.org/10.1016/S0015-0282\(03\)00266-8](https://doi.org/10.1016/S0015-0282(03)00266-8)

TANIGUCHI H, Yokomizo Y, Okuda K. 2002. Fas-Fas ligand system mediates luteal cell death in bovine corpus luteum. *Biology of Reproduction*. 66(3):754-759. <https://doi.org/10.1095/biolreprod66.3.754>

THORNEBERRY NA, Lazebnik Y. 1998. Caspases: enemies within. *Science*. 281(5381):1312-1316. DOI:10.1126/science.281.5381.1312

TILLY JL. 1996. Apoptosis and ovarian function. *Reviews of Reproduction*. 1(3):162-172. Online ISSN: 1741-7899; Print ISSN: 1470-1626.

VANDENABEELE P, Galluzzi L, Berghe TV, Kroemer G. 2010. Molecular mechanisms of necroptosis: an ordered cellular explosion. *Nature Reviews Molecular Cell Biology*. 11(10):700-714. <https://doi.org/10.1038/nrm2970>

VANLANGENAKKER N, Berghe TV, Vandenabeele P. 2012. Many stimuli pull the necrotic trigger, an overview. *Cell Death and Differentiation*. 19(1):75-86. <https://doi.org/10.1038/cdd.2011.164>

- VAN LANGENDONCKT A, Casanas-Roux F, Donnez J. 2002. Oxidative stress and peritoneal endometriosis. *Fertility and Sterility*. 77(5):861-870. [https://doi.org/10.1016/S0015-0282\(02\)02959-X](https://doi.org/10.1016/S0015-0282(02)02959-X)
- WILTBANK MC, Shiao TF, Bergfelt DR, Ginther OJ. 1995. Prostaglandin F2 α receptors in the early bovine corpus luteum. *Biology of Reproduction*. 52(1): 74-78. <https://doi.org/10.1095/biolreprod52.1.74>
- WILTBANK MC, Gümen A, Sartori R. 2002. Physiological classification of anovulatory conditions in cattle. *Theriogenology*. 57(1):21-52. [https://doi.org/10.1016/S0093-691X\(01\)00656-2](https://doi.org/10.1016/S0093-691X(01)00656-2)
- WILTBANK MC, Souza AH, Carvalho PD, Cunha AP. 2014. Physiological and practical effects of progesterone on reproduction in dairy cattle. *New Science-New Practices International Cow Fertility Conference*. Westport, Ireland. Pp.70-81. <https://doi.org/10.1017/S1751731114000585>
- YOUNG IS, Woodside JV. 2001. Antioxidants in health and disease. *Journal of Clinical Pathology*. 54(3):176-186. <http://dx.doi.org/10.1136/jcp.54.3.176>
- YOUNG JM, McNeilly AS. 2010. Theca: the forgotten cell of the ovarian follicle. *Reproduction*. 140(4):489-504. <https://doi.org/10.1530/REP-10-0094>
- ZHENG J, Redmer DA, Reynolds LP. 1993. Vascular development and heparin-binding growth factors in the bovine corpus luteum at several stages of the estrous cycle. *Biology of Reproduction*. 49(6):1177-1189. <https://doi.org/10.1095/biolreprod49.6.1177>
- ZERANI M, Catone G, Betti G, Parillo F. 2013. Immunopresence and functional activity of prostaglandin-endoperoxidase synthases and nitric oxide synthase in bovine corpora lutea during diestrus. *Folia Morphological*. 72(1): 36-40. DOI: 10.5603/FM.2013.0006
- ZHANG DW, Shao J, Lin J, Zhang N, Lu BJ, Lin SC, Dong MQ, Han J. 2009. RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. *Science*. DOI: 10.1126/science.1172308.