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# Prostaglandins as local regulators of ovarian physiology in ruminants

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## Abstract

Prostaglandins are synthesized from arachidonic acid through the catalytic activities of cyclooxygenase, while the production of different prostaglandin types, prostaglandin F2 alpha (PGF) and prostaglandin E2 (PGE), are regulated by specific prostaglandin synthases (PGFS and PGES). Prostaglandin ligands (PGF and PGE) bind to specific high-affinity receptors and initiate biologically distinct signalling pathways. In the ovaries, prostaglandins are known to be important endocrine regulators of female reproduction, in addition to maintaining local function through autocrine and/or paracrine effect. Many research groups in different animal species have already identified a variety of factors and molecular mechanisms that are responsible for the regulation of prostaglandin functions. In addition, prostaglandins stimulate their intrafollicular and intraluteal production via the pathway of prostaglandin self-regulation in the ovary. Therefore, the objective of the review article is to discuss recent findings about local regulation patterns of prostaglandin ligands PGF and PGE during different physiological stages of ovarian function in domestic ruminants, especially in bovine. In conclusion, the discussed local regulation mechanisms of prostaglandins in the ovary may stimulate further research activities in different methodological approaches, especially during final follicle maturation and ovulation, as well as corpus luteum formation and function.

**KEYWORDS**

corpus luteum, follicle, luteolysis, ovarian function, ovulation, prostaglandins, ruminants

## 1 | INTRODUCTION

Prostaglandins belong to the family of lipids, which are crucial mediators of the female reproductive processes and ovary function. The ovarian cycle in ruminants is regulated by repetitive patterns of ovarian cell proliferation, differentiation and transformation that accompany follicle growth and maturation until ovulation. This is followed by the follicular-luteal transition and succeeding corpus luteum (CL) formation (Fortune, 1994; Fraser & Lunn, 2000; Meidan & Levy, 2007; Woad & Robinson, 2016). It is well documented that the physiology of the ovary in domestic ruminants and pigs, particularly the oestrous cycle, is regulated by endocrine as well as local/intraluteal (autocrine/paracrine) factors and specific molecular mechanisms (Berisha et al., 2002; Hunter et al., 2004; Mishra et al., 2017;

Rawlings et al., 2003; Robinson et al., 2009; Schams et al., 2009). The endocrine activity of the ovary also relies on the paracrine action of locally produced factors, including extracellular matrix-degrading proteases, various cytokines, growth factors and steroid hormones, while prostaglandins produced intraovarian seem to be essential mediators in the regulation of the oestrous cycle (Acosta et al., 2005; Berisha, Schams, Rodler, Sinowatz, & Pfaffl, 2016; Kliem et al., 2007, 2009; Kobayashi, Acosta, Ozawa, et al., 2002; Smith et al., 1999).

Prostaglandins are synthesized from arachidonic acid, primarily through the catalytic activities of cyclooxygenase (COX). The production of different prostaglandin types, namely prostaglandin F2 alpha (PGF) and prostaglandin E2 (PGE), are regulated by specific prostaglandin synthases (prostaglandin F2 alpha syntheses—PGFS, and prostaglandin E2 syntheses—PGES). Prostaglandin ligands bind to specific high-affinity receptors, initiating biologically distinct signalling pathways, even in the bovine and primate ovary (Arosh et al., 2003; Harris et al., 2011; Markosyan & Duffy, 2009; Sharif et al., 1998; Shirasuna, Nitta, et al., 2012). In addition to their well-known endocrine role (uterine origin), prostaglandins are also shown to be important for their local function (autocrine/paracrine actions) in the female reproductive organs, particularly within the ovary structures (Kobayashi, Acosta, Hayashi, et al., 2002; Kobayashi, Acosta, Ozawa, et al., 2002; Tsafriri et al., 1972; Wiltbank & Ottobre, 2003). Local prostaglandin effects, part of the pathway of prostaglandin self-regulation, are physiologically significant, regulating the oestrous cycle, primarily during the final follicular development and ovulation and after CL formation and its functioning in several species (Arosh et al., 2004; Del Vecchio et al., 1996; Fernandez-Moro et al., 2008; Fierro et al., 2011; Milvae & Hansel, 1983; Vonnahme et al., 2006; Wiltbank & Ottobre, 2003).

This review aims to discuss previous research results in domestic ruminants (bovine, ovine and caprine) while highlighting current findings on local regulation patterns of the prostaglandin system members during different physiological stages of the ovarian cycle, with a special focus on prostaglandin ligands during follicle growth and ovulation as well as CL formation in various animal models and experimental conditions.

