Maintenance or regression of the corpus luteum during multiple decisive periods of bovine pregnancy

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Abstract

In ruminants, there are specific times during the estrous cycle or pregnancy when the corpus luteum (CL) may undergo regression. This review has attempted to summarize the physiological and cellular mechanisms involved in CL regression or maintenance during four distinct periods. The first period is near day 7 when animals that are ovulating after a period of low circulating progesterone (P4), such as first pubertal ovulation or first postpartum ovulation, are at risk of having a premature increase in Prostaglandin F2α (PGF) secreted from the uterus resulting in early CL regression and a short estrous cycle. The second period is when normal luteolysis occurs at day 18-25 of the cycle or when the CL is rescued by interferon-tau secreted by the elongating embryo. The uterine mechanisms that determine the timing of this luteolysis or the prevention of luteolysis have been generally defined. Induction and activation of endometrial E2 receptors result in induction of endometrial oxytocin receptors that can now be activated by normal pulses of oxytocin. Of particular importance is the observation that the primary mechanisms are only activated through local (ipsilateral) and not a systemic route due to transfer of PGF from the uterine vein to the ovarian artery. In addition at the CL level, studies are providing definition to the cellular and molecular mechanisms that are activated in response to uterine PGF pulses or pregnancy. The third period that is discussed occurs in the second month of pregnancy (day 28-60) when undefined mechanisms result in CL maintenance of an ipsilateral CL but regression of a contralateral (opposite side from pregnancy) CL. The final period that is discussed is regression of the CL just prior to parturition. Although, cortisol from the fetus appears to be the primary initiator of luteolysis, PGF seems to be the final signal that causes regression of the CL. Thus, in all four periods, regression of the CL is likely to be caused by the direct actions of PGF that is secreted from the uterus. The uterine mechanisms that result in secretion of PGF seem to be normally inhibited during the early luteal phase, making short luteal phases not a normal event, and are altered during early pregnancy (day 18-25) resulting in prevention of luteolysis. During much of pregnancy, the mechanisms that cause PGF secretion from the uterus in response to oxytocin are intact but luteolysis does not normally occur, perhaps due to lack of efficient utero-ovarian transfer of PGF.

Introduction

Alterations in the development, function, and regression of the corpus luteum (CL) is a primary feature of the reproductive cycle and pregnancy of mammals. The primary role of the CL in these processes is due to secretion of the hormone progesterone (P4). From a historical perspective, the first detailed description of CL was by Regnier deGraaf (1641-1673) when he described the "globules" and explained that in rabbits "the number of globules equals the number of offspring from a particular mating" (deGraaf, 1672 cited by Jocelyn and Setchell, 1972). Later, Gustav Born (1851-1900), an excellent histologist, forwarded the idea that it was a gland of internal secretion, based on the high vascularity and lack of ducts, and speculated that it could be involved in pregnancy (see excellent reviews by Simmer, 1971; Magnus and Simmer, 1972). Two of his students, Ludwig Fraenkel and Vilhelm Magnus, independently tested this hypothesis in their own laboratories using slightly different experimental methods. In Germany, Ludwig Fraenkel performed bilateral ovariectomy or electrocautery of all CL in mated rabbits and found that they did not maintain their pregnancies (Fraenkel and Cohn, 1901). In Norway, Vilhelm Magnus performed galvano-cautery of all CL as well as bilateral ovarian removal in mated rabbits and also reported that pregnancy was not maintained (Magnus, 1901). Both researchers reached the same conclusion that the CL was essential for maintenance of pregnancy. Magnus later called the pregnancy-maintaining endocrine secretion from the CL "differentieringsstofe" (differentiating stuff), the first name given to the hormone later known as progesterone (P4; Magnus, 1901). The initial reports were met with some skepticism. Fraenkel doggedly continued his research during the next decade on more than 160 rabbits eventually concluding that "Thus by the power of large numbers my thesis is proven: The ovary, in particular the CL, regulates the implantation and initial development of the embryo" (Fraenkel, 1910).

Possibly the most interesting biological properties of the CL are related to the incredible dynamics of this tissue. From the remains of the ovulated follicle, a new distinct structure is born (Smith *et al.*, 1994). After differentiation, the CL is composed of multiple cell types (Wiltbank, 1994). The thecal and

granulosa cells of the follicle, differentiate into the small and large steroidogenic cells of the CL. This transformation involves a steroidogenic change as these cells develop the enzymatic machinery to produce tremendous quantities of P4. From a mass perspective, the granulosa cell is only 10 μm in diameter prior to the LH surge but increases to 38 μm when it develops into the fully-functional bovine large luteal cell. This calculates to an increase in volume from about 500 μm^3 in the granulosa cell to almost 30,000 μm^3 in the large luteal cell, over a 50-fold increase in cellular volume (Wiltbank *et al.*, 2012). In addition, there is rapid and extensive angiogenesis as the avascular follicular antrum remodels into a highly vascularized structure with every large luteal cell adjacent to multiple capillaries (Ellinwood *et al.*, 1978) and the highest blood flow per gram of tissue in the body (Wiltbank *et al.*, 1989). Then, abruptly, at specific, critical times during the cycle or pregnancy, the structure is put to death. For example, the bovine CL goes from a fully-functional structure of 4 to 6 g, to a structure with little production of P4, low blood flow (Zalman *et al.*, 2012), and structurally <20% of the original volume, a process known as luteolysis or CL regression.

There are four time periods that will be discussed in this review article when CL regression commonly occurs in dairy and beef cattle (Fig. 1). The first potential luteolysis period that will be discussed is at about day 7. In most beef cattle and many dairy cattle, the first post-partum estrous cycle and rarely, other later estrous cycles, will have a short duration of ~10 days, due to early regression of the CL at ~day 7. Luteolysis at this stage is not prevented by pregnancy but specific mechanisms prevent this early regression during most estrous cycles. The second period is the classical time for luteolysis in non-pregnant cows, near day 18-25. In pregnancy, maintenance of the CL during this period has been termed "Maternal Recognition of Pregnancy". There is a great deal of information available on the factors, events, and mechanisms related to luteolysis and prevention of luteolysis during this period. For example, there is a primary role for uterine prostaglandin F2α (PGF), acting in a local manner, as the initiator of luteolysis during this classical period of luteolysis, with many of the uterine and luteal mechanisms that determine this process being clearly defined. In addition, a primary role for embryonic interferon-tau (IFNT) in preventing luteolysis has been clearly demonstrated with the precise mechanisms still an active area of research. The third period is during the second month of pregnancy or day 30 to 60 when CL regression can occur but is generally prevented through mechanisms that remain undefined. The final period of luteolysis occurs near the end of pregnancy with an increase in circulating estradiol (E2) followed by a tremendous increase in circulating PGF that is associated with an abrupt decrease in circulating P4 due to CL regression. Regression of the CL at this time is critical for the timing and physiology of the normal parturition process. The CL is the primary source of P4 throughout the estrous cycle and pregnancy, although during mid to late pregnancy the placenta secretes a variable amount of P4 in individual pregnant cows (Fig. 1). This review will emphasize the similarities and differences during these times of luteolysis, in terms of origin of PGF and intrauterine and intraluteal mechanisms that underlie each occurrence of luteolysis.
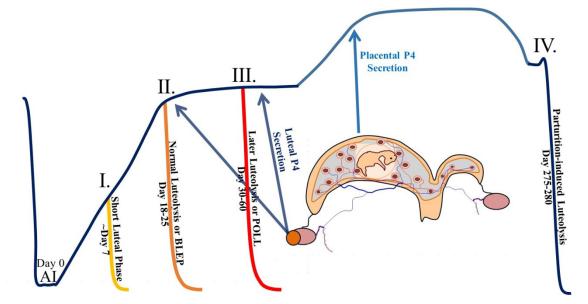

