Journal of Sustainable Veterinary & Allied Sciences
P-ISSN-2695-2661 e-ISSN: 2811-1346
JoSVAS 2022, Vol 2, Issue 1: 52-57

Review Article

Luteolysis and luteostasis – the tripod of life or death for corpus luteum and its synthesis of progesterone in mammals

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ABSTRACT

Corpus luteum (CL) is a transient organ with primary function of producing progesterone, which is essentially required for establishment and sustainance of pregnancy. Luteolysis and luteostasis are two major events that determine life span of corpus luteum within the anatomical space of the ovary and physiological time frame of oestrous cycle that is designated as oestrus to oestrus in a non-conceptive cycle or oestrus to parturition in a conceptive cycle. During oestrus cycle, corpus luteum usually undergoes degradation and hence, cessation of CL synthesis of progesterone so that the animal could return back to oestrus sequel to removal of progesterone inhibition on the release of the gonadotropins that initiate folliculogenesis and ovulation. During pregnancy, corpus luteum must not regress; rather it must be sustained for continual production of progesterone which is essentially required for establishment and maintainance of pregnancy. Therefore, luteolysis must be abrogated and it is called luteostasis. Abrogation of luteolysis during pregnancy to rescue corpus luteum is initiated via different mechanisms in different mammalian species in a phenomenon called maternal recognition of pregnancy. Luteolysis during pregnancy leads to abortion while failure of luteolysis to occur in a non-conceptive cycle keeps the animal in dioestrus stage of the cycle and non-return to oestrus. Luteolysis and luteostasis are reciprocally connected and represent well-orchestrated mechanisms strictly under hormonal regulation that occur throughout mammalian reproductive life. The molecular mechanisms underlying the two opposing reproductive phenomena are further discussed in this review.

Keywords: Corpus luteum, luteolysis, luteostasis, progesterone, prostaglandin$F_{2\alpha}$.

INTRODUCTION

Luteolysis and luteostasis are inversely connected while they occur continuously in different phases through the entire reproductive life of female mammals. A female mammal usually undergoes ovulation during oestrus stage of ovarian cycle. Ovulated follicle becomes luteinized (luteogenesis) to give rise to the corpus luteum and subsequently transforms the cycle into luteal phase as CL is formed and commences the synthesis of progesterone. At late dioestrus, CL has to undergo luteolysis for the same animal to return to follicular phase. During pregnancy, luteostasis is important to sustain CL for continued synthesis of progesterone (P_4) which is essential for sustenance and maintenance of pregnancy (Senger, 2012). Luteolysis and luteostasis are strictly regulated by hormones (ovarian steroids and gonadotropin), occurring within an anatomical space of the ovary and physiological time-frame of reproductive cycle designated as oestrus to oestrus or oestrus to parturition in animal species but menses to menses or menses to parturition in huma. Asynchrony in any one of these twin reproductive events could result into a number of pathological conditions with serious adverse effect on fertility. Where there is failure of luteostasis during pregnancy, early embryo loss is imminent (Noakes *et al.*, 2009). Absence of luteolysis in non-conceptive cycle culminates into persistence of corpus luteum and prolonged dioestrus stage of the cycle as well as sexual inactivity (Lashari & Tasawar, 2012). Regression of CL during follicular phase (luteolysis) and its continuous sustenance during pregnancy (luteostasis) as well as

http://doi.org/10.54328/covm.josvas.2022.065

steroidogenesis are the subject matters of this review. Using current and updated understandings on these themes, molecular mechanisms underlying formation and control of corpus luteum and its synthesis of progesterone in mammalian species are expatiated.

LUTEOLYSIS

a) BACKGROUND

In a non-conceptive cycle, the corpus luteum undergoes luteolysis during the late luteal phase of the ovarian cycle to return the cycle to follicular phase. In cattle and pig, endometrium is a key player in luteolysis since it produces the luteolytic agent, Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Spencer & Bazer, 2002) unlike primate and human where the source of $PGF_{2\alpha}$ is the CL itself.