## 2 | OVARIAN CYCLE IN RUMINANTS

As the main event of reproduction, the ovarian cycle physiologically develops similarly in domestic ruminants, with changes in its duration depending on the species. In addition to well-studied endocrine factors, like gonadotropins, steroids and other hormones, paracrine (locally produced) factors seem to play an important role in the regulation of the ovarian cycle, even in ruminants (Berisha & Schams, 2005; Castilho et al., 2008; Niswender et al., 1985). Numerous studies have highlighted the influence of growth factors and other locally produced mediators, through different molecular mechanisms, have influenced all phases of the ovarian cycle, from follicle development and ovulation to CL formation and function (Berisha et al., 2017; Davis & Rueda, 2002; Wise et al., 1982).

The periodic changes in blood vessel formation (angiogenesis) and degradation (angiolysis) during the ovarian cycle are regulated by the specific molecular mechanisms and synchronous communication of various locally produced factors (Berisha et al., 2009; Fraser & Lunn, 2000; Goede et al., 1998; Plendl, 2000). Angiogenesis, the cyclical building of new blood capillaries from existing vessels, is considered the most crucial event for ovary function (reviewed by Berisha, Schams, Rodler, & Pfaffl, 2016; Woad & Robinson, 2016). Among the local mediators with proangiogenic effects, several members stand out, including hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), angiopoietin (ANPT), fibroblast growth factor (FGF) and insulin-like growth factor (IGF). The essential role of these angiogenic factors and the process of angiogenesis in the follicles or CL have now been fully confirmed (Chouhan et al., 2013; Pepper et al., 1992; Robinson et al., 2009; Woad & Robinson, 2016). Underdeveloped blood vessels (vasculature) system in these ovarian structures can be the reason for various ovarian dysfunctions, such as luteal insufficiency, and may lead to severe problems in reproduction (Berisha & Schams, 2005).

### 2.1 | Follicle development and ovulation

In ruminants, folliculogenesis, which encompasses the growth and development of follicles, is the process during which the recruited primordial follicle grows and develops at the tertiary level (Graafian follicle) with the potential to ovulate its egg for fertilization (Fortune, 1994; Scaramuzzi et al., 2011). It has also been proven that oocytes in the secretion growth factors that play a central role in the regulation of folliculogenesis, granulosa and cumulus cell differentiation and ovulation (Gilchrist et al., 2004; McNatty et al., 2004).

The regulatory mechanisms leading to the selection of the ovulatory follicle are still to be clarified. However, the essential role of pituitary gonadotropins (FSH—follicle stimulating hormone and LH—luteinizing hormone) and steroids (oestradiol and progesterone) in the process of folliculogenesis and ovulation has been verified and confirmed (Berisha & Schams, 2005; Savio et al., 1988). This process explains the induction of the follicular phase and the sequence of events leading to the LH surge and ovulation (Scaramuzzi et al., 2011).

The immediate change in progesterone and oestradiol concentration in preovulatory follicles' follicular fluid indicates their essential role in the ovulation process (Ireland & Roche, 1982; Komar et al., 2001). Ovulation follows as a result of a dynamic endocrine action of gonadotropins (primarily LH peak) and steroid hormones (primarily oestrogens), regulated and controlled by a neuroendocrine system and complex feedback mechanisms also in dynamic interaction with paracrine (local production) factors (Berisha et al., 2008; Fortune, 1994).

## 2.1.1 | Local produced factors in follicles

In recent years, the important role of locally produced mediators (paracrine actions) such as growth factors, cytokines and various peptides in modulating folliculogenesis and ovulation has been established (Hunter et al., 2004; Mishra et al., 2017; Nwachukwu et al., 2023; Rawlings et al., 2003; Scaramuzzi et al., 2011; Schams et al., 2009). During the ovulation process, the LH peak stimulates molecular mechanisms and different locally produced factors, which support the effect of gonadotropins in the completion of the ovulation process and the formation of the CL (Berisha & Schams, 2005; Juengel et al., 2021).

