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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

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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 F2α (PGF2α) 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. Sí, 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 F2α (PGF2α) 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 teak 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 F2α (PGF2α) 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 PGF2α 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 (teak and granulose). 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 teak 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 autocratic and paracrine bio-regulators (Skarzynski and Okuda, 1999; Duras *et al*., 2005). In addition, it stimulates the production of prostaglandins (F2α and E2) and oxytocin at the beginning of the cycle, but inhibits the secretion of prostaglandin F2α in the middle part (Sarzynski 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 (ON) (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 F2α (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 F2α, 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 F2α 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 F2α 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 F2α and stimulates the synthesis of receptors for oxytocin in the endometrium; Oxytocin acts on the uterine endometrium, stimulating the secretion of prostaglandin F2α in pulsatile form. Prostaglandin F2α of uterine origin stimulates the secretion of F2α in luteal cells, in a process of self-amplification to complete luteolysis (Kumagai *et al*., 2014).

The action of prostaglandin F2α on the corpus luteum is both functional and structural; both reactive oxygen species (ROS), which include nitric oxide (NO), superoxide and the anion hyperioxide 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 Langendonckt *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). PGF2α binds to its receptors in the plasma membrane of luteal cells, the formation of the PGF2α 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 F2α-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 PGF2α, 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-βHSD 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 (Sakumoto *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 Caspasa 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 propoptotic expression, with no effect on the expression of Fas and Bcl-2 RNAm (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 PGF2α 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 H_2O_2 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 F2α participates in vasodilation and in the vasoconstriction of CL (Wiltbank *et al*., 1995; Díaz *et al*., 2002); in spontaneous luteolysis and application of exogenous F2α 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 F2α on nitric oxide has been proven by its effect on intermediates.

The application of prostaglandin F2α 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 (Shirasuma *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 F2α, and delays the onset of luteolysis (Shirasuma *et al*., 2008b).

Prostaglandin F2α, after its vasodilator effect, limits the supply of oxygen and nutrients to the corpus luteum to culminate luteolysis by inhibiting angiogenesis, angiolysis and vasoconstriction (Guilbault *et al*., 1984; Acosta *et al*., 2002). Thirty minutes after the injection of prostaglandin F2α 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 F2α inhibits the development of thin and subsequently thick blood vessels (Hojo *et al*., 2009).

Prostaglandin F2α 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 F2α 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 PGF2α, 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. PGF2α 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.

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