CL is formed during the luteal phase of the ovarian cycle and regresses at the end of the same luteal phase. In most mammals, CL is not responsive to luteolytic effect $PGF_{2\alpha}$ during the earlier period of luteal phase while similar concentration of $PGF_{2\alpha}$ is effective to cause luteolysis during late cycle. For instance, one or two doses of $PGF_{2\alpha}$ failed to cause luteolysis on day 5 (day 0 = oestrus) in non-lactating cow (Nascimento *et al.*, 2014). This has led to the hypothesis that CL needs to acquire luteolytic capacity before it is able to respond optimally to $PGF_{2\alpha}$ (Diaz & Wiltbank, 2005). This concept informed the conventional two-time injection of $PGF_{2\alpha}$ or its analogues for oestrus synchronisation in farm animal usually given at about ten days apart so that all the animals in the herd are captured at least once during the latter period (dioestrus) of oestrous cycle Xu, (2011). Irrespective of the debate about luteolytic capacity of CL, the obvious is that between day I-5 of oestrous cycle, the corpus luteum is still in the formative stage undergoing luteinisation/angiogenesis and getting ready for P_4 synthesis, the major reason for its non-responsive to $PGF_{2\alpha}$ at this time.

Dioestrus stage is the longest stage of the oestrous cycle usually about 10 days in cow (day 7-18, day 0 = oestrus) during which the predominant hormone is P_4. At this time, P_4 exerts a negative feedback on the release of the gonadotropin from the anterior pituitary via its influence on the Gonadotropin releasing hormone (GnRH) neurons of the hypothalamus (Bashour & Wray, 2012). Therefore, the implication of failure of luteolysis to occur is simply elongation of CL life span and subsequent prolongation of the dioestrus stage of the oestrous cycle in farm animals that include pig, horse, and ruminant.

However, during late dioestrus progesterone abolishes its own receptors from endometrial epithelia cells (Wathes *et al.*, 1996) to allow for up-regulation of oestrogen receptor and oxytocin receptor within the endometrium which trigger the release of $PGF_{2\alpha}$ from the endometrium (McCracken *et al.*, 1999). $PGF_{2\alpha}$ produced in the endometrium needs to get to the CL to directly cause regression of this organ while the *de novo* source of $PGF_{2\alpha}$ within human CL has no need for such transportation.

b) TRANSPORTATION OF LUTEOLYTIC AGENT TO THE OVARY

In farm animals, the luteolytic $PGF_{2\alpha}$ is produced by the endometrium, however, $PGF_{2\alpha}$ goes through different pathways of blood and/or lymphatic circulations to get to the ovary where it initiates luteolysis. This brings to the limelight the roles played by the special blood circulation network connecting the brain (hypothalamus and pituitary) to the gonads (ovary and testis) called hypothalamic pituitary-gonadal axis (Vadakkadath & Atwood, 2005). Reproductive hormones from point of synthesis in the brain are transported through the blood and bind to their respective receptors on the target organ (gonads). Hypothalamic pituitary-gonadal axis special portal system enables the concentration of hormone to be maintained by going directly to the gonads with minimum deviation to other body organs. In the case of $PGF_{2\alpha}$, the unique structure of the vascular utero-ovarian plexus allows transport of luteolytic $PGF_{2\alpha}$ pulses directly from the uterus to the ovary thus bypassing the systemic circulation via inter-current exchange. In the latter, there is passive diffusion of $PGF_{2\alpha}$ across a concentration gradient from the uterine vein into the ovarian artery.