Recent studies have documented the essential role of VEGF, ANPT, HIF, FGF, IGF and other proangiogenic mediators for the development of antral follicles, the ovulation process, and the formation and maintenance of the CL (Berisha, 2022; Mishra et al., 2017; Pepper et al., 1992; Schams et al., 2009; Schams & Berisha, 2002). Growth factors like IGF system members can stimulate either the proliferation or the differentiation and differentiated functions of granulosa cells, depending on the follicle's development stage (Scaramuzzi et al., 2011). While the last publication of Nwachukwu et al. (2023) highlights the importance of IGF signalling in regulating luteal angiogenesis and function in the cow. In addition, some research groups have demonstrated the importance of adipokines system members like adiponectin, resistin, chemerin, visfatin and apelin in the regulation of bovine ovarian function (Juengel et al., 2021; Kurowska et al., 2021; Thaqi et al., 2023).

Some recent studies have indicated the necessity of intraovarian prostaglandins and various angiogenic factors in angiogenesis during folliculogenesis, particularly during the final phases of ovulation, respectively, during the follicular-luteal transition and CL formation (Algire et al., 1992; Berisha, Schams, Rodler, & Pfaffl, 2016; Fortune et al., 2009; Hunter et al., 2004).

## 2.2 | Corpus luteum (CL) formation and function

The LH peak regulates steroid hormones and molecular mechanisms leading to final follicle development, subsequent ovulation and CL formation (Fortune, 1994). This endocrine action affects the transformation of former follicular theca interna cells (TI) and granulosa cells (GC) into steroidogenic luteal cells through the process called luteinization. This newly formed endocrine organ, the corpus luteum, consists not only of small and large luteal cells, but also of other cells such as fibroblasts, endothelial cells and immune cells. These diverse cell types contribute to the optimal development of the CL, enabling the production of its primary hormone, progesterone (Berisha & Schams, 2005; Niswender et al., 1985; Wise et al., 1982). There are also other hormones, especially growth hormone (GH), which is described as having an essential contribution to the formation, growth, and development of the CL and the stimulation of progesterone production in ruminants (Juengel et al., 1997; Kobayashi, Acosta, Ozawa, et al., 2002; Kobayashi et al., 2001; Lucy et al., 1994). Progesterone during the oestrous cycle, among others, is responsible for preparing the uterus for an eventual pregnancy, and for maintaining the pregnancy (Weems et al., 2006).

The last phase of the oestrous cycle, between days 11–13 in sheep and 15–17 in cattle, marks acritical moment, the beginning of luteolysis or pregnancy (McCracken et al., 1999; Weems et al., 2006). In ruminants, the luteolytic signal is PGF, which is secreted (at this stage of the cycle) in a pulsatile manner by the uterus (McCracken et al., 1999). The episodic secretion of PGF from the uterus reaches the CL through the complex counter-current system. However, other important mechanisms that control the function of the CL have also been established (Pexton et al., 1975; Thatcher et al., 2001).

In cases of an infertile cycle, uterine prostaglandins (PGF) regulate the luteal regression process (luteolysis), the necessary functional phase of the CL that enables the beginning of the next oestrous cycle (Jimoh et al., 2022; Weems et al., 2006). The typical symptoms of luteal regression are the immediate decline in progesterone production, which is accompanied by obstructions in the vasculature, blood flow decline, as well as the initiation of the rapid death of CL cells (Acosta et al., 2002; Pate & Hughes, 2023).

## 2.2.1 | Local produced factors in corpus luteum

The CL is among the rare examples in physiology where this endocrine organ's formation, growth, functioning and decomposition can be seen periodically (during regular periods of the ovarian cycle). The periodic formation of the blood capillary system (angiogenesis) during oestrous cycle and also their periodic breakdown (angiolysis) have a critical role in the physiology of the CL (Goede et al., 1998; Reynolds et al., 1994; Schams & Berisha, 2002).

In addition to endocrine factors, the optimal luteal function also depends on the activity of many paracrine factors locally produced in the CL. Of the numerous family members that have been identified, the most important appear to be the group of growth factors, peptides, steroids and prostaglandins that stimulate cell growth, differentiation and survival of luteal cells (Gabler et al., 2004; Nwachukwu et al., 2023; Richards et al., 2002). These factors are not only necessary for the establishment of the capillary system (angiogenesis) in the tissues of the CL, but they are also important mediators for the stimulation of progesterone and other hormones that enable the optimal functioning of the CL during the oestrous cycle and pregnancy (Kobayashi et al., 2001; Levy et al., 2000; Neuvians et al., 2003a; Pate, 1988).