Figure 1. Theoretical diagram of circulating progesterone (P4) concentrations during pregnancy in cattle emphasizing the four key periods when luteolysis can occur. Period I - Luteolysis happens near day 7 and this leads to a short luteal phase. Pregnancy does not protect from this early luteolysis. Period II - Normal time of luteolysis at day 18-25 when prostaglandin F2α pulses from the uterus regress the corpus luteum. During pregnancy, secretion of interferon-tau from the uterus leads to Blockade of Luteolysis in Early Pregnancy (BLEP) and maintenance of CL structure and function. Period III - Later luteolysis that can occur during the second month of pregnancy leading to pregnancy loss. During these stages of pregnancy, there are still undefined mechanisms that produce Prevention of Later Luteolysis (POLL) extending the CL lifespan through later pregnancy. Period IV - Parturition-induced luteolysis occurs about 2 days before parturition and allows continuation of the cascade of events that produce parturition.

Period I: Short luteal phase and early CL regression - day 5-7

In ruminants, short cycles, due to an inadequate luteal phase, occur in some specific physiological situations. For example, short cycles have been documented in cattle and sheep following the first ovulation after puberty (Berardinelli and Butcher, 1979; Berardinelli *et al.*, 1979), following the first ovulation post-partum in dairy and beef cattle (Garverick *et al.*, 1992b), and after the first ovulation of the breeding season in ewes that were previously not cycling (Hunter, 1991). For example, in beef cattle that have been induced to ovulate by calf removal or treatment with an ovulation inducing agent, such as human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone (GnRH), there is generally a very high incidence of shortened luteal phases (~80%). In dairy cattle, the first post-partum ovulation can be followed by a short cycle, but a much lower incidence has been reported (~27%; Table 1). It seems obvious that the presence of short cycles can reduce fertility since pregnancies are unlikely to occur because the embryo has generally not hatched from the zona pellucida and definitely not undergone embryonic elongation at the time of this early CL regression. Thus, fertility is absent in these cows, whether or not they have had fertilization and an appropriately-developing embryo.

Table 1. Incidence of short luteal phases or short cycles in dairy cattle.

Type of cattle	Short cycle (%)	Reference
Dairy cattle		
Lactating Holstein	76/281 (27.1%)	Fallon (1958)
Lactating Holstein	16/118 (13.6%)	Hinshelwood *et al.* (1982)
Lactating Holstein	9/27 (33.0%)	Stevenson and Britt (1979)
Lactating Friesian	5/18 (27.8)	Savio *et al.* (1990)
Lactating Holstein	21/39 (53.8%)	Staples *et al.* (1990)
Lactating Holstein	176/645 (27.3%)	Royal *et al.* (2000)
Total dairy	303/1,128 (26.9%)	

It is also clear that the short cycle is due to a shortened lifespan of the CL, for example in cattle, the CL regresses at 6-7 days after previous estrus. The cow then shows a subsequent estrus at 8-11 days after the previous estrus. As evidenced by the physiological conditions that result in short cycles, one of the primary risk factors for the shortened CL lifespan is an extended period without circulating P4 prior to the ovulation that produces the inadequate CL.

To understand the physiological mechanisms that produce the short estrous cycle, a number of different ruminant experimental models have been utilized. One model that has been utilized is the ewe in the non-breeding season that is induced to ovulate with GnRH treatment (Hunter, 1991; 0.25 µg every 2 h for 18-24 h, followed by an ovulatory dose of GnRH, 125 µg). Pretreatment for 36 h with P4 resulted in 100% of ewes with a normal CL lifespan, whereas, induction of ovulation with this protocol without pretreatment with P4 resulted in ~70% shortened luteal phases. In ewes, CL regression occurs between day 4 and 6 after the induced LH surge (Robinson *et al.*, 2008). In beef cattle, induction of the first post-partum ovulation by early weaning or temporary calf removal or by using hormonal treatments, such as GnRH or hCG, results in a high percentage of cows with short cycles, whereas pretreatment with P4 or progestogens before these induction procedures prevents these short cycles (Copelin *et al.*, 1988; Salfen *et al.*, 1995). Finally, in cycling dairy heifers or cows, a high percentage of short cycles is induced if cows are given a premature treatment with GnRH following induction of luteolysis with PGF (0 or 24 h after PGF given on day 6 or 7 of the estrous cycle; Peters and Pursley, 2003; Rantala *et al.*, 2009). Each of these models is characterized by inadequate circulating E2 during the proestrous period, generally ovulation of a smaller follicle, production of a CL with a shortened lifespan, and a short estrous cycle.

Using these animal models, the mechanisms that produce early regression of the CL have generally been divided into effects related to: 1) the preovulatory follicle, 2) the CL, and/or 3) the uterus. Related to the follicle, there are clear differences between the preovulatory follicle of ewes or cattle that have a shortened luteal phase including: decreased LH receptors in granulosa cells and decreased follicular E2 production, as evidenced by decreased circulating E2 or decreased E2 in follicular fluid (Hunter *et al.*, 1986; White *et al.*, 1987; Inskeep *et al.*, 1988; Braden *et al.*, 1989a, b). Thus, follicular function prior to short estrous cycles is clearly defective, and preovulatory circulating E2 concentrations are reduced in each of the physiological situations that result in a shortened luteal phase.