In ruminant, counter current exchange of substances between the ovarian arteries and uterine veins does the work. The peak concentrations of $PGF_{2\alpha}$ in venous drainage of sheep and cattle during luteolysis are 0.6-9 ng/ml (Pate *et al.*, 2012). The synthesised $PGF_{2\alpha}$ escaped into the uterine vein which is adequately surrounded (coiling) by ovarian arteries. This allows diffusion of $PGF_{2\alpha}$ into the ovarian arteries carrying blood into the ovary. Luteolysis is local and ipsilateral to the horn having the corpus luteum (Baez *et al.*, 2017) with high concentration of prostaglandin dehyrodgenase, an enzyme responsible for synthesis of $PGF_{2\alpha}$ (Madore *et al.*, 2003). Right ovary is ipsilateral to the right uterine horn while the left ovary is contralateral to right horn. During pregnancy, day 16-25 in cow and 12-13 in sheep are critical periods for maternal recognition to occur, otherwise, any anti-luteolytic process then after this period may not be able to rescue demise of CL already sets in motion (Shorten *et al.*, 2010).

In porcine, there is also counter current exchange of substances between ovarian arteries and uterine vein. However, luteolysis is both local and systemic and hence, luteolysis is ipsilateral and contra lateral to the horn carrying the corpus luteum. The implication of this is that $PGF_{2\alpha}$ from the right horn gets to the right ovary through counter current exchange between ovarian arteries and uterine veins (Einer-Jensen & Hunter, 2005) and also gets to the left horn through the systemic circulation where it causes regression of the corpus luteum contralateral to the source of the $PGF_{2\alpha}$.

Therefore, it is very crucial that there are at least a minimum of two embryos, one in each of the horn (Ziecik *et al.*, 2006). Otherwise, the horn without an embryo is still capable of producing $PGF_{2\alpha}$ which gets to the horn carrying the embryo and causes embryo loss.

In Equine, there is no counter current mechanism. Luteolysis is systemic and $PGF_{2\alpha}$ is the luteolytic agent (Aurich & Budik, 2015). Secretion of $PGF_{2\alpha}$ follows the same pattern with ruminant model where pulsatile secretion of oxytocin from the posterior pituitary triggers episodic release of uterine $PGF_{2\alpha}$ (Shand *et al.*, 2000). Day 12-14 are critical days during pregnancy. In human and primate, the luteolytic $PGF_{2\alpha}$ is produced by the CL itself (Devoto *et al.*, 2009). Therefore, internal synthesis of $PGF_{2\alpha}$ eliminates the need for further transport to same CL to initiate luteolysis.

c) LUTEOLYTIC MECHANISM

Luteolysis is the regression of luteal tissue and loss of steroidogenesis by the same tissue that culminates into formation of corpus albican. The whole process may be divided into two main stages namely structural luteolysis and functional luteolysis (Sugino & Okuda, 2007). Functional luteolysis is rapid reduction of steroidogenesis particularly P_4 synthesis in the CL to complete loss of synthesis and occurs prior to structural luteolysis. Precursors of P_4 synthesis are conveyed to the CL through the vascular system which also played an important role in transportation of P_4 to the target tissue post synthesis. Therefore, choosing disruption in blood supply to CL as the first potent mechanism to explain functional luteolysis is logical. Arterio-venous anastomosis-like vessels were recently established in bovine CL undergoing luteolysis (Nio-Kobayashi *et al.*, 2016). The smooth muscle actin in these compromised vessels initiated constriction of the vascular lumen (less than 1.5 cm) and ultimately led to significant reduction in the amount of blood supplied to the CL. The result is gradual reduction to total loss of steroidogenic potential of the luteal tissue (Senger, 2012).

Structural luteolysis involves cells death, alteration of resident immune cell phenotype, cytokine production and finally, tissue involution (Hughes & Pate, 2019). Two types of cell deaths have been identified, namely apoptosis and necroptosis (Jonczyk *et al.*, 2019). Apoptosis is a programmed cell death and happened to be the first of the two (Niswender *et al.*, 1994), initiated by cytokine through Fas –Fas ligand system, a molecular pathway of cytokine-induced cell death (Taniguchi *et al.*, 2002). Necroptosis is another mechanism responsible for structural CL regression during $PGF_{2\alpha}$-induced luteolysis in bovine CL (Jonczyk *et al.*, 2019). In clear contrast to apoptosis, necroptosis is mediated via necrosis and inflammatory cells death and may arise from cellular damage or infiltration by pathogens.