Besides their essential importance for the formation and function of the CL, most paracrine factors are also necessary during the luteal regression (luteolysis). This includes extracellular matrix-degrading proteases, the group of above-mentioned angiogenic factors, vasoactive peptides, apoptotic factors and other different cytokines, which are considered to be critical contributors to the cascade of actions leading to functional luteolysis and subsequent

structural breakdown of CL (Al-Gubory et al., 2005; Hinckley & Milvae, 2011; Knickerbocker et al., 1988; Miyamoto et al., 2013; Neuvians et al., 2003b; Tanaka et al., 2004; Watanabe et al., 2006).

## 3 | PROSTAGLANDINS AND OVARIAN FUNCTION

Prostaglandins have aroused researchers' interest in the field of reproduction due to their multifaceted in physiology. Through their endocrine and paracrine effects, they are considered to be among the most important regulators of the physiology of female reproduction. Here, we can mention the essential role of prostaglandins during the ovarian cycle, endometrial receptivity, embryo implantation, pregnancy, parturition and postpartum stage (Weems et al., 2006). Recognizing the undoubted importance of above-mentioned mediators in reproduction processes, our research group focused on the main phases of ovarian function, using different experimental models and analytical methods (Berisha et al., 2019, 2020, 2022; Livak & Schmittgen, 2001; Mueller et al., 2004).

Prostaglandins (PGE and PGF) control multiple biological functions based on the diversity of their large family and the diversity of their receptor isoforms. PGE binds to four distinct subtypes of receptors (EP1-EP4), whereas PGF binds to the FP receptor (Biringer, 2021). Prostaglandin receptors are coupled to different G proteins and induce different signalling pathways. Among the prostaglandin receptors studied in ovarian tissue, the PGE receptors (specifically EP2 and EP4) signal through Gs-mediated increases in cAMP (cyclic adenosine 3′,5′-monophosphate), whereas the PGF receptor (FP) signals through Gq-mediated increases in intracellular calcium, mechanisms which then activate ovarian cells to stimulate the induction of specific genes related to different functions of the ovary (Cha et al., 2006; Chen et al., 2001; Davis et al., 1987; Hatae et al., 2002). Because PGE and PGF have different actions, multiple signalling pathways are involved in the regulation of various endocrine-paracrine factors (chemokine and cytokine) that could lead to local modulation of the final biological actions (Berisha et al., 2022; Plewes et al., 2023; Xu et al., 2015).

Prostaglandin receptors are widely expressed in reproductive organs with the highest amounts also in the ovary tissue, and their regulation has been shown to be modulated in several different ways (Arosh et al., 2003). The localization of prostaglandin receptors in follicle and luteal cells is essential for successful growth and development of follicles and for the formation and function of the CL (Arosh et al., 2004). Another aspect of their actions is inflammatory-like physiological developments, responsible for tissue remodelling during ovulation, as well as the luteolysis, in which processes prostaglandins are considered to have an essential role (Pereira de Moraes et al., 2021; Ye et al., 2020).

In our discussion in this overview, we are trying to provide a closer look at molecular mechanisms of locally synthesized prostaglandin ligands, namely PGF and PGE, through different phases of ovarian function, starting with antral follicle development, ovulation

and CL development in several animal models and various experimental conditions. Specific studies in humans, primates and different species of ruminants namely, bovine, ovine and caprine have demonstrated the important role of prostaglandins during follicle development, ovulation, and CL formation and function (Berisha et al., 2018; Del Vecchio et al., 1996; Fernandez-Moro et al., 2008; Fierro et al., 2011; McNatty et al., 1982; Milvae & Hansel, 1983; Murdoch et al., 1981; Peters et al., 2004).

### 3.1 | Prostaglandins during follicle development and ovulation

Although the role of prostaglandins during folliculogenesis has not yet been sufficiently clarified, their crucial role in follicle development and the ovulation process in different species of ruminants has been widely confirmed (Sharma & Sharma, 2020; Weems et al., 2006). The effect of PGF in increasing the sensitivity of the pituitary to GnRH (gonadotropin-releasing hormone) for the release of LH is also known, which affects the increase of prostaglandins from preovulatory follicles, which is obligatory for ovulation in ruminants (Armstrong, 1981; Fortune et al., 2009; Pereira de Moraes et al., 2021).