Related to the CL, initial development and function of the CL were similar until 4 days after the LH surge in ewes with normal or shortened luteal phases. After that time, the CL regressed rapidly in a manner that closely resembled the timing of CL regression at the end of the luteal phase (Hunter *et al.*, 1989). In beef cattle, the patterns of P4 were similar until day 5 after estrus and subsequently there was a rapid decrease in circulating P4 as CL regression ensued (Copelin *et al.*, 1987). One suggestion has been that short-lifespan CL lack gonadotropin support or gonadotropin responsiveness. Contrary to this idea, there were no differences in LH receptors or adenylate cyclase activity in early CL that were destined for short-lifespan vs. longer lifespan (Smith *et al.*, 1996). In addition, there were no detectable differences in LH secretion during the early luteal phase for these two types of animals (Garverick *et al.*, 1988). Further, treatments with luteotropins, such as treatment with

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GnRH pulses or hCG, were unable to overcome the shortened luteal lifespan (Smith *et al.*, 1996). In addition, there are no differences in PGF responsiveness of CL destined to have normal or short lifespan (Copelin *et al.*, 1988). Thus, although the CL clearly regresses prematurely in cows or ewes with a short cycle, there is no evidence that the CL is functionally incompetent or that it regresses due to mechanisms that are internal to the CL.

Finally, most evidence is consistent with a primary role for the uterus in shortened luteal lifespan in ruminants. The most definitive experiments utilized hysterectomized cattle or ewes that were induced to ovulate. Intact cows had an estrous cycle of 8.8 days, whereas, hysterectomized cows that were treated similarly had a prolonged functional CL and did not return to estrus (Copelin *et al.*, 1987). Similarly, hysterectomy resulted in normal CL function in ewes destined to have short-lived CL (Southee *et al.*, 1988). Thus, it seems clear that the shortened luteal lifespan is due to a direct effect of the uterus. Active immunization against PGF (Copelin *et al.*, 1989) or inhibition of PGF secretion were both effective in extending the CL lifespan and increasing P4 secretion by the CL, indicating that uterine PGF is the primary cause of the shortened luteal phase. Consistent with this idea, cows destined to have short-lived CL have early secretion of PGF from the uterus (Zollers *et al.*, 1991) and an early increase in circulating metabolite of PGF that begins near the time of the first increases in circulating E2 during the first follicular wave (Southee *et al.*, 1988; Hunter *et al.*, 1989; Cooper *et al.*, 1991; Hunter, 1991; Garverick *et al.*, 1992b). In addition, intrauterine infusion of IFNT, the protein that normally causes maintenance of the CL during pregnancy in ruminants, can prevent short luteal phases (Garverick *et al.*, 1992a). At least part of the action of IFNT is a reduction in uterine secretion of PGF. Thus, all of these diverse types of evidence clearly point to premature secretion of PGF from the uterus as the direct initiator of premature luteolysis in cows with a short-lived CL.

There also seems to be a critical role for E2 from the follicle in development of the mechanisms associated with a shortened CL lifespan. Reduced preovulatory E2 can produce a short CL lifespan (Vasconcelos *et al.*, 2001; Peters and Pursley, 2003; Rantala *et al.*, 2009), even in animals with elevations in P4 prior to the preovulatory period. However, supplementation of early postpartum beef cattle with E2 alone was not sufficient to restore normal luteal phases but they required both elevated P4 prior to the preovulatory period and elevated E2 during the preovulatory period to have normal CL lifespan (Sa *et al.*, 2009). Thus, elevated circulating P4, followed by a decrease in P4 and an increase in circulating E2 are important components that regulate a lack of development of oxytocin responsiveness during the early luteal phase and prevent short-lived CL, in normal physiological situations (Hunter *et al.*, 1989; Hunter, 1991; Beard and Hunter, 1996). In addition, there is a critical role for E2 from the dominant follicle of the first follicular wave, after ovulation, in the mechanisms that

underlie premature PGF secretion in short luteal phases (Beard and Hunter, 1994). This is evidenced by the fact that treatment with steroid-stripped follicular fluid inhibited growth of the dominant follicle and premature development of oxytocin-responsiveness in ewes destined to have a short-lived CL. Thus, it seems clear that elevated P4 followed by elevated E2 in the absence of P4 are critical for preventing premature E2-induction of oxytocin responsiveness during the early luteal phase and induction of early luteolysis.

Figure 2 shows a theoretical, simplified model comparing changes in the uterine endometrial cells during the early luteal phase in animals destined to have CL with normal or shortened CL lifespan. In animals destined to have a normal lifespan, at day 5-7 the endometrial cells do not have E2 responsiveness, due to action of P4 and E2 prior to ovulation. Therefore, even though there is an increase in E2 during the first follicular wave, this E2 does not have an effect on the uterine endometrial cells, preventing induction of oxytocin receptors, and preventing premature luteolysis. However, in animals that will have a short life-span CL, E2 responsiveness is present in the uterine endometrial cells and the increase in circulating E2 during the first follicular wave allows induction of oxytocin receptors, with subsequent oxytocin-induced PGF secretion, and premature luteolysis. These events resemble the events that occur at day 17-20 in the uterine endometrial cells of animals destined to have normal CL lifespan.

Period II: Normal luteolysis: role of uterus and PGF - days 18-25 of estrous cycle

Under normal conditions, if no fertilization occurs during an estrous cycle, the CL will regress at ~18-19 days after previous estrus. This process is referred to as normal luteolysis, and involves a decrease in P4 (functional luteolysis) as well as a decrease in CL volume and blood flow (structural luteolysis). Functional luteolysis occurs over a period of ~24 h in individual cows or sheep, if luteolysis is designated as circulating P4 < 1 ng/ml, or in ~32 h if <0.5 ng/ml is used as the designation for functional luteolysis (Ginther *et al.*, 2007).

The role of the uterus in determining the lifespan of the CL was first demonstrated in guinea pigs by showing that CL were maintained after hysterectomy (Loeb, 1927). In ruminants, a clear demonstration of the role of the uterus in luteolysis was published in 1956 by using hysterectomy of both sheep and cattle (Wiltbank and Casida, 1956). Sheep and cattle that had complete removal of the uterus did not return to estrus and CL lifespan was greatly prolonged. For example, sheep with CL marked with India ink were still present at 52, 53, 76, 98, and 107 days after hysterectomy. Similarly, cows that had complete hysterectomy had large, marked CL present at 27, 98, and 154 days after hysterectomy (Wiltbank and Casida, 1956). Thus, complete removal of uterus led to maintenance for a long but not yet clearly defined time. Interestingly, when part of the uterus (ipsilateral to the CL) remained after the hysterectomy surgery, CL regression occurred and

animals returned to estrus. Numerous hysterectomy and unilateral hysterectomy studies have been performed and the role of the uterus in luteolysis is clearly delineated (Collins *et al.*, 1966). In addition, ipsilateral (uterine horn on the same side as CL) hysterectomy invariably prolonged the lifespan of the CL, while contralateral hysterectomy consistently failed to affect the CL lifespan (Inskeep and Butcher, 1966).

