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Review Article

USE OF $PGF_2\alpha$ IN OVARIAN AND UTERINE PATHOLOGICAL CONDITIONS OF BOVINE : A THERAPEUTIC APPROACH

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ABSTRACT: The use of $PGF_2\alpha$ is based on its luteolytic effect causing regression of corpus luteum and allows development of dominant follicle on the ovary that result in estrus and ovulation in 72 to 96 hours after its administration. Moreover, the $PGF_2\alpha$ also causes relaxation of cervix and smooth muscle contractions of uterus. The use of $PGF_2\alpha$ may provide microbial resistance in uterine environment, on one hand and can favour and enhance body defense mechanism / phagocytic activity on the other hand. $PGF_2\alpha$ is widely used to get rid of from the conditions like luteal cystic ovarian disease, persistent corpus luteum, endometritis, abnormal pregnancy, pyometra, retention of placenta and mummification. It has been now in vogue to administer $PGF_2\alpha$ or its analogue in early postpartum cows and buffaloes in order to hasten early resumption of cyclic ovarian activity and thereby to increase the reproductive efficiency.

Key words: Prostaglandin ($PGF_2\alpha$), Luteolysis, Ovarian and Uterine conditions, Bovine.

INTRODUCTION

Prostaglandins are the members of a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5 carbon ring. They are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue (Weems *et al.* 2006). Prostaglandins are found in most tissues and organs. They are produced by all nucleated cells except lymphocytes (Laneuville 2003). They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the essential fatty acids (Komoto *et al.* 2004). Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in cattle causes regression of corpus luteum and the benefit from $PGF_2\alpha$ administration is

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believed to arise from induction of estrus in cows having a $PGF_2\alpha$ responsive corpus luteum; the estrus leads to physical expulsion of bacterial contaminants and inflammatory products as well as a possible improvement in the uterine defences under low progesterone and thus estrogen enhances blood supply to uterine mucosa that increases phagocytosis by the exposure of blood to the site of infection (Kasimanickam *et al*. 2005).

OVARIAN CONDITIONS

Cystic Ovarian Disease: It is resulted from malfunctioning of neuroendocrine mechanism which control ovulation and in consequences interfere in the estrous cycle. It is characterized by the presence of large, persistent, anovulatory follicles in the ovaries (Wiltbank *et al.* 2002). Cystic ovarian disease is a major cause of reduced reproductive efficiency and economic loss to the dairy industry. The incidence of COD increases with parity, especially after the first lactation; the incidence in first-lactation cows is 40 to 80 per cent lower than in the general cow population. Cows with abnormal postpartum conditions including retained fetal membranes, metritis, ketosis and lameness are 1.4 to 2.9 times more likely to develop COD than cows having a disease free postpartum period (Brito and Palmer 2004). Ovarian cysts can be classified as follicular or luteal depending upon steroid production. Luteal cysts are thick-walled, fluid filled structures having more than 25 mm in diameter that secrete normal to above normal amounts of progesterone. Most luteal cysts probably form through luteinization of follicular cyst and can cause infertility, if they persist and maintain systemic progesterone levels that inhibit the LH surge and ovulation. The thick wall of luteal cysts is composed of luteal tissue and in contrast to cystic follicles; the fluid-filled cavities of cystic CL often contain numerous intertwining trabeculas that can be easily resolved using ultrasonography (Brito and Palmer 2004). While the normal CL contains cavities ranging from less than 2 mm to greater than 10 mm in diameter during estrous cycle and early pregnancy (Kastelic *et al.* 1990). Once formed, regression of luteal cyst can be induced by administration of $PGF_2\alpha$. Ovsynch, a protocol for synchronizing ovulation in lactating dairy cows, uses injections of both GnRH and $PGF_2\alpha$ may be an effective treatment for ovarian cysts (Brito and Palmer 2004). Treatment with Ovsynch induced ovulation of a follicle other than the cyst that was present at the time of the second GnRH injection and these synchronized cystic cows conceived after a timed AI. Hence use of Ovsynch as a treatment of choice for cows exhibiting all classifications of ovarian cysts.