Studies in cattle and sheep have shown the regulation of steroids and prostaglandins in follicular tissue and follicular fluid of preovulatory follicles (Fortune et al., 2009; Ireland & Roche, 1982; Murdoch et al., 1986; Shemesh, 1979). The immediate rise in the level of steroids (oestradiol and progesterone) immediately after the LH peak in the follicular fluid implicates their role in the ovulation process (Berisha et al., 2019). It is interesting that in sheep, after the LH peak, no significant change of PGF and PGE in the follicular fluid has been observed (Armstrong, 1981; Murdoch et al., 1981; Randel et al., 1996). In contrast, in cattle, a rapid rise of both prostaglandins in the follicular fluid was found after the LH peak and especially in the preovulatory period (Berisha et al., 2019; McCracken et al., 1999; Murdoch et al., 1986; Shemesh, 1979). This seems to be expected since it has been reported that granulosa cells produce both prostaglandins, PGF and PGE (Weems et al., 2006). It is assumed that both PGE and PGF have numerous cell-specific functions throughout follicle development, ovulation and subsequent luteinization of follicle cells (Bridges & Fortune, 2007). Some recent studies considered PGE2 the key ovulatory prostaglandin, locally produced by follicular cells after the LH surge in all species investigated (Duffy et al., 2019). Although prostaglandin PGF is also synthesized in response to LH surge, its mechanism of action during the ovulatory process in cattle remains to be clarified (Pereira de Moraes et al., 2021).

In our previous studies, we have shown that LH peak stimulates prostaglandin system members, starting with the major enzymes responsible for prostaglandin production (COX-2, PGFS, PGES), as well as the regulation of the prostaglandin ligands and their receptors (Berisha et al., 2019). The present study demonstrates the expression pattern of prostaglandin ligands (PGF, PGE) in timely
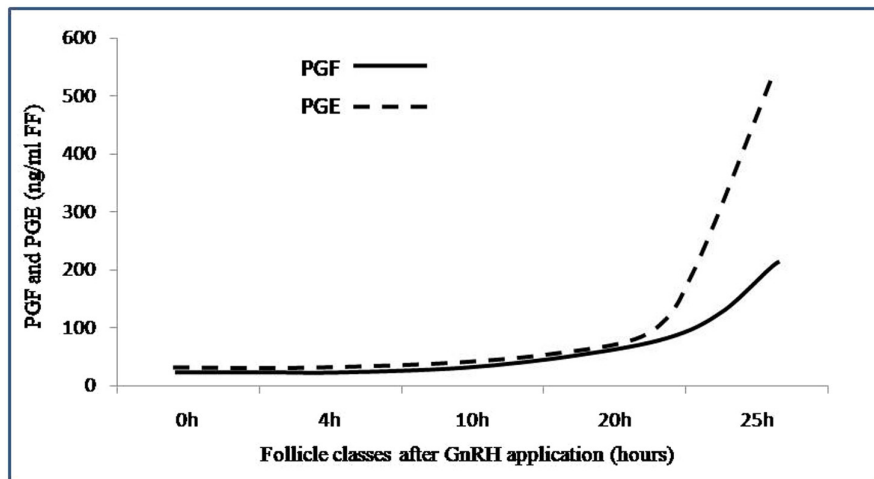
defined follicle groups around ovulation, schematically presented in Figure 1. The results of our experimental study have shown shallow levels of PGF and PGE concentration in follicular fluid before the LH peak (Figure 1).

Small amounts of prostaglandins are produced even in follicular fluid of follicles after LH peak. At the same time, the concentration, especially PGE, increases rapidly and significantly only during ovulation (25 h after GnRH). These results are consistent with studies of other authors, supporting the hypothesis that local intrafollicular prostaglandins, particularly PGE, stimulate progesterone secretion in both follicular cell types (Armstrong, 1981; Bridges & Fortune, 2007; Murdoch et al., 1981; Shemesh, 1979). This hypothesis is also supported by previous studies that have clearly shown that ovulation depends on the intrafollicular production of prostaglandin system members (Algire et al., 1992; Murdoch et al., 1986; Peters et al., 2004; Randel et al., 1996; Shemesh, 1979).

Our previous immunohistochemistry results show a distinct localization of COX-2 and PGE synthases in cow's tissue structures of different preovulatory follicles (Berisha et al., 2019). Granulosa cell layers of preovulatory follicles showed distinct COX-2 and PGES immunostaining, with increased intensity towards the basement membrane (BM) and weaker staining of the theca interna (TI) tissue. The more significant increase of PGE concentration during ovulation (Figure 1) is also supported by several studies, which have documented the essential role of PGE as a key local mediator of LH peak in the ovulation and CL formation (Bridges et al., 2006; Kotwica et al., 2003; Peters et al., 2004). Recent research assumes that LH modulates the secretion of local prostaglandins and angiogenic factors, which appears to be critical in the transition and differentiation of follicular cells into luteal ones (luteinization) as well as in the formation of the CL (Acosta & Miyamoto, 2004; Duffy et al., 2019; Grazul et al., 1989; Kawaguchi et al., 2013; Wiltbank & Ottobre, 2003). To summarize, prostaglandins' essential role, especially PGE, in ovulation in ruminants is well established. In addition, PGE and PGF regulate follicle angiogenesis, immune cell function and tissue remodelling during the follicular-luteal transition and CL formation.