It was soon realized that the uterine-derived luteolysin that regressed the CL was able to arrive at the ipsilateral CL through a local veno-arterial transfer pathway. The ovarian artery in ruminants is extremely convoluted and in close apposition to the uterine vein, thus allowing transfer of the uterine luteolysin, PGF, to the ovarian artery (Ginther and Del Campo, 1974; Mapletoft *et al.*, 1976a). In an experiment in which the convoluted ovarian artery was separated from the uterine vein, three out of four ewes maintained the CL until slaughter on day 25 (Barrett *et al.*, 1971). Experiments involving unilateral hysterectomy and subsequent cross-over anastomosis of the uterine veins provided strong evidence for the local delivery of a uterine luteolysin to the ovarian artery (Mapletoft *et al.*, 1976a). When the uterine vein from the intact horn was joined with the uterine vein on the hysterectomized side with the CL, the CL regressed at the normal time clearly demonstrating the involvement of the local utero-ovarian, veno-arterial pathway in luteolysis during this period (Mapletoft *et al.*, 1976a).

The possibility that PGF was the luteolytic agent was first suggested during a reproductive workshop in 1965 (Hansel, 1966). Evidence was subsequently provided in rats that treatment with PGF2α produced luteolysis (Gutknecht *et al.*, 1969; Pharriss and Wyngarde 1969). Thereafter, a series of experiments by McCracken using auto-transplanted ovaries demonstrated the luteolytic effect of PGF in sheep (Goding *et al.*, 1967; McCracken, 1971). There are now multiple types of evidence that convincingly demonstrate that PGF is the uterine luteolysin in ruminants (Knickerbocker *et al.*, 1988). First, PGF is abundantly produced in the uterus of non-pregnant ruminants (McCracken *et al.*, 1972) and there are increased concentrations of PGF in uterine venous drainage, uterine flushings, and uterine tissue near the expected time of luteolysis (Wilson *et al.*, 1972). Second, pulses of uterine vein PGF and the circulating concentrations of the PGF metabolite (PGFM; 15-Keto-13,14-dihydro-PGF2α) correspond to the time of decreasing P4 in non-pregnant heifers (Kindahl *et al.*, 1976; Ginther *et al.*, 2007). Third, inhibition of uterine PGF production prevents spontaneous luteolysis in both ewes and heifers (Lewis and Warren, 1977). Fourth, passive immunization with antibodies that are specific to PGF prolonged the lifespan of the CL (Fairclough *et al.*, 1981). Fifth, there is good evidence that PGF can be efficiently exchanged from the uterine vein to the ovarian artery in sufficient quantities to make the local mechanisms physiologically feasible (Lamond *et al.*, 1973; McCracken *et al.*, 1981). Finally, treatment with pulses of PGF that mimic the natural PGF pulses can induce complete luteolysis that resembles natural

luteolysis (Schramm *et al.*, 1983; Ginther *et al.*, 2009; Atli *et al.*, 2012). Thus, evidence is compelling that luteolysis in ruminants is initiated by PGF coming from the non-pregnant uterus.

The pattern of PGF secretion has clearly been shown to be pulsatile. Figure 3 shows a typical pattern for PGFM, oxytocin, and P4 during luteolysis in an individual cow undergoing luteolysis between day 18 and 20. As shown, P4 concentrations decrease rapidly with most of the decrease occurring in a 24 h period. The decrease in P4 is associated with four distinct pulses of PGF, which are reflected in the circulating PGFM pulses shown in Fig. 3. Finally, pulses of circulating oxytocin occur routinely prior to luteolysis with little effect on circulating PGFM. However, during the time of luteolysis, each oxytocin pulse is associated with a pulse of PGFM. This pattern emphasizes the critical role for oxytocin responsiveness, i.e. oxytocin receptors, in production of PGFM pulses and ultimately luteolysis.

The cellular mechanisms within the uterine endometrial cells that produce the PGF pulses was shown in a simplified manner in Fig. 2 and is shown in greater detail in other reviews (McCracken *et al.*, 1999; Spencer and Hansen, 2015). Clearly the induction of E2 receptors has a central role in the mechanisms that initiate these pulses. During most of the normal luteal phase, expression of E2 receptors in endometrial cells is inhibited by elevated circulating P4 acting on P4 receptors in these cells. Near the end of the luteal phase, elevated P4 begins to downregulate P4 receptors and this allows E2 receptor expression near the time of luteolysis (Spencer and Bazer, 1995; Spencer *et al.*, 1995). Initiation of luteolysis is dependent upon activation of these E2 receptors by the increase in circulating E2 that accompanies development of a dominant follicle in the preovulatory follicular wave. This is illustrated by the delay in luteolysis that is caused by elimination of circulating E2 by either ultrasound-guided ablation of follicles (Araujo *et al.*, 2009) or inhibition of follicle growth by treatment with steroid-stripped follicular fluid (Salfen *et al.*, 1996). This delay in luteolysis is prevented by treatment with low doses of E2 (Salfen *et al.*, 1996; Araujo *et al.*, 2009). One of the major actions of E2 in the endometrial cell at this time is the induction of oxytocin receptors (Robinson *et al.*, 2001). After induction of oxytocin receptors, uterine endometrial cells produce pulses of PGF secretion in response to the natural pulses of oxytocin that occur during the day (Ginther *et al.*, 2012).

Thus, natural luteolysis is connected to distinct PGF pulses from the uterine endometrial cells that are induced by oxytocin pulses. Studies using [³H]-PGF have indicated that during the peak of a PGF pulse, ~10% of secreted PGF will be transported from the uterine vein to the ovarian artery (Lamond *et al.*, 1973; McCracken *et al.*, 2010). How this PGF is transported between the vascular systems has been delineated in elegant recent studies that showed expression of a specific PG Transporter in the three layers, tunica intima, tunica media, and tunica adventitia, of both the utero-ovarian vein and the ovarian artery (Lee *et al.*,