Persistent Corpus Luteum: The cells that developed within the follicle undergo differentiation process (luteinization) following ovulation by action of pituitary hormones that gives to raise the second ovarian structure, the corpora lutea (Rowlands and Weir 1984). A blood clotted structure forms in the cavity left by the ruptured follicle known as corpora hemorrhagicum which is transformed into corpus luteum (CL) by day 5 of estrous cycle. The CL is functional from the day 5 to day 15 of estrous cycle and secrete progesterone hormone. If the female does not pregnant, the CL begins to regress and formed corpus albican (Hafez and Hafez 2013). Occasionally the CL does not regress normally even though the animal does not become pregnant and continue to produce enough progesterone to prevent further follicular

development, ovulation and estrus. Persistent corpus luteum has been reported as low as 2 per cent and as high as 33 per cent (Yu 2001). Any condition that prolongs the life span of CL leads to higher levels of progesterone in circulation same as resemble to pregnancy (Gordon 1996). Persistent CL reduces the fertility and productivity of female animals as a result of lengthening of service period and calving intervals. The prevalence of PCL in Sahiwal Cow was 11 per cent reported by Lashari and Tasawar (2012). Diagnosis of PCL was confirmed by rectal palpation and milk progesterone assay. The concentrations of progesterone in weekly samples for three weeks were more than 5 ng/ml indicate PCL. Lashari and Tasawar (2012) corrected 85 per cent of the cases of PCL and majority of animals who showed response to this treatment were pregnant to first service (71%) and remaining were repeat breeders (29%). It indicates the treatment had the potential to improve the fertility in lactating cows and thereby enhances the life time productivity of cows.

UTERINE CONDITIONS

Endometritis: It is defined as a superficial inflammation of the endometrium, which extends no deeper than the stratum spongiosum. Histologically, there is some disruption of the surface epithelium, infiltration of inflammatory cells and vascular congestion (Sheldon *et al.* 2004). The most common form of uterine inflammation is a chronic form that is often called endometritis (also whites or dirty cows). It is seen from 3 weeks after calving up to three months of lactation. Various amount of uterine discharge can be observed particularly when the cow is in heat and cervix opens up. The affected cows are seldom severely ill as a result of endometritis, the condition is considered important as it results in poor conception rates and prolongs the inter-calving intervals. Clinical endometritis is characterized by the presence of purulent material in the vagina 21 days or more post partum, and is often associated with delayed uterine involution. Using the presence of purulent vaginal mucus, the incidence of endometritis has been reported to be around 10 to 20 per cent in dairy herds (LeBlanc *et al*. 2002; Sheldon *et al*. 2004) although it can vary with season. The causes of postpartum endometritis are retained placenta, poor calving hygiene, difficult or abnormal calving, over-fat cows and calves born dead. It has been hypothesized that progesterone changes the uterine environment from resistant to susceptible towards infections. It has been accepted that estrogen has a protective effect, while progesterone makes the uterus more susceptible to infection. Nevertheless, the ability of progesterone to make the uterus more susceptible to infection has been substantiated by research (Lewis 2004), which showed that progesterone is the primary ovarian steroid governing the susceptibility of the uterus to pathogenic bacteria. The bovine uterus is susceptible to infection when progesterone concentrations increase, and is resistant to infection when progesterone concentrations are decreased (Seals *et al*. 2003; Wulster *et al*. 2003).

It has been considered to cause bacterial elimination of the uterus and improve reproductive efficiency by administering prostaglandin-$F_2\alpha$ ($PGF_2\alpha$). However, there are conflicting reports on the effectiveness of exogenously administered $PGF_2\alpha$ to increase the rate of uterine involution cause evacuation of bacterial contamination from the uterus and