## 3.2 | Prostaglandins during corpus luteum formation and function

The important role of prostaglandins has also been found in the CL through their formation and function, especially for their local effects (paracrine action) during the oestrous cycle and pregnancy (Kobayashi, Acosta, Ozawa, et al., 2002; Kobayashi et al., 2001; Vonnahme et al., 2006; Weems et al., 2014). An in vitro study (intraluteal microdialysis) has documented the production of PGF and PGE by luteal tissue on the early CL (Day 3) of the oestrous cycle (Kobayashi, Acosta, Hayashi, et al., 2002). Another study has shown specific expression of different members of the prostaglandin family, starting with specific enzymes (COX-2, PGFS, PGES), prostaglandin ligands (PGF and PGE) and their receptors, during different phases of the oestrous cycle in cattle. In addition, it is suggested that prostaglandin involvement in local-paracrine mechanisms is responsible for regulating CL function during the oestrous cycle and pregnancy (Berisha et al., 2018; Okuda & Skarzynski, 2000).

Our present PGF and PGE concentration results in CL sample groups during the early, mid and late, and regression stages of the oestrous cycle are shown schematically in Figure 2. The high level of PGF ligand during the early phase of CL development decreases significantly during the mid-luteal phase, rising again in the late luteal phase and especially during CL regression. PGE tissue concentration showed a similar expression profile, significantly increasing during the late luteal phase (Days 13–17) and an immediate decrease during the luteal regression (Figure 2).

Interestingly, in ruminants, the CL synthesizes PGF and PGE in high concentrations, equal to or greater than those secreted by the uterus (Pate & Hughes, 2023). Prostaglandins (PGF and PGE) are involved in local (paracrine) mechanisms that regulate CL formation, stimulating progesterone production by bovine luteal cells (Kotwica et al., 2003). After ovulation (CL, Days 1–2), many former GCs (granulosa luteal cells) show distinct immunostaining for COX-2 and PGES. Also, on Days 3–4, most luteal cells continue to be stained with COX-2 and PGES (Berisha et al., 2019). Even during the later phases of CL development during the oestrous cycle in
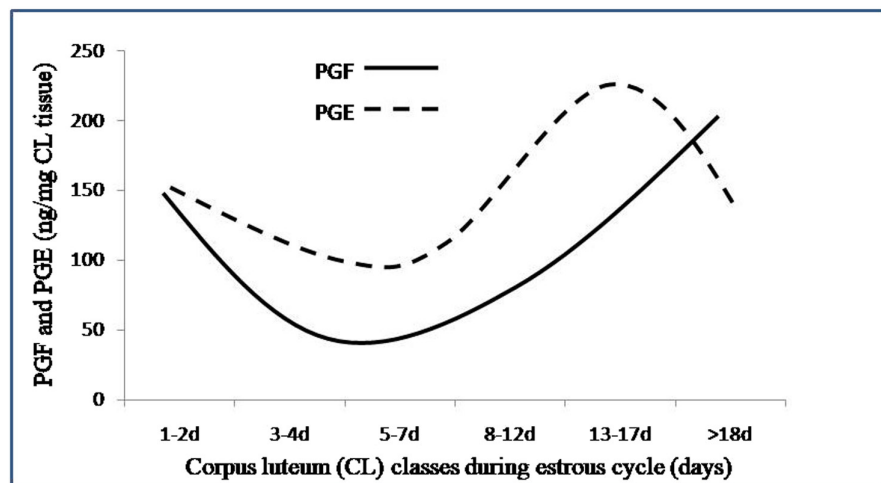
**FIGURE 2** Schematic presentation of concentration profile of prostaglandin F2 alpha (PGF) and prostaglandin E2 (PGE) in corpus luteum (CL) classes during oestrous cycle at days: 1–2, 3–4, 5–7, 8–12, 13–17 and >18 (after luteolysis) in the cow (adapted from Berisha et al., 2018).

cows, COX-2 and PGES showed a similar time course of the immunolocalization (Berisha et al., 2018). The COX-2 and PGES immunolocalization during the late luteal phase (Days 15–17) shows many positive luteal cells, followed by lower activity afterward during luteolysis (Berisha et al., 2022).