2010; McCracken *et al.*, 2011). The primary PG Transporter is a member of the organic solute carrier family that has 12-transmembrane domains and is termed SLCO2A1, also known as OATP2A1 (Kanai *et al.*, 1995; Schuster, 1998, 2002). A specific inhibitor of the PG Transporter, DIDS, was able to block luteolysis but did not change expression of E2 receptor, oxytocin receptor, Cox-2, PG transporter, or uterine production of PGF (Lee *et al.*, 2013). Thus, all luteolytic mechanisms were intact but still efficient PGF transport, in this case out of the endometrial cells, is needed for the luteolytic process.
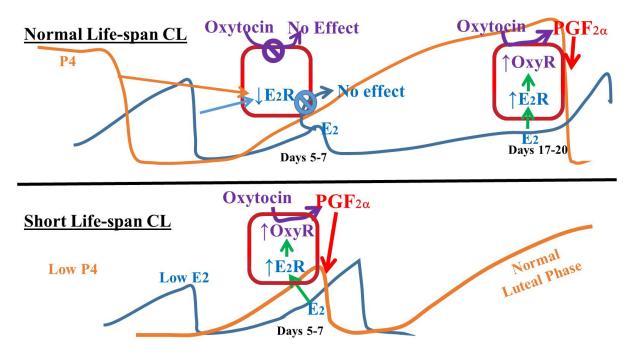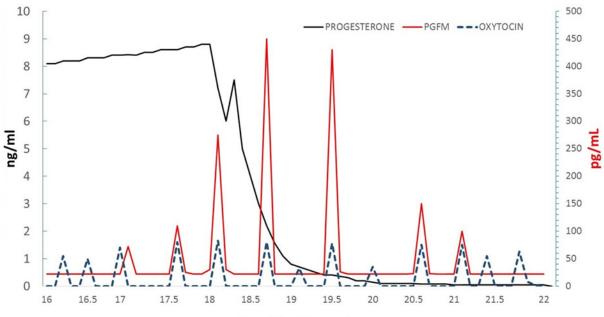

Figure 2. Proposed physiological model for the mechanisms that produce a CL with a short or normal life-span. The cell that is shown is the uterine endometrial cell at day 5-7 or at day 17-20 during the normal CL lifespan. Text discusses the mechanisms shown in the figure. E2R = estradiol receptor; OxyR = Oxytocin Receptor; P4 = progesterone; E2 = estradiol-17β; PGF2α = prostaglandin F2α.

Figure 3. Diagram of the patterns of circulating progesterone, oxytocin, and PGFM concentrations during the time of luteolysis in cattle. As luteolysis approaches, pulses of oxytocin act on the uterine endometrial cells to cause production of pulses of PGF, detected as PGFM in the peripheral circulation, and these pulses cause the decrease in circulating P4 and luteolysis.

Once PGF reaches the CL, some of the most exciting cellular and molecular processes are activated, resulting in the complete luteolytic process. Although many studies have evaluated the processes that are involved in the biological action of PGF in the CL, most of these studies utilized supra-physiological doses of PGF. Recent studies have either monitored the mechanisms that follow natural PGF pulses (Ginther and Beg, 2009) or used more physiological pulses of PGF in an attempt to mimic and synchronize the mechanisms that occur during natural luteolysis (Ginther *et al.*, 2009; McCracken *et al.*, 2012). Our laboratory has given intrauterine injections of low doses of PGF in order to evaluate gene expression in response to synchronized PGF pulses (Atli *et al.*, 2012). Figure 4 shows a simplified view of some of the gene expression changes that are happening within the CL following each PGF pulse. Although only a single cell is shown, ostensibly a large luteal cell since they contain most of the PGF receptors, it should be understood that multiple cell types and complex processes are occurring during luteolysis.

Five key types of gene expression events are illustrated in response to each PGF pulse. The early response gene, Jun, is shown to increase in response to each PGF pulse, which is representative of many early response genes (Atli *et al.*, 2011). The PGF synthesis pathways are complex but two genes are shown, one involved in PGF production, prostaglandin G/H Synthase-2 (PTGS2), and one involved in PGF metabolism, prostaglandin Dehydrogenase (PGDH). After the first PGF pulse both genes are stimulated, in spite of the fact that PGDH will eventually be inhibited during the luteolysis process, after the third pulse. The continued induction of the PGF synthesis pathways and the eventual inhibition of the PGF metabolism pathways will allow intraluteal PGF production and an

autoamplification pathway for PGF production (Tsai and Wiltbank, 1996, 1997). Production of P4 is eventually inhibited but, similar to PGDH, steroidogenic acute regulatory protein or StAR, is stimulated by the first pulse of PGF but then inhibited by pulse 2, 3, and 4. Eventually all of the steroidogenic pathway genes are inhibited but StAR is the most acutely regulated.

Many genes that are associated with immune function are stimulated during the luteolytic process. Some may be due to production of immunomodulatory molecules from luteal cells and eventually increased expression is due to influx of immune cells into the CL during the luteolytic process. Thus, immune-related genes begin to be stimulated mostly after the 2nd PGF pulse and continue to increase after the 3rd and 4th pulses. Alterations in angiogenic pathways are a key part of the luteolysis process. Expression of VEGFA is shown as an example of alterations in angiogenesis during pulses of PGF. After the first pulse there is a paradoxical increase in VEGF mRNA expression and then all subsequent pulses produce inhibition of genes that are involved in stimulating blood vessel formation and function.

Thus, this simple diagram illustrates some of the key pathways that are being activated during the luteolytic process. Transcriptional pathways, such as the ones regulated by some of the early response genes, are activated and are likely to mediate the subsequent changes in gene expression. Steroidogenesis is decreased as the CL proceeds through functional luteolysis. Structural luteolysis proceeds as blood vessels begin to breakdown and immune cells are involved in key structural and functional changes that occur during luteolysis. Finally, although PGF pulses from the uterus are the initiators of luteolysis, intraluteal production of PGF is probably important for expression of the complete luteolytic pathways.
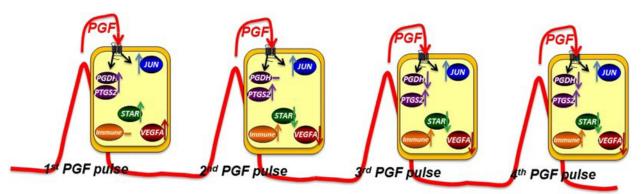

Figure 4. Physiological model of the changes in gene expression within the CL during intrauterine injection of low doses of PGF, designed to mimic physiological pulses of PGF occurring during luteolysis. See text for details.