subsequently improve conception rate (LeBlanc *et al*. 2002; Kasimanickam *et al*. 2005; Drillich *et al*. 2005). Some of these reports indicate the use of $PGF_2\alpha$ on either one or two occasions on random days postpartum without regard to the presence or absence of a functional corpus luteum (CL). Nevertheless, it has been suggested that exogenously administered $PGF_2\alpha$ in the early postpartum period could have a direct beneficial effect on the uterus of cows that calved normally or abnormally, and this effect could occur in the absence of a CL. However, $PGF_2\alpha$ and its various analogues have been used to apparently resolve clinical endometritis. The effectiveness of $PGF_2\alpha$ improves, if there is a presence of CL and although it may help in cases without a CL due to its direct effect on the myometrium, and there may be some later impacts on pregnancy rate (LeBlanc *et al*. 2002). Exogenous $PGF_2\alpha$ can induce regression of the CL (luteolysis), which reduces circulating progesterone concentrations, and permits the uterus to clear infection (Lewis 2004). $PGF_2\alpha$ stimulates uterine contractions that expel bacteria from the uterus. Nevertheless, uterine contractions do not destroy the bacteria in the uterus, which are likely to proliferate under favorable conditions. A research (Hirsbrunner *et al*. 2003) showed that cloprostenol (a potent analogue of $PGF_2\alpha$) enhanced uterine contractions for approximately 45 minutes after injection, and intrauterine pressure was increased for only 15 minutes after injection. However, some consideration should be given to the evidence which suggests that exogenous $PGF_2\alpha$ has direct effects on uterine immune defenses. Thus exogenous $PGF_2\alpha$ can enhance uterine defenses and mitigate the immunosuppressive effects of progesterone (Lewis 2004).

In fact, exogenous $PGF_2\alpha$ has been shown to increase uterine $PGF_2\alpha$ and luteal leukotriene B_4 (LTB_4). This LTB_4 enhances chemotaxis, random migration and antibody independent cell-mediated cytotoxicity (Hoedemaker *et al*. 1992). In addition, it has been shown in cows that LTB_4 could promote uterine involution and reduce the risk of uterine infection (Slama *et al*. 1993). *In vitro* studies have indicated that $PGF_2\alpha$ enhances neutrophil chemotaxis and the ability of neutrophils to ingest bacteria. It is also known that $PGF_2\alpha$ is a proinflammatory molecule that may stimulate production of proinflammatory cytokines that enhance phagocytosis and lymphocyte functions (Kelly *et al*. 2001; Seals *et al*. 2003). An alternative approach for the treatment of clinical endometritis without a corpus luteum is use of the Presynch or Ovsynch protocol for dairy animals (Moreira *et al*. 2000).

Induction of Parturition: Therapeutic termination of pregnancy is used in pain of traumatic reticulopertonitis, cardiovascular diseases, bronchopneumonia and prepartum prolapsed vagina. Cow suffering from hydroallontois will frequently respond to induced parturition. For the treatment of uterine hydrops, cardiac failure and other health related matters either to save dam or to save the calf because of the dam's deteriorating condition. In case of prevent dystocia due to overweight calf near to end of gestation (Arthur *et al*. 2001). The most undesirable effect of induced parturition was high incidence of retained placenta. Parturition was induced two week before the term; there was high incidence of retained fetal membrane and uterine infection (Kask *et al*. 1999). The frequency of clinical diseases and mortality in induced cows were greatest among older cows (Morton and Butler

1995). Parturient paresis occurs more frequently among older cows during induction of parturition due to calcium imbalance. Induced parturition increase the incidence of fetal membrane with increase the postpartum interval and decrease in subsequent pregnancy rate (Bellow and Short 1994).

To terminate pregnancy during the first 5 months, $PGF_2\alpha$ is useful whereas, during the 6^{th}, 7^{th} and 8^{th} month use of $PGF_2\alpha$ plus corticosteroid (usually dexamethasone) is more beneficial treatment. If $PGF_2\alpha$ is used alone at this stage, there is sometimes incomplete luteolysis and placental progesterone production may rescue the pregnancy (Szenci 2016). Corticosteroids alone can reduce placental secretion of progesterone but do not cause luteolysis until the last month of gestation. The feto-placental unit must be mature in order for corticosteroids to terminate pregnancy. Colak *et al.* (2008) reported that the intra-vulvo submucosal administration of cloprostenol is more economical than its intramuscular administration to terminate gestation. Parturition can be induced in the cow by treating with estrogens, corticosteroids and prostaglandins. Hormones used to induce parturition initiated endocrine events normally triggered by fetal cortisol. Corticosteroids appeared to efficiently remove the placental source of progesterone by induction of enzymes that converted placental progesterone to estrogen. Failure of corticosteroids to induce parturition may be due to failure to remove the ovarian source of progesterone. Conversely, failure of $PGF_2\alpha$ to induce parturition may be due to failure to remove the placental source of progesterone. However, a combination of the two hormones acted in concert to remove both sources of progesterone, resulting in fewer induction failures and less variability in the interval from treatment to parturition (Lewing *et al*.1985). The use of long acting corticosteroids for the induction of parturition resulted in a low incidence of retained placenta, but predictability of calving time and calf viability were unsatisfactory. It appeared that the long acting corticosteroids more closely mimicked the natural endocrine events of gradually rising circulating cortisol concentrations, resulting in placental maturation. An induction regime combining the use of a long acting corticosteroid pretreatment followed by dexamethasone and $PGF_2\alpha$ could resulted in predictable calving times, high calf viability and low incidence of retained placenta (Szenci 2016).

Uterine Involution: It is normally completed between 26 to 52 days postpartum but changes after 20 to 25 days are often imperceptible (Drillich *et al*. 2005). Inadequate production of endogenous prostaglandin has been associated with delay in uterine involution. Normal myoelectrical activity of the uterus is greater at calving and decreases drastically around 7 to 9 day postpartum. However, when exogenous uterotonic products are administered (oxytocin or prostaglandins), the myometrium responded with strong contractions (Gajewski *et al*. 1999). Interestingly, although an inflamed uterus (metritis) produces additional prostaglandins, the uterine musculature does not respond to these endogenous prostaglandins, and the involution process is delayed (Kindahl *et al*. 1980). Conversely, other mechanisms such as leukocyte function, cytokines, endotoxin response and antibody production might play additional roles in uterine involution (Mateus *et al*. 2003). Repeated administration of prostaglandin ($PGF_2\alpha$) twice daily from days 3

to 13 after calving shortened the time needed for uterine involution by 6 days. In the early postpartum period, administration of $PGF_2\alpha$ does accelerate uterine involution and hasten a return to fertile ovarian cyclicity. Single administrations of $PGF_2\alpha$ in 14 to 28 days postpartum resulted in an enhanced first service conception rate. The beneficial effect of $PGF_2\alpha$ administered postpartum is result of myometrial contraction and thereby accelerated uterine involution (Hirsbrunner 2003). Melendez *et al.* (2004) reported that two doses of $PGF_2\alpha$ at 8 hour apart on 8 day postpartum in cows treated along with Ceftiofur hydrochloride reduced the size of the previously gravid uterine horn, increased the tonicity of uterus, decreased concentrations of the α1-acid glycoprotein and increased conception rate of first service in primiparous lactating dairy cows. Hence use of $PGF_2\alpha$ during the early postpartum period to improve uterine involution and fertility in dairy cattle.

Mummification of Fetus: Fetal mummification has been reported in several species, but it is more common in cattle. Breed like Guernsey and Jersey cattle and previous occurrence seem to be risk factors in cows that experienced a similar event in previous gestation (Roberts 2004). In cattle, fetal mummification occurs after formation of the placenta and fetal ossification (70 day gestation). Most often, mummification occurs between the 3rd and 8th months of gestation, without concomitant luteolysis of the corpus luteum and opening of the cervix. Fetal mummification associated with persistent CL is observed mainly in cattle and goats, both species being dependent on progesterone produced by the CL for the maintenance of pregnancy. In cattle, however the placenta is capable of producing sufficient amount of progesterone to maintain pregnancy between days 150 and 200 of gestation. After fetal death, the amniotic and allantoic fluids are reabsorbed, dehydrating the fetal tissues and annex membranes (Johnson *et al.* 1981). Treatment of fetal mummification is accomplished by administering $PGF_2\alpha$ (with or without estrogen) to lyse the CL. Steroids are ineffective with dead fetus and non-functioning placenta. The treatment of choice for fetal mummification is lysis of the CL by injection of $PGF_2\alpha$, which usually results in the satisfactory and safe expulsion of the fetus within 2 to 4 day of post-treatment. Estrogens are also effective at provoking the regression of the CL and inducing contraction of uterine muscles, relaxation of the cervix and expulsion of the mummified fetus in the cow (Roberts 2004). The administration of diethylstilbestrol (DES) for period of 2 to 6 day at doses ranging from 60 to 800 mg intramuscularly was effective in causing expulsion of mummified fetuses diagnosed between 4th and 8th month of gestation. Estrogens are effective for expelling a uterine mummified fetus, and it could assume that estrogens stimulate $PGF_2\alpha$ production from the endometrium (Vandeplassche *et al.* 1974). Lefebvre (2009) reported that the cows do not always respond to treatment with $PGF_2\alpha$ and hysterectomy being represented an effective approach for extracting mummified fetuses from cows that did not respond to $PGF_2\alpha$ treatment. When $PGF_2\alpha$ alone did not lead to the expulsion of the mummified fetus. Hirsbrunner *et al.* (2000) reported that combined treatment of $PGF_2\alpha$ and Prostaglandin-E_2 (PGE_2) for a period of 3 to 6 days is beneficial and expel the mummified fetus. In addition to their luteolytic properties,

$PGF_2\alpha$ and PGE_2 have a direct effect on contractility of the myometrium. Combined administration of $PGF_2\alpha$ and PGE_2 resulted in more effective uterine contractions than the injection of $PGF_2\alpha$ alone. The synergistic effect of both prostaglandins could increase success rate relative to the use of $PGF_2\alpha$ alone.

Retention of Placenta: It is defined as condition in which the cow fails to release the placenta within 12 to 24 hours after calving (Galvao 2012). ROP is one of the main causes of endometritis in cattle. The incidence of retained placenta varies from 4 to 18 per cent of calving (Philips 2004; Han and Kim 2005). Para-hormone *i.e.* prostaglandin ($PGF_2\alpha$) plays an important role in the separation of placenta. The $PGF_2\alpha$ and its derivatives have been used as ecbolic agents and its use was more common than that of oxytocin. Prostaglandins may assist in detachment of the membranes through direct actions upon the placentomes rather than an ecbolic action. The most rational treatment for retained placenta would be to stimulate adequate myometrial contractions so that the expulsion could occur (Szenci 2016). It might be expected that differences in prostaglandin synthesis exist between normal cows and those with RFM. *In vitro* studies of placentomes from cows that had RFM showed that they produced less $PGF_2\alpha$ and more PGE than those from normal cows. Retention of placenta was treated with $PGF_2\alpha$ at 1 hour or 12 hours after calving, found beneficial results in the hope of both placental expulsion and enhance the natural uterine defense mechanisms.

Pyometra: It is characterized by the accumulation of purulent or mucopurulent exudates within the uterine lumen and distension of the uterus, in the presence of an active corpus luteum. There are often an increased number of pathogenic bacteria within the uterine lumen. There is a functional closure of the cervix, the lumen is not always completely occluded and some pus may discharge through the cervix into the vaginal lumen (Sheldon *et al.* 2006). In most cases, pyometra occurs as a sequel of chronic endometritis when the uterus ceases to produce or release of the endogenous luteolysin. The corpus luteum of diestrus persists and since the genital tract remains under the continuous influence of progesterone, the infection is not eliminated because of the cervix remains fairly tightly closed the purulent exudates accumulates within the uterine lumen, although occasionally there is slight purulent discharge occurs (Arthur *et al.* 2001). Administration of $PGF_2\alpha$ causes regression of corpus luteum, dilatation of cervix and myometrial contraction. Expulsion of the purulent fluid from uterus was started emptying within the 24 hour after the treatment.

CONCLUSION

It was concluded that the use of $PGF_2\alpha$ is more effective for the treatment of first degree of endometritis in cows and after $PGF_2\alpha$ treatment animal should be inseminated during the second estrus that follows the induced estrus. This will increase curative as well as conception percentage. Intra-vulvo submucosal administration of $PGF_2\alpha$ is economically more feasible and reliable than its intramuscular administration to terminate gestation when parturition is indicated. $PGF_2\alpha$ has been used for stimulating uterine involution and for enhancing fertility parameters during the post partum period. It has been proved to administer $PGF_2\alpha$ or its analogue in early postpartum cows and buffaloes in order to hasten early

resumption of cyclic ovarian activity and thereby to increase the reproductive efficiency.

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