As discussed above, ovarian LH peak plays an essential role in the stimulation of progesterone and the production of prostaglandins, which affect the formation of the CL and the maintenance of its function (Grazul et al., 1989; Kawaguchi et al., 2013). During the final follicle development, the primary source of prostaglandins is believed to be the granulosa cells. In contrast, after ovulation (cell transformation), the large luteal cells mainly produce prostaglandin in the CL (Fortune et al., 2009). The high concentration of PGF during the early luteal phase (Figure 2) correlates well with the expression of COX-2 and PGFS (Berisha et al., 2018). The high level of PGF in the early stages of CL development is consistent with other previous observations (Arosh et al., 2004; Milvae & Hansel, 1983). In this context, numerous studies have shown that different signalling molecules (growth factor, cytokines, etc.) produced by various CL cells (immune cells like eosinophils, neutrophils and macrophages) can modify the local production of prostaglandins (Kawaguchi et al., 2013; Meidan & Levy, 2007; Pate et al., 2010; Penny et al., 1999; Shirasuna, Nitta, et al., 2012; Smith & Meidan, 2014).

It has also been documented that luteal prostaglandins stimulate their production in CL tissue (Tsafriri et al., 1972; Wiltbank & Ottobre, 2003). They protect luteal cells from apoptosis and regulate the expression of factors responsible for angiogenesis (creating a network of new capillaries), depending on the luteal phase, which is considered essential for optimal CL function (Bowolaksono et al., 2008; Pate et al., 2010; Walusimbi & Pate, 2013; Zalman et al., 2012). Previous studies have shown high regulation of angiogenic factors namely VEGF, FGF, HIF and angiopoietins, immediately after LH peak, around ovulation and during CL formation and function (Berisha et al., 2008, 2019; Miyamoto et al., 2013; Robinson et al., 2009; Weems et al., 2014).

Besides stimulating prostaglandins, the large amounts of angiogenic factors in CL tissue, especially during the early luteal stages, suggest their active role in the growth and survival of endothelial and luteal cells. Therefore, the role of angiogenic factors and prostaglandins

during the oestrous cycle, especially in the early stages of luteal development, helps in the functional maintenance of the CL. Furthermore, angiogenic factors affect some other physiological functions within CL tissue (like cell differentiation, intracellular communication, etc.), which require further specific research in the future (Berisha et al., 2018; Wiltbank & Ottobre, 2003; Woad & Robinson, 2016).

Like formation and function, the CL regression at the end of a non-fertile oestrous cycle depends on endocrine factors, particularly those produced within the CL tissue (paracrine action). Besides endocrine (uterine PGF), intraluteal prostaglandins and a range of other paracrine factors are considered crucial in the luteolytic cascade. The above-mentioned angiogenic factors (VEGF, FGF, HIF, ANPT), especially vasoactive peptides (endothelin and angiotensin), extracellular matrix-degrading proteases, apoptotic factors and a range of specific cytokines and enzymes seem to be very important even during the CL regression (Atli et al., 2022; Berisha et al., 2009; Jaroszewski et al., 2003; Pate & Hughes, 2023; Smith et al., 1999).

Regression of CL (luteolysis), caused by uterine PGF, develops in two stages: (1) functional phase, during the first 12 h, which is characterized by a rapid decline in progesterone secretion, and (2) structural phase, after 12 h, characterized by the demise of the CL (Niswender et al., 2000; Shrestha, 2021). The level of PGF in our experiment shows the first increase immediately after application of PGF (functional luteolysis), while the second increase comes 24 h later (structural luteolysis). In contrast, high levels of PGE during physiological luteolysis decrease significantly after 48 h, indicating that the CL is undergoing structural luteolysis (Figure 3). In addition, some previous reports documented the luteolytic effects of PGF and the luteoprotective role of PGE in the ovary of various ruminant species (Lee et al., 2012; Niswender et al., 2000; Weems et al., 2006).

Decreased progesterone levels during the luteolysis process result in the apoptotic demise of luteal cells (Rueda et al., 2000; Socha et al., 2022). This phenomenon exhibits variations in different species (Sugino & Okuda, 2007). An interesting finding was reported by Lee et al. (2012) that endocrine (uterine) PGF initiates functional luteolysis, whereas intraluteal (paracrine) PGF is necessary for structural luteolysis (which implies rapid cell death and CL breakdown). In a

**FIGURE 3** Schematic presentation of concentration profile of prostaglandin F2 alpha (PGF) and prostaglandin E2 (PGE) in corpus luteum (CL) classes after experimentally induced luteolysis (hours): 0, 0.5, 2, 4, 12, 24, 48 and 64h in the cow (adapted from Berisha et al., 2022).
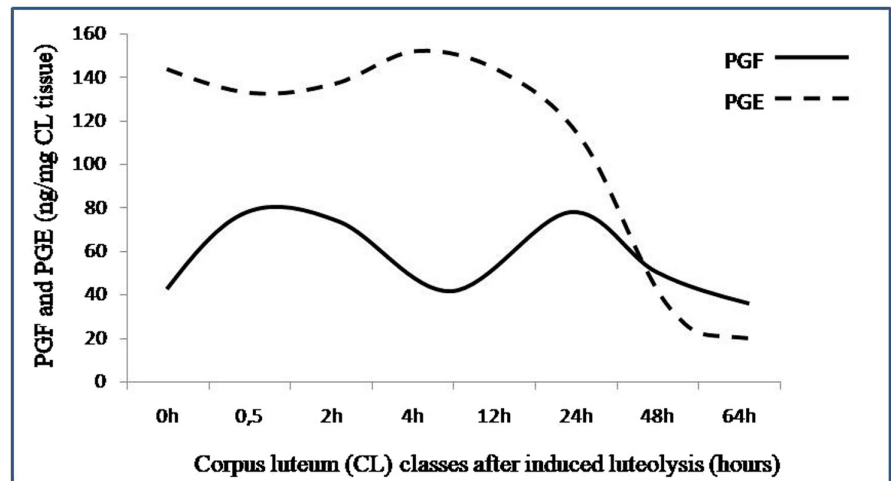


previously published experimental paper, we documented specific expression patterns of prostaglandin system members (responsible enzymes, ligands and their receptors) in CL groups collected before and after PGF injection in cows (Berisha et al., 2022). The increase in PGF concentration (Figure 3) immediately after the start of luteolysis (after 2h) correlates well with the enzyme responsible for its production (PGFS) and with the increased expression of its specific receptor (PGFR), documented before (Berisha et al., 2022). This also agrees with Shirasuna, Akabane, et al.'s (2012) findings that binding PGF to its receptor is essential for initiating the luteolytic cascade in bovine.

Taken together, in ruminants, the secretion of uterine PGF is the signal that initiates luteolysis, which is initially manifested as a rapid decrease in steroidogenesis of the gland. It is also associated with subsequent changes in locally produced proangiogenic mediators such as HIF, VEGF and angiopoietins, which have a crucial impact on the vascular stability of the CL as an important component in the luteolytic cascade. During experimental luteolysis, functional effects of exogenous PGF have been documented in the regulation of extracellular matrix-degrading proteases, vasoactive peptides, and various growth factors and other peptides (Atli et al., 2012; Berisha, Schams, Rodler, & Pfaffl, 2016; Galvão et al., 2018; Jiang et al., 2011; Nishimura & Okuda, 2020; Pate, 2020; Pate & Hughes, 2023). In addition, they affect the regulation of various proinflammatory cytokines, which promote apoptotic death of endothelial and luteal cells and support phagocytosis, especially during the structural luteolysis, leading to the demise of the gland (Friedman et al., 2000; Hojo et al., 2019; Jonczyk et al., 2019; Knickerbocker et al., 1988; Meidan et al., 1999; Pate & Hughes, 2023).

## 4 | GENERAL CONCLUSIONS

As discussed above, the research results in different domestic ruminant species have documented the vital role of gonadotropins during follicle development, especially the LH peak's central role in the local regulation of prostaglandins. Prostaglandins are considered essential in the physiology of ovulation, especially for their possible role in follicular tissue remodelling (theca interna and granulosa

cells) and the subsequent transition of follicular to luteal cells during CL formation. Various scientific studies have also shown that members of the prostaglandin family (COX-2, PGFS, PGES, PGF, PGE and their specific receptors) are involved in local molecular mechanisms, regulating CL function during different stages of the oestrous cycle. In addition, prostaglandins' specific expression and localization pattern in the CL showed that prostaglandins might be key elements of local regulation. Prostaglandins, and other endocrine and intraluteal factors discussed in this study also regulate the luteal regression process (luteolysis), the necessary functional phase of the CL, that enables the beginning of the next oestrous cycle.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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