Period II. Blockade of luteolysis in early pregnancy - day 18-25 of pregnancy

Pregnancy causes a blockade of luteolysis that has been sometimes termed "Maternal recognition of pregnancy". In ruminants, the pregnancy protects the CL from regression through local and not systemic pathways. This has been clearly demonstrated in a series of elegant experiments with isolated horns or vascular

anastomoses. For example, transfer of embryos into a surgically-isolated uterine horn resulted in CL regression if the embryo was transferred contralateral to the CL but the CL was maintained if the embryo was transferred ipsilateral to the pregnancy in both cows (Del Campo *et al.*, 1977) and ewes (Moor, 1968). In surgically-isolated horns, surgical anastomosis of the main uterine vein from the gravid side to the uterine vein on the non-gravid side resulted in maintenance of

the CL on the non-gravid side in both ewes (Mapletoft *et al*. 1975) and cows (Del Campo *et al*., 1980). This demonstrated that the pregnancy signal was local and not systemic and was carried in the local uterine vein. Similarly, anastomoses of the ovarian artery from the gravid side to the non-gravid side resulted in CL maintenance (Mapletoft and Ginther, 1975; Mapletoft *et al*., 1976c) demonstrating that the signal passed from the uterine vein to the ovarian artery, only on the same side and not the opposite side from the pregnancy. Thus, it is clear that even though some pregnancy signals may escape the uterus, the critical pregnancy signal that protects the CL in ruminants during early pregnancy is acting locally by passing from the uterine vein to the ovarian artery and not through the systemic circulation. In addition, these studies demonstrated that maintenance of pregnancy is not just the absence of a signal, such as the absence of PGF pulses, but the active blockade of luteolysis. This is clear since uterine vein blood from the non-gravid horn is still present when the blood from uterine vein of the gravid horn is added and the CL is protected. The two ewes that had clots in the anastomosis had normal CL regression.

Early embryo transfer experiments showed that if the embryo was flushed from the uterus on day 13 or before in the ewe (Moor and Rowson, 1966; Moor *et al*., 1969) or day 16 or before in the cow (Northey and French, 1980) there was normal timing of CL regression. In contrast if the embryo was flushed from the uterus after this "critical period", the CL lifespan was extended, demonstrating the time when the pregnancy signal began to be secreted by the embryo. In cyclic ewes, intrauterine infusion of homogenates or secreted proteins from day 14-15 embryos extended CL lifespan, whereas, homogenates of day 21-25 embryos did not alter CL lifespan (Rowson and Moor 1967; Godkin *et al*., 1984b), demonstrating the limited interval during pregnancy when the signal is secreted by the conceptus. The active principal in the homogenates was heat and protease-labile, and had properties consistent with a low molecular weight protein (Rowson and Moor, 1967; Martal *et al*., 1979; Godkin *et al*., 1982). Later studies showed that a single protein, termed ovine or bovine trophoblast protein-1 at the time and later IFNT, was solely responsible for maintenance of the CL during pregnancy in ruminants (Godkin *et al*., 1984a, 1997; Thatcher *et al*., 1984).

Thus, during the critical period of day 17 to 25 in cattle, the embryo is dramatically elongating, nourished by histotroph in the uterine lumen. The ruminant trophectoderm secretes IFNT during elongation of the early embryo and IFNT has been shown to be the definitive signal for CL maintenance during early pregnancy (Roberts, 1996; Bazer *et al*., 1997). In uterus, IFNT acts in a paracrine manner to prevent expression of estrogen receptor alpha and oxytocin receptor in endometrial luminal epithelium and superficial glandular epithelium, thereby altering release of luteolytic pulses of PGF (Spencer *et al*., 2007b). Interferon-tau also stimulates expression of specific genes, termed interferon-stimulated genes (Antoniazzi *et al*., 2013), in the uterus (Johnson *et al*., 1999) and in

peripheral tissues such as the CL (Oliveira *et al*., 2008; Bott *et al*., 2010) and peripheral blood cells (Gifford *et al*., 2007; Shirasuna *et al*., 2012). Thus, circulating IFNT that escapes the uterine lumen might prevent CL regression by acting directly on CL and this action could be independent or synergistic with the actions of IFNT on uterine PGF secretion.

Previous studies have also indicated that the CL of pregnancy has reduced sensitivity to PGF (Silvia and Niswender, 1984, 1986; Silvia *et al*., 1984a). Much of this resistance to PGF action is ascribed to actions of prostaglandin E2 and E1 (termed PGE in this proposal) coming from the pregnant uterus. Indeed, PGE can block natural or PGF-induced luteolysis either *in vivo* or *in vitro* (Michael *et al*., 1993; Miyamoto *et al*., 1993; Fortier *et al*., 2004; Weems *et al*., 2011). In addition, recent studies showed that endocrine delivery of recombinant ovine IFNT, via uterine or jugular vein, protected the ovine CL from the luteolytic actions of PGF, maintaining intraluteal and circulating P4 and CL volume (Antoniazzi *et al*., 2013).

It is clearly established that P4 from the CL is essential for maintenance of pregnancy and that IFNT from the elongating embryo is the definitive signal for CL maintenance during early pregnancy (Roberts, 1996; Bazer *et al*., 1997; Spencer *et al*., 2007b; Dorniak *et al*., 2013). At this time, there is still substantial controversy regarding the precise endocrine pathways involved in maintenance of the CL by IFNT with three potential pathways being most supported but by different research groups. First, the classical mechanism is that IFNT changes uterine gene expression resulting in reduced pulses of PGF and thus lack of luteolysis (Thatcher *et al*., 1984; Knickerbocker *et al*., 1986; Danet-Desnoyers *et al*., 1994; Spencer *et al*., 2007a; Dorniak *et al*., 2013). Second, IFNT increases uterine production of PGEs (PGE1 and PGE2) and PGE blocks the action of PGF at the CL, maintaining CL function (Ottobre *et al*., 1984; Silvia *et al*., 1984a, b; Wiltbank and Ottobre, 2003; Krishnaswamy *et al*., 2009; Weems *et al*., 2011, 2012; Lee *et al*., 2012). Third, recent convincing evidence demonstrates that IFNT exits the uterine lumen and interacts directly with the CL and may directly block PGF action at the CL (Gifford *et al*., 2007; Oliveira *et al*., 2008; Bott *et al*., 2010; Hansen *et al*., 2010; Antoniazzi *et al*., 2013).

Although it will not be possible in this manuscript to definitely select which of these endocrine mechanism(s) is most important in maintenance of the CL during early pregnancy, some perspective can be thought-provoking. Although the exit of IFNT from the uterus into the systemic circulation seems irrefutable, the systemic mechanism required for this pathway is not consistent with most of the older studies that definitely show a local and not a systemic mechanism involved in CL maintenance in ruminants. Thus, the third mechanism is unlikely to be the sole anti-luteolytic mechanism, although, recent studies showed that endocrine delivery of IFNT, via uterine or jugular vein, protected the ovine CL from the luteolytic actions of PGF, maintaining intraluteal and circulating P4 and CL volume (Antoniazzi *et al*., 2013). Nevertheless, it seems

possible that endocrine delivery of IFNT could still be acting on the uterine endometrial cells. Related to the first mechanism, circulating PGF is generally found to be higher in the pregnant than the non-pregnant ruminant (Lewis *et al.*, 1977; Vincent and Inskeep 1986; Arosh *et al.*, 2004), although pulses of PGF may differ in pregnant and non-pregnant ruminants. Finally, previous studies have indicated that the CL of pregnancy has reduced sensitivity to PGF (Silvia and Niswender, 1984, 1986; Silvia *et al.*, 1984a). Much of this resistance to PGF action is ascribed to actions of PG E2 and E1 (PGE) coming from the pregnant uterus. In addition, PGE2, but not IFNT, is transported through the utero-ovarian plexus consistent with a local signal occurring during early pregnancy (Lee *et al.*, 2012). Further, the PGE2:PGF2α ratio in the utero ovarian vein was ~72-fold higher, and, in the ovarian artery, was ~115-fold higher on day 16 of pregnancy versus the estrous cycle of ewes, indicating the efficiency of utero-ovarian PGE2 transport. Based on all of these various findings, it seems likely that uterine PGE, secreted in response to IFNT from the elongating embryo, has a key role in protection of the CL from luteolysis during early pregnancy (day 18-25 in cattle).

Period III. Prevention of later luteolysis during pregnancy – day 30-60 of pregnancy

The second month of pregnancy is not a typical time to think of luteolysis. However, IFNT is likely to no longer be a major factor in maintaining the CL during the second month of pregnancy since IFNT secretion from the developing conceptus peaks by day 23 of pregnancy and then dramatically decreases during the next few weeks (Godkin *et al.*, 1988; Stojkovic *et al.*, 1995). This provokes the obvious question: What maintains the CL after day 30 of pregnancy when IFNT is no longer present? Related to this question is the observation of pregnancy loss during 30-60 days of pregnancy. For example, we recently summarized the results from 46 recent studies and ~25,000 pregnancies that were evaluated by ultrasound on ~day 32 and again at ~day 60 and found 11.95% pregnancy loss during this period (Wiltbank *et al.*, 2016). The pregnancy loss during this time period is even greater for clones. The primary cause of pregnancy loss during this period could be initial embryonic death and subsequent luteolysis or, alternatively, could be initiated by inappropriate luteolysis during this period followed by loss of the pregnancy (Giordano *et al.*, 2010). No studies have clearly differentiated these two distinct causes.

We became more interested in luteolysis during this time period, based on recent observations that we made on timing of CL regression in accessory CL that are contralateral to the pregnancy (Wiltbank *et al.*, 2016). In this experiment, we induced accessory CL in lactating cows by treatment with GnRH on day 5 after AI. Pregnant cows could therefore have an accessory CL present on either the same side as the pregnancy (ipsilateral) or on the opposite ovary (contralateral). Intriguingly, although ipsilateral CL rarely regressed,

almost all contralateral CL regressed during the pregnancy. Of particularly interest, most accessory CL regressed during the second month of pregnancy. Thus, mechanisms are present on the same side as the pregnancy that allow maintenance of the ipsilateral CL, whereas, in the contralateral horn, mechanisms occur that result in regression of the CL. This result also demonstrates that local and not systemic mechanisms are responsible for maintenance or regression of the CL during this period.

What are the local mechanisms that result in maintenance of the CL during the second month of pregnancy, but that are not present, at least in sufficient quantities, to maintain the CL on the contralateral ovary? There are a few things to consider. First, it seems likely that the contralateral CL regresses due to PGF secretion from the contralateral uterine horn, since CL do not undergo spontaneous regression in ruminants with the uterus removed (Wiltbank and Casida, 1956; Mapletoft *et al.*, 1976b). Related to this idea, responsiveness to oxytocin and the ability of the uterus to synthesize and secrete PGF persists throughout pregnancy with increases in concentrations of PGFM of approximately 6-fold when oxytocin is administered to cows between day 50 and 280 of pregnancy (Schallenberger *et al.*, 1989; Fuchs *et al.*, 1996). Second, the uterine horns were not isolated in our experiment and therefore whatever local agent is involved in this process must have a difference in action on the ipsilateral than the contralateral ovary. Thus, there could be a protective substance that is present in larger concentrations on the ipsilateral than the contralateral side. Nevertheless, the most likely explanation, in our opinion, is that the ipsilateral uterine horn has greater blood flow than the contralateral horn, as previously reported (Ford *et al.*, 1979; Ford and Chenault, 1981; Panarace *et al.*, 2006). Thus in this scenario, high uterine blood flow would not allow efficient transfer of uterine-secreted PGF from the uterine vein to the ovarian artery on the ipsilateral side but efficient PGF transport would continue to occur on the contralateral side, potentially due to reduced uterine blood flow (Ford *et al.*, 1979). Thus, the blood flow explanation is the simplest explanation for the differential CL regression between ipsilateral and contralateral ovaries, although differential secretion of PGF or a luteal protective substance cannot be ruled out at this time.

One topic to consider is whether contralateral CL regression may represent a condition that is germane to the practical issue of pregnancy loss during the second month of pregnancy. Since pregnancy loss can be initiated by death of the embryo or alternatively by regression of the CL (Kastelic *et al.*, 1991; Giordano *et al.*, 2012), it seems likely that any losses due to CL regression utilize similar mechanisms as observed with contralateral CL regression during this time. Thus, a pregnancy that had not increased uterine blood flow sufficiently between 30 and 60 days of pregnancy, would be susceptible to loss by uterine-derived PGF. We speculate that PGF is secreted by the uterine horns throughout pregnancy, but the elevated uterine blood

flow does not allow this PGF to be transferred to the ovarian artery. Obviously a great deal of research remains to be done to fully explain this potentially critical period for CL regression or maintenance.

Period IV. Parturition-induced luteolysis– day 270-290 of pregnancy

In ruminants, the signal to end gestation arises from the fetus. It appears that the timing of parturition is encoded in the fetal genome and the mechanisms are activated by specific developmental events that occur in the developing fetus (Jenkin and Young, 2004). The signal from the fetus to initiate parturition in ruminants has been clearly shown to be the glucocorticoid, cortisol, coming from the maturing hypothalamo-pituitary-adrenal axis. The circulating cortisol concentrations increase exponentially during the final weeks of gestation, producing what is termed the "cortisol surge" (Poore *et al.*, 1998). When the cortisol surge is mimicked by treatment of the lamb with betamethasone (glucocorticoid), a consistent change in gene expression happened at specific times after treatment: placental aromatase mRNA increased by 14 h, endometrial luminal epithelial cells dramatically increased E2 receptor expression by 28 h, and increased oxytocin mRNA and oxytocin binding at 28 h, with a consistent increase in electromyographic uterine contractile activity at 48-50 h, with definitive labor onset occurring at 56.6 ± 0.8 h after treatment (Wathes *et al.*, 1996). Thus, a similar sequence of events may occur in the uterus during parturition as occurs at the normal time of luteolysis at day 18-20, with first E2 receptor expression, then activation of the E2 receptors by circulating E2, and rapid induction of oxytocin receptors. Oxytocin binding to oxytocin receptors is likely to be driving myometrial contractions during labor, and induction of oxytocin receptors was observed during natural parturition (Wathes *et al.*, 1996) but not during betamethasone-induced parturition (Leung *et al.*, 1999). It seems likely that activation of oxytocin receptors by pulses of oxytocin underlies the large amount of PGF secretion and regression of the CL before parturition.

Figure 5 shows the changes in hormonal concentrations near the time of parturition in Holstein cattle (From adaptation of Rasmussen *et al.*, 1996; Mattos *et al.*, 2004). Concentrations of P4 remain elevated until about 36 h prior to calving and then promptly decrease to less than half the concentrations at 24 h before calving and reaching basal concentrations by 12 h before calving (Rasmussen *et al.*, 1996). The circulating concentrations of PGFM follow an opposite pattern with basal concentration up until about 48 h prior to calving when circulating PGFM starts to dramatically increase (Mattos *et al.*, 2004), most likely due to increased secretion by cells of the uterus. After parturition, concentrations of PGFM remain elevated, consistent with secretion from the uterus since the placenta has been lost by 24 h after parturition. The PGFM concentrations near this time are more than 5-fold greater (2000 pg/ml) than the peak concentrations of PGFM in a luteolytic pulse (300-400 pg/ml during peak luteolysis) during normal luteolysis on day 18-20 (Ginther *et al.*, 2010). Circulating E2 concentrations also increase dramatically and peak at more than 600 pg/ml or almost 100-fold greater than the peak circulating E2 concentrations near estrus (Sartori *et al.*, 2004). This E2 is coming from the placenta, as evidenced by the dramatic decrease in cows with normal placental loss after parturition and continued elevation in cows with retained placenta (Rasmussen *et al.*, 1996).
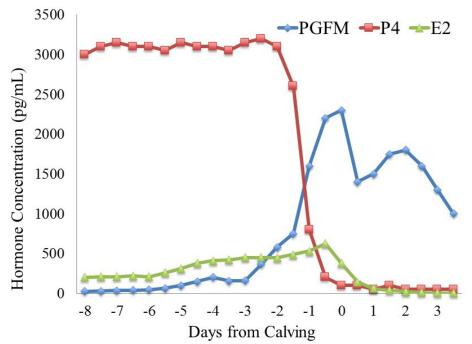

Figure 5. Circulating concentrations of progesterone (P4), estradiol (E2), and PGFM, normalized to the time of parturition in Holstein dairy cattle. From Rasmussen *et al*. (1996) and Mattos *et al*. (2004).

There are dramatic changes in PG production near parturition from different tissues and due to different regulatory mechanisms. During the last 15-20 days of gestation there is an increase in PGE2 in the fetal circulation, closely matching the slow increase in fetal cortisol during this time. There is also the dramatic increase in PGF secretion, reflected in the increase in PGFM, however this is a late event occurring within 2 days of parturition. The PGE2 originates from the placenta due to induction of PGH2 in placental cells by the low amounts of cortisol that begin to come from the developing fetus. This increase in PGE2 secretion is not dependent upon circulating E2, since treatment with an aromatase inhibitor does not alter the increase in PGE2 in fetal circulation (Whittle *et al.*, 2000). Interestingly, this PGE2 may be important for induction of aromatase near the time of parturition which drives the dramatic increase in E2 production by the placenta. Subsequently, rising cortisol, combined with the rising E2 concentrations, now induce PGH2 expression in maternal uterine cells and this causes the dramatic increase in PGF secretion observed just before parturition. That both E2 and cortisol are required for the increase in PGFM is demonstrated by the dramatic increase in PGFM (>500 pg/ml) in response to cortisol in the presence of physiological concentrations of E2 but no increase when cortisol is given in the absence of E2 due to simultaneous treatment with an aromatase inhibitor (Whittle *et al.*, 2000).

There is substantial evidence that PGF has an obligatory role in parturition-induced luteolysis, as seen by the patterns of PGFM discussed above. Treatments that initiate premature delivery, also induce the characteristic increase in PGF secretion from the uterus before luteolysis and parturition (Wu *et al.*, 2004). Inhibition of PGF production by treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) will delay or prevent luteolysis near parturition (Jenkin, 1992; Sugimoto *et al.*, 1998; Jenkin and Young, 2004). Finally, mice that have a knockout of the PGF receptor do not undergo luteolysis and therefore do not go through normal parturition, unless the ovaries/CL are removed (Sugimoto *et al.*, 1997; Tsuboi *et al.*, 2003).

Conclusions

Three of the four time period of luteolysis have been well-characterized. In each case, there is a clear role for E2 receptors in the induction of oxytocin receptors. This happens prematurely in the short luteal phase, also during the normal luteolytic process at about day 18-20 in cattle, and during the luteolytic process that results in parturition. After oxytocin receptors are present, oxytocin then induces secretion of PGF from the uterine endometrial cells in each of these luteolytic events. Thus, uterine PGF secretion is an essential part of each time of luteolysis that has been well-studied. In the short luteal phase and normal luteolysis, uterine-produced PGF is transferred through a local veno-arterial pathways and sufficient PGF eventually reaches to CL to result in luteolysis, following multiple PGF pulses. During parturition, it seems likely that there are

such high quantities of PGF being secreted by the uterus (10-fold higher PGFM) that PGF may reach the CL through the systemic circulation. After completing this review of the literature, it clearly does not seem typical and the authors could find no convincingly-researched physiological situation that demonstrates spontaneous regression of the ruminant CL in the absence of uterine-derived or exogenous PGF. Thus, the concept that PGF causes all types of luteolysis in ruminants is strongly supported by each type of well-investigated luteolytic event.

The key question that puzzles us after this review of the literature is how is the CL protected from luteolysis during pregnancy, after the interval when IFNT is secreted by the ruminant embryo. During most of pregnancy, the uterus will respond to oxytocin with PGF pulses (Schallenberger *et al.*, 1989; Fuchs *et al.*, 1996) but still luteolysis does not occur. For us, the two most logical responses to this physiological question are: 1) There is a substance protecting the CL from PGF action during much of pregnancy or 2) PGF does not reach the CL during most of pregnancy, perhaps due to lack of PGF transport via the normal local transport pathways. Future research will continue to unlock this and other mysteries about the endocrine and cellular/molecular mechanisms that produce luteolysis and protection from luteolysis in ruminants.

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