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## **A Discussion on Risk Factors, Therapeutic Approach of Endometritis and Metritis in Cattle**

**Devender Kumar, Satish\* and G.N. Purohit**

*Department of Veterinary Gynecology and Obstetrics, College of Veterinary and Animal Sciences, Bikaner, RJVVAS Bikaner, Rajasthan 304001, India*

\*Corresponding author

### **A B S T R A C T**

Metritis and endometritis are the very common postpartum uterine infections that results into infertility in dairy cattle, production loss and economical losses to the farmer. As postpartum uterus favors bacterial growth so it is frequently found in almost of unhygienic environment reared animals. Breaching of birth canal during dystocia, retention of placenta, wet environment during winter season and immunosuppression due to many reasons are the risk factors for the bacteria invasion to uterus. Although in normal condition these infections are eliminated in animals by uterine involution, passage of lochia, and through the mobilization of immune defense system within few weeks after parturition. Bacterial products causes inflammation, suppress pituitary LH secretion, and postpartum ovarian follicular growth and function, which disrupts ovulation, makes cattle infertile and can cause some severe systemic illness, even death of animal. Metritis and endometritis generally treated with the systemic antibiotics. As many study suggested that there is not so significant beneficial effect of intrauterine antibiotic infusions but not to be negated as some found positive effect. Neomycin is only labeled drug for intrauterine preparations. Ceftiofur and oxytetracycline parentally are good choice for the treatment of metritis and endometritis. Thus, metritis and endometritis affected animal having lower conception rates, increased intervals from calving to first service or conception.

#### **Keywords**

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### **Introduction**

After parturition, uterine involution, regeneration of the endometrium, return of ovarian cyclic activity and the control of pathogenic bacteria in the uterus is required before cows are likely to conceive again (Gautam *et al.*, 2009). Uterine infections during the postpartum period such as metritis and endometritis affect a large population of

cattle and are associated with economical as well as production losses in dairy animals (Fourichon *et al.*, 1999, 2000).

Calving associated problems such as dystocia, twins, retained placenta, and stillbirth are the common risk factors for development of metritis and endometritis (Grohn *et al.*, 1990; Correa *et al.*, 1993). Metritis is characterized as more severe inflammatory response to

bacterial infection that occurs within all the layers of the uterus as endometrium, submucosa, myometrium and perimetrium are involved (Sheldon *et al.*, 2006).

Up to 40% animals develop metritis within the first 14 days of calving and 10 to 15% of these animals have persistent infection for another three weeks leading to a chronic uterine disease that involving only the endometrium affects (Sheldon and Dobson, 2004).

Normal Uterine function are affected by pathogenic bacterial contamination after calving, causing uterine disease that are causes of infertility. The postpartum uterine lