ROLE OF EXOGENOUS $PGF_2\alpha$ ON POSTPARTUM PERIOD REPRODUCTIVE PERFORMANCE IN BOVINES-REVIEW

Selvaraju.M* and Ravikumar.K**
*Professor and Head **Assistant Professor,
Department of Clinics, Veterinary College and Research Institute, Namakkal, Tamil Nadu
Department of Clinics, Teaching Veterinary Clinical Complex,
Veterinary College and Research Institute, Namakkal, Tamil Nadu

Received: 15-06-2014, Accepted: 30-06-2014

Parturition is a very traumatic event, and the ability to control ovarian and uterine events in the postpartum cow could play an important role in achieving subsequent fertility. The future reproductive capability of the dairy cow, a major concern for its economic value, is related frequently to postpartum events. Undesirable events during the periparturient period might result in culling or even death of the cow. Parturition is one of the most critical stages of the reproductive cycle of the dairy cow. It is a period of significant death rate, as well as potentially severe debilitating injury to both dam and neonate. Future efficiency of reproduction and milk yield can be affected adversely at this time, and for this reason, major efforts have been directed toward minimizing problems during parturition. Keeping cows healthy is one of the most important steps in maintaining good fertility and maximal milk yield. Healthy cows produce more milk, rebreed sooner, and have lower culling rates than unhealthy herd mates. Poor health, regardless of its cause, usually leads to infertility.

The profitability of a commercial dairy farm is based in part on the calving interval of the cows. In order to maximize the economic profitability of the farm, cows must return to ovarian cyclicity, express estrus and be bred within 85 days postpartum. The optimal calving interval is 365 days. There are two physiologic factors which influence reproductive success in the postpartum dairy cow. The first is ovarian cyclicity, and the second is uterine health.

The resumption of ovarian cyclicity is dependent on a number of factors including clearance of bacterial contamination from the uterus (Sheldon *et al.,* 2002). Bacterial contamination of the uterus occurs within the first week post partum (Elliott *et al.,* 1968) with spontaneous contamination, clearance and recontamination occurring up to seven weeks post partum (Griffin *et al*., 1974). Some cows have the ability to clear these infections but others do not and the reasons for this variability between cows are unknown. Bacterial contamination of the uterus has a direct effect on the ability of the cow to conceive and maintain a conceptus. Conception and the maintenance of pregnancy are, therefore, dependent on a healthy uterine environment. The focus of this paper will be the interrelationship of Prostaglandins with various periparturient reproductive disorders and their collective impact on reproductive performance in the dairy cow.

Prostaglandins

Prostaglandins (PGs) affect ovulation, luteal regression, the implantation and maintenance of pregnancy, parturition, postpartum physiology, and have been used for synchronization of oestrus alone or with progestins, oestrogens, and gonadotropin releasing hormone (GnRH). To understand PGs and reproduction, knowledge of their metabolism is important.

Prostaglandins were independently isolated from human seminal plasma in the 1930s by Gold blatt and von Euler. Prostaglandins are formed by most mammalian tissues and by tissues of lower vertebrates and certain invertebrates (Samuelsson *et al.,* 1978). All mammalian cells types have the capacity for converting the membrane bound fatty acids into prostaglandins (Murray *et al.,* 1996). Prostaglandins act as local hormones, having important physiological and pharmacologic activities (Murray *et al.,* 1996). There are many stimuli (hormonal, nervous, other chemical, mechanical stimuli) known to activate phospholipase and initiate prostaglandin synthesis (Granström, 1981). The products formed and the amounts produced will vary within the same tissue under different conditions (Granström, 1981).

Metabolism

Prostaglandins belong to a group of unsaturated fatty acids called eicosanoids. Eicosanoids are not stored in cells, but are released upon synthesis and their biosynthesis is limited by the availability of free precursor fatty acid (Katzung, 1995). Prostaglandins are rapidly inactivated in the body. Oxidation of the secondary alcohol group at C-15 is catalyzed by the enzyme, 15-hydroxyprostanoate dehydrogenase (PGDH). The main sources of PGDH are the lungs, spleen and kidney. The lungs have the highest enzyme activity and with its vast vascular bed can render large amounts of prostaglandins biologically inactive. Urinary excretion was completed in approximately 6 hours.

Mechanism of Action

The eicosanoids are short-lived, highly potent local mediators that produce an astonishing array of biological effects by binding to specific cell surface receptors (Katzung, 1995). All binding appears to involve a G-protein linkage (Katzung, 1995). Receptor binding initiates a signal transduction pathway, which links the regulatory substance (PGF2α) with its intracellular effect (s).

Prostaglandin $F_2\alpha$ is released from the uterus, and transferred from the utero-ovarian vein to the ovarian artery by a countercurrent mechanism. On reaching the ovary, PGF2α binds to high and low affinity-binding sites (receptors) located in the plasma membrane of the corpus luteum (Samuelsson *et al.,* 1978). These receptors are G protein-coupled receptors. The high affinity-binding site requires calcium ions in order to be detected (Samuelsson *et al.,* 1978). Calcium is required for the activation of PKC and DAG increasing PKC's affinity for Ca2+. Activation of PKC leads to the opening of calcium channels. Calcium and PKC promote protein phosphorylation and this eventually leads to the inhibition of progesterone secretion and regression of the corpus luteum (Samuelsson *et al.,* 1978).

$PGF_2\alpha$ secretion in the Reproductive Tract

During the bovine estrous cycle, $PGF_2\alpha$ is released for 2 to 3 days as rapid pulses with duration of 1 to 5 hours prior to and during luteolysis (Kindahl, 1980). The precise release of $PGF_2\alpha$ throughout the bovine estrous cycle presupposes that there is an inhibiting factor in the uterus. This inhibiting factor is important for the regulation of the physiologic PG biosynthesis and thus regulates its production to prevent premature lysis of the corpus luteum. Wlodawer *et al.* (1976) noted that an inhibiting factor was found in bovine uterine preparations that suppressed the fatty acid cyclooxygenase. Knickerbocker *et al.* (1986) noted that the bovine conceptus suppressed uterine production of $PGF_2\alpha$ production during pregnancy recognition by what was then called bovine conceptus secretory proteins (CPS) and is now known as interferon tau (INF-τ). However, the suppression of $PGF_2\alpha$ release from the endometrium is regulated by a number of hormones; estrogen, progesterone, oxytocin and endothelin-1 (ET-1).

Progesterone directly influenced the basal secretion of $PGF_2\alpha$ by the endometrium (Xiao *et al.* 1998). Progesterone has been shown to stimulate basal $PGF_2\alpha$ secretion by bovine endometrial cells and tissues. However, it inhibits oxytocin-induced $PGF_2\alpha$ secretion while in luteal cell culture while estrogen stimulated only $PGF_2\alpha$ secretion.

Post-partum Involution of Uterus

In postpartum dairy cows, rapid uterine involution is a prerequisite for a high conception rate and short interval from calving to conception (Opsomer *et al.,* 2000). Uterine involution was defined as the process associated with the return of the postpartum uterus to the state of initiating and supporting another pregnancy (Zemjanis, 1970). The uterus was considered as involuted when each of its horns was equal to two fingers and its body was palpated in the pelvic cavity (Arthur *et al.,* 1996).

Uterine involution involves physical shrinkage, necrosis and sloughing of caruncles, and the regeneration of the endometrium. Following the loss of the allantochorion, there is necrosis of the uterine caruncles, which are usually sloughed by 12 days after parturition. Sloughing of the uterine caruncles contributes significantly to the rapid reduction in weight of the involuting postpartum uterus from 13 kg at parturition to about 1 kg 3 weeks later, because the caruncles account for over half of the weight of the uterus. The sloughed caruncles form the lochial discharge, along with the remains of fetal fluids and blood from the ruptured umbilicus. There is initially regeneration of the endometrium in the inter-caruncular areas and then by centripetal growth of the cells over the caruncle. Epithelial regeneration is complete by about 25 days after parturition, but the deeper layers of tissues are not fully restored until 6–8 weeks after calving.

Factors such as periparturient diseases and uterine infection (Mateus *et al.,* 2002; Sheldon *et al.,*2006 and Herath *et al*.,2009), parity (El-Din Zain *et al.,* 1995 and Hajurka *et al.*, 2005), breed (Rao and Rao, 1980), normal or abnormal parturition, calf birth weight (Stevenson, 1997), retention of fetal membranes (El-Din Zain *et al.,*1995), postpartum nutritional status (Butler, 2003 and Wathes *et al.,* 2007), milk production (Bahga *et al.* 1988) and season (Chaudhry *et al.,*1987 and El-Din Zain *et al.,* 1995) at calving have been related to delayed uterine involution in cattle.

The administration of prostaglandin $F_2\alpha$ has been shown to decrease the time for complete involution of the uterus as detected by rectal palpation (Lindell and Kindahl, 1983). Lindell *et al.* (1982) demonstrated that there is a massive release of $PGF_2\alpha$ postpartum, which continues for 2 to 3 weeks. It was also deduced from this study that cows that had a shorter interval from parturition to uterine involution had a longer period of postpartum $PGF_2\alpha$ release.

Prostaglandins have also been shown to have a direct effect on the bovine myometrium. (Patil *et al.,* 1980). The primary role of endometrial $PGF_2\alpha$ in postpartum cows may be for tissue repair and uterine involution. In vitro studies carried out on the bovine myometrium indicate that $PGF_2\alpha$ has the ability to increase uterine tone and motility (Patil *et al.,* 1980). Uterine involution was dependent on both the magnitude and duration of $PGF_2\alpha$ release (Madej *et al.,* 1984). This increase in $PGF_2\alpha$ concentration appeared to be extremely important for normal uterine involution. The $PGF_2\alpha$ levels coincided with the rate of uterine involution with a peak at day 4 postpartum and thereafter remain elevated for up to 20 days (Kindahl *et al.,* 1980 and Lindell *et al.,*. 1982). Inadequate production of endogenous $PGF_2\alpha$

has been associated with delay in uterine involution (Kindahl *et al.,* 1984 and Madej *et al.,* 1984). A decrease in the estradiol 17-beta/17-alpha ratio has been reported to result in a reduced rate of release of prostaglandins from the uterus and a slower rate of uterine involution (Madej *et al.,* 1984).

Injection of prostaglandin at the first, second and fourth weeks postpartum had an ecbolic effect that reduced the time of uterine involution in cows (Young *et al.*,1984). Repeated administration of $PGF_2\alpha$ twice daily from days 3 to 13 after calving shortened the time needed for uterine involution by 6 days (Lindell and Kindahl, 1983). Sequential treatment with $PGF_2\alpha$ during the third, fifth or the eighth week postpartum stimulated early cyclicity in dairy cows (Risco *et al.,* 1995). It was reported that exogenous $PGF_2\alpha$ enhanced immune functions or increased the uterine motility to help the uterus resolve infections in animals that did not have active corpora lutea (Hirsbrunner *et al.,* 2003).

Khatri (2013) concluded that administration of $PGF_2\alpha$ and oxytocin in postpartum buffaloes accelerated the process of uterine involution, reduced the time period of first postpartum oestrus and induced early expulsion of fetal membranes in Kundhi buffaloes. In cows, uterine involution took 23 – 35 days (Lech *et al.,* 1998) and depended upon myometrial contractions stimulated by combined actions of $PGF_2\alpha$, oestrogen and oxytocin, bacterial elimination and endometrial regeneration (Bondurant, 1999).

Retained Placenta:

The placenta is normally expelled within 6 h of expulsion of the calf but if still present by 24 h, it is defined as a retained placenta. The risk factors associated with RP include twins, dystocia, stillborn calf, induced parturition, abortion, milk fever, and increasing age, as well as conflicting seasonal effects (Sandals *et al.,* 1979; Correa *et al.,* 1993 and Grohn and Rajala-Schultz, 2000).

The key event in the pathogenesis of RP is a failure of prompt breakdown of the cotyledon–caruncle attachment after delivery of the calf. Failure of placental detachment appears to be largely mediated by failure of the immune system to successfully degrade the plancentomes at the end of pregnancy. Cows in a greater degree of negative energy balance prepartum, as evidenced by higher non-esterified fatty acid (NEFA) concentration were 80% more likely to have RP, and accounting for the effect of NEFA, those with lower circulating vitamin E were at greater risk of RP (LeBlanc *et al.,* 2004). This supports the notion that premature, or severe negative energy balance impairs immune function, which in turn makes RP more likely (Goff and Horst, 1997), but it also underlines the fact that the development of RP is multifactorial. Retained placenta is associated with increased risk of subsequent ketosis, abomasal displacement and mastitis (Grohn *et al.,* 1990 and Oltenacu *et al.,* 1990).

Immediate postpartum treatments with oxytocin, PGF2α or calcium have generally failed to prevent RP (Stevens and Dinsmore, 1997 and Hernandez *et al.,* 1999), or hasten the passage of retained fetal membranes (Stevens *et al.,* 1995 and Frazer, 2005).

Induction of cyclicity in postpartum cows with prostaglandin $F_2\alpha$

The luteolytic effect of prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in cattle was described by several workers in the early 1970s. Several studies demonstrated the capacity of $PGF_2\alpha$ and its synthetic analogues, alfaprostol, cloprostenol, fenprostalene, and luprostiol to trigger the regression of mature corpus lutea in the ovary, thus provoking and synchronizing estrus.When $PGF_2\alpha$ was administered to cows with a functionally mature corpus luteum, 85% to

95% reached estrus within 7 days of treatment; 70% to 90% showed signs of estrus 3 to 5 days after treatment.

For $PGF_2\alpha$ treatment to achieve its luteolytic effects, the cows must be in the diestrus stage of the estrous cycle (day 7 to 17). Prostaglandin treatment in the early stage of estrous cycle (first 5 days) was found to be ineffective in causing a luteolytic response in cattle. Consequently, a double protocol in which PGF2α was given at a 7, 11, or 14 day intervals was developed so that cows at a stage in the estrous cycle other than diestrus would have a functional corpus luteum when they received the second $PGF_2\alpha$ dose.

The time elapsed between $PGF_2\alpha$ treatment and the onset of estrus depends on the stage of the estrous cycle at the time of $PGF_2\alpha$ treatment The mean interval to estrus was 48 to 72 h when $PGF_2\alpha$ was administered on estrous cycle Day 5 or Day 8 in dairy cows. Prosta glandin administration in mid-cycle (day 8 to day 11) or later in the luteal phase resulted in a mean time to estrus of 70 and 62 hours, respectively. There are also reports of higher progesterone concentrations at the time of prostaglandin administration being associated with a delayed onset of estrus. The stage of follicular wave development at the time of $PGF_2\alpha$ treatment appears to be the factor determining the time of estrus onset. Kastelic and Ginther (1991) reported that the time from $PGF_2\alpha$ administration to ovulation was dependent on the maturity and size of the most emergent dominant follicle, because a small dominant follicle takes longer to grow into an ovulatory follicle. When the dominant follicle had reached the static phase, the time from treatment to ovulation was 3 days, and if a new dominant follicle had emerged at the time of luteolysis, this time period increased to 4.5 days. Smith et al. (1998) reported that the onset of estrus was significantly and inversely related to the size of the cavity of the smallest follicle over 5 mm in diameter.

Several researchers have noted normal or above normal fertility following synchronization of estrus with $PGF_2\alpha$ in cows (Lucy et al., 1986 and Mcmillan and Day, 1982). Young and Henderson (1981) found no significant difference in conception rates among cows inseminated at the fixed time of 75 to 80 hours (46%), after a double 11 day interval treatment regimen using a prostaglandin analogue, cows inseminated twice at 72 and at 96 hours (47%) after the same treatment and control untreated cows (50%). However, improved conception rates have been noted after AI at detected estrus compared with timed AI after prostaglandin administration, due to variations in the time of ovulation (Stevenson *et al.* 1987 and Archbald *et al.,* 1992).

There is considerable evidence that $PGF_2\alpha$ is capable of improving the reproductive performance of dairy cows when given before the end of the voluntary waiting period (White and Dobson, 1990 and Stevens *et al.,* 1995). Administering $PGF_2\alpha$ during the early postpartum period led to increased first service conception rates related to the associated benefits of enhancing uterine activity (Young *et al.,* 1984), thereby decreasing the interval between calving and conception. However, others suggest that the diminished inter calving period may be an effect of luteolysis and an increased number of estrus cycles (Benmrad and Stevenson, 1986; Thatcher and Wilcox, 1973 and Young, 1983). In a meta-analysis, Burton and Lean (1995) explored the effects of prostaglandin given in the early postpartum on the subsequent reproductive performance of dairy cattle. Their pooled data corresponded to 21 independent trails performed on 2,646 cows described in 10 papers. Meta-analysis of the effect of prostaglandin treatment during the early postpartum period revealed no increase in pregnancy rate to first artificial insemination in cows with a normal or abnormal puerperium, while the period from calving to first AI was significantly reduced, thus reducing the number of days open in the dairy farm.

Prostaglandin $F_2\alpha$ Vs postpartum infections

Prostaglandin $F_2\alpha$ has been use in cattle for postpartum infections: pyometra, metritis and endometritis.

Pyometra:

Pyometra is defined as a condition associated with accumulation of purulent material in the uterus, persistence of a CL and anestrus (Roberts, 1989). Corpus luteum often persists longer than the expected duration of the luteal phase. It has been suggested that it is the presence of this structure, with its secretion of progesterone that results in endometritis developing into pyometra. Early ovulation after parturition and formation of an active corpus luteum may predispose to pyometra. On the other hand, the retention of the corpus luteum may be associated with failure of luteolysis. The role of progesterone may be to maintain functional closure of the cervix, as well as increasing the susceptibility to persistent infection, especially with A. pyogenes and anaerobic bacteria.

The mode of action of $PGF_2\alpha$ in the treatment of cows with postpartum infection is based on its luteolytic activity. In cases of pyometra, treatment leads to the regression of the CL resulting in emptying of the uterus. Prostaglandin $F_2\alpha$ has been shown to stimulate the myometrium and may aid in the physical evacuation of purulent material from the uterus (Ott and Gustafsson, 1981).

The use of the term pyometra should also be differentiated from clinical endometritis. Pyometra implies accumulation of pus within the uterine lumen associated with a closed cervix and a corpus luteum. There is often a corpus luteum present in animals with endometritis but the cervix is patent, often with pus discharging from the uterus into the vagina. In our experience, clinical endometritis is common whilst pyometra is relatively rare, comprising <5% of clinical cases of uterine disease. Fortunately treatment with prostaglandin (PG) $F_2\alpha$ is equally effective in both cases.

Postpartum Endometritis

Puerperal metritis is defined as an animal with an abnormally enlarged uterus and a fetid watery red-brown uterine discharge, associated with signs of systemic illness (decreased milk yield, dullness or other signs of toxaemia) and fever >39.5°C, within 21 days after parturition. Animals that are not systemically ill, but have an abnormally enlarged uterus and a purulent uterine discharge detectable in the vagina, within 21 days after calving, may be classified as having **clinical metritis**.

Clinical endometritis is characterized by the presence of purulent (>50% pus) uterine discharge detectable in the vagina 21 days or more after parturition, or mucopurulent (approximately 50% pus, 50% mucus) discharge detectable in the vagina after 26 days. In the absence of clinical endometritis, a cow with **subclinical endometritis** is defined by >18% neutrophils in uterine cytology samples collected 21–33 days after calving, or >10% neutrophils at 34–47 days. Pyometra is defined as the accumulation of purulent material within the uterine lumen in the presence of a persistent corpus luteum and a closed cervix.

In particular it is important to differentiate animals with metritis from those with endometritis. Metritis is infection of the cavity, lining and deeper layers of the uterus. On the other hand, endometritis is a localised infection of the lining of the uterus, which is inflamed with white pus mixed with mucus discharging from the uterus into the vagina. The deeper layers of the uterus are not affected by endometritis, so the uterus is not much bigger than that of a normal animal. Clearly, metritis is a much more severe disease than endometritis, requiring a different therapeutic approach. Firstly, it is much more urgent to identify cows with metritis promptly and, secondly, these animals need systemic treatments to counter the uterine infection and alleviate the generalized ill-health.

Postpartum endometritis is a pathologic condition usually diagnosed during the intermediate postpartum period (Ball *et al.,* 1984 and Olson et al 1984) during routine postpartum examination of the cow or heifer. It is commonly characterized by the absence of estrus, a vaginal discharge of creamy-white or yellow pus and a large doughy uterus that fails to involute. Postpartum endometritis is the most common cause of infertility in cows. It delays uterine involution, prolongs the time to first estrus, increases the number of services per conception and prolongs the interval to calving.

Uterine disease is commonly associated with *Escherichia coli, Arcanobacterium pyogenes, Fusobacterium necrophorum* and *Prevotella species*. Indeed, *A. pyogenes, F. necrophorum* and *Prevotella* species have been shown to act synergistically to enhance the likelihood of uterine disease, and increase the risk of clinical endometritis and its severity (Olson *et al.,* 1984). Numerically the most prevalent pathogens are *E. coli* (37% of pathogenic bacteria isolated) and *A. pyogenes* (49%) (Williams *et al.,* 2005). Furthermore, the *E. coli* infections appear to precede and pave the way for the *A. pyogenes* infection (Williams *et al.,* 2007).

The incidence of endometritis is greatest during the first 14 days post partum based on cultures of uterine fluids and uterine biopsies (Griffin *et al.,* 1974). Failure to clear bacterial contamination by first ovulation post partum and corpus luteum formation could place the contaminated uterus under the influence of progesterone. Progesterone makes the uterus more prone to uterine infection (Hawk *et al.,* 1964) with the incidence of severe endometritis increasing around Day 15 to Day 21 postpartum. This increase in the severity of endometritis coincides with the time of first post partum ovulation (i.e., 15 to 28 days post partum).

The administration of $PGF_2\alpha$ during the early postpartum period would reduce the incidence of mucopurulent discharge, size of the cervix, size of the previously pregnant uterine horn and increase first service pregnancy rates.

Exogenous $PGF_2\alpha$ on uterine infections

In cyclic cows, $PGF_2\alpha$ causes luteolysis of a responsive corpus luteum (CL) resulting in decreased progesterone level and subsequent estrus, with increased estrogen level and myometrial contractions. These events are all plausibly favourable for clearance of uterine infection. The precise mechanism by which $PGF_2\alpha$ resolves uterine infection is not known (Lewis, 2004). There is controversy about the possible effect of $PGF_2\alpha$ other than to cause luteolysis and its consequential actions (Gilbert and Schwark, 1992), although PGF2α receptors are apparently present in the myometrium. There is some evidence that $PGF_2\alpha$ may exert a direct short-term contractile effect on the uterus (Rodriquez-Martinez *et al.,* 1987 and Hirsbrunner *et al.,* 1998). The hypothesis of an effect of $PGF_2\alpha$ other than luteolysis is supported by several studies that have reported beneficial effects of $PGF_2\alpha$ in the first month postpartum on reproductive performance parameters, in both normal and abnormal cows with low circulating progesterone levels (Steffan *et al.,* 1984; Etherington *et al.,* 1984; Young *et al.,* 1984; Young and Anderson, 1986 and McClary *et al.,* 1989). However, other reports indicate that $PGF_2\alpha$ is more effective when progesterone levels are high or a CL is palpable (Sheldon and Noakes, 1998; LeBlanc *et al.,* 2002). The optimum timing of administration of $PGF_2\alpha$ for treatment of endometritis is unclear. Numerous studies have assessed the putative therapeutic effect of $PGF_2\alpha$ in 'abnormal' cows in the first 5 weeks postpartum, all of which have failed to find statistically significant benefits in reproductive performance compared to untreated cows (Archbald *et al.,* 1990; Risco *et al.,* 1994). Numerous reviewers have concluded that $PGF_2\alpha$ appears to be at least as effective for endometritis as any available alternative therapy, and presents minimal risk of harm to the uterus or presence of residues in milk or meat (Gilbert, 1992).

Several studies have reported a benefit of routine treatment of normal cows or all cows with a single injection of $PGF_2\alpha$ in the postpartum period (Etherington *et al.,* 1984; Young *et al.,* 1984; Young and Anderson, 1986 and McClary *et al.,* 1989), while others have found no benefit (White and Dobson 1990; Morton et al., 1992 and Gay and Upham, 1994).

In summary, there are numerous studies that report improved reproductive performance when cows were routinely given at least one injection of $PGF_2\alpha$ between 4 and 6 weeks postpartum, but there are also numerous studies that report no benefit of routine postpartum $PGF_2\alpha$. There is little evidence to support the use of $PGF_2\alpha$ before 4 weeks postpartum. On balance, there is reasonable support for routine use of $PGF_2\alpha$ at approximately 4 and 6 weeks postpartum in herds with a high prevalence of RP and metritis. There is a lack of specific evidence for improved reproductive performance among cows with, or at risk of, clinical endometritis and treated with $PGF_2\alpha$. Further research is needed on the optimum timing postpartum, relationship with ovular status, and the number of doses of $PGF_2\alpha$ that may improve reproductive performance in cows with endometritis.

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