Immune cells are characteristically resident cells of CL and their alteration occurs during time of luteolysis. Such alteration favours expression of macrophages, T lymphocytes and major histocompatibility complex class II molecules (Penny *et al.*, 1999). Specific functions of immune cells during luteolysis are to get rid of the dead cell debris via phagocytosis and abate any possible inflammatory response generated by dead and/or dying luteal cells (Pate & Landis-Keyes, 2001). Immune cells also control expression of other cytokines such as tumour growth factor (TGF) and anti-oxidants (Hou *et al.*, 2008).

The outcome of a successful luteolysis of CL is formation of small somewhat whitish scar-like structure called corpus albican. Presence of rough surfaces on the ovary due to many scars (of previous cycles) on the ovary are felt during trans-rectal palpation is an indication that the animal has been cycling. Luteolysis is desirable in a non-conceptive cycle to return the animal to follicular phase. Pathological conditions such as endometritis due to *Staphylococcus aereus* and *Eischeria coli* are able to delay luteolysis and extend CL life span in does (Boiti *et al.*, 1999), sequel to impairment in CL synthesis of luteolytic $PGF_{2\alpha}$.

LUTEOSTASIS

a) BACKGROUND

In a conceptive cycle, persistence of CL is critical for maintenance of P_4 production by corpus luteum, otherwise the regression of corpus luteum initiates embryo loss. This was first demonstrated in rabbit after a range of ovariectomy and lutectomy in 1900. The trio scientists Gustav Born, Ludwig Fraenkel and Vilhelm Magnus were the first scientists to conduct series of experiments that gave a clue to endocrine support of pregnancy by CL before extraction of P_4 from the CL at a much later date (Simmer, 1972).

The rescue of CL from luteolysis in a conceptive cycle is called luteostasis. In other words, luteostasis is the sustenance of CL for continued P_4 synthesis during the late period of the cycle. According to Hughes & Pate (2019), the mechanisms of luteostasis in mammalian species have been delineated into two broad categories, namely luteotrophic and anti-luteolytic. Anti-luteolytic is generation of opposing agents or substances that nullify the luteolytic effect of $PGF_2\alpha$ as found in food animal species. Luteotrophic supports development/sustainance of CL as well as P_4 synthesis which abrogates luteolysis as observed in primates and rodents. Luteotrophic factors include PGE_2 in dog (Kowalewski *et al.*, 2013), equine chorionic gonadotropin (eCG) in horse (Flores-Flores *et al.*, 2014) and human chorionic gonadotropin (hCG) in human(Vergani *et al.*, 2020).

Generally, the phenomenon through which CL is retained for continued synthesis of P_4 and luteolysis is abrogated

represents the first series of communication between the conceptus and the maternal endometrium is called maternal recognition of pregnancy (MRP). MRP was first coined in 1969 by Short according to Mori & Kanzaki, (1994). In other words, the ultimate aim of MRP agent is to sustain CL and initiate luteostasis. Therefore, it is reasonable labelling MRP agents as agent of luteostasis.

(b) AGENTS OF LUTEOSTASIS IN DIFFERENT SPECIES

Agents of MRP vary from one species to another and have been reviewed extensively elsewhere (Raheem, 2015). Briefly, agent of MRP in ruminant is interferon tau IFN-t. It was initially known as caprine trophoblastic protein, ovine trophoblastic protein and bovine trophoblastic protein in goat, sheep and cattle respectively before the adoption of Interferon tau (IFN-t) after its identification and molecular characterisation that occurred precisely 34 years ago (Ealy & Wooldridge, 2017). Interferon tau is essentially produced on day 14-17 in goat (Guillomot *et al.*, 1998), day 12-13 in sheep (Farin *et al.*, 1990) and day 16-18 in cow. The period of blastocyst elongation of blastocyst coincides with the time of generation of MRP/IFN-t in cow. It is also noted that elongation of blastocyst during this period is responsible for increase in the amount of IFN-t synthesised by the bovine blastocyst (Robinson *et al.*, 2006). A number of mechanisms have been hypothesised to explain how IFN-t abrogates luteolysis in ruminant. The most favoured mechanism is IFN-t suppression of oxytocin receptor which is essential for $PGF_{2\alpha}$ synthesis and release from the endometrium (Hansen *et al.*, 2017).

The agent of maternal recognition of pregnancy in mare remains controversial despite some authors suggesting proteins, PGE_2 and oestrogen (Klein & Troedsson, 2011). Two peculiarities of reproduction in mare include ovulation occurring in a particular region of the ovary called ovulation fossa (Walt *et al.*, 1979) and absence of concessional agent of MRP. A mechanical signalling that involves the embryo moving round the poles of the endometrium rather than chemical agent seems to be most acceptable condition essential for sustainance of CL during pregnancy (Swegen, 2021). The fact that demobilising a conceptus or mimicking embryo movement using a peanut initiates luteostasis further gives credence to this line of thought (Wilsher & Allen, 2011). Prostaglandin E_2 and $PGF_{2\alpha}$ produced by the embryo are primarily responsible for the peristaltic contraction of myometrium propelling the spherical embryo through the endometrium between day 16 to 26 post ovulation (Stout & Allen, 2001). PGE_2 produced by the embryo apart from initiating embryo descent from oviduct into uterine horn is also luteotrophic. In addition, endometrial cups also synthesises equine chorionic gonadotropin (eCG), a luteotrophic factor that support CL and synthesis of P_4 (Allen & Wilsher, 2009). Urinary equine chorionic gonadotrophin level in pregnant mare correlates with plasma concentration as reported by Roser & Lofstedt, (1989) hence, it can be used and may be used for pregnancy diagnosis in mare. Endometrial cup is as ephemeral as CL is destined to disappear at about 140 days of gestation.

In sow, the MRP signal is oestrogen which is produced by the blastocyst on day 14-18 post ovulation (Geisert *et al.*, 1990). The need for a minimum of one embryo on each horn has been emphasised in previous section because of system circulation of $PGF_{2\alpha}$ from the horn without embryo to the gravid horn and cause luteolysis there in (Senger, 2012). $PGF_{2\alpha}$ as an endocrine substance is usually transported via the blood and oestrogen luteostasis message is conveyed by redirecting the $PGF_{2\alpha}$ synthesis from endocrine (into blood) to exocrine that gets into the endometrial lumen (Bazer, 2013). In the lumen, $PGF_{2\alpha}$ is metabolised so far away from the CL in the ovary (Ref).

In human, CL is responsible for its own demise as the source of luteolytic $PGF_{2\alpha}$. The agent for MRP is human chorionic gonadotropin (hCG) (Ross, 1978). Human chorionic gonadotropin (hCG) is luteotrophic and is produced by the blastocyst about days 4 (day 0 = ovulation) as soon as the embryo descends from the oviduct into the endometrium. Aside primary function as agent of MRP to abolish luteolysis, hCG reportedly enhanced embryo implantation and survival, stimulation of trophoblast growth and differentiation (Ticconi *et al.*, 2007). The hormone is excreted and subsequently detectable in the urine of pregnant woman, which formed the basis for its use in pregnancy diagnostic strips.

CONCLUSION

The formation, maintenance, and regression of CL and steroidogenesis of the CL through luteogenesis, luteolysis and luteostasis are among the most significant and closely regulated events by hormones in mammalian reproduction which have been discussed in details in this review. Certainly, understanding the dynamics associated with these reproductive events occurring within the same anatomical space of the ovary will enable manipulating these processes to improve fertility in one hand or develop contraceptive measures on the other hand as seen in the use of $PGF_{2\alpha}$ for oestrus synchronisation or its combination with gonadotropins for super ovulation in farm animals.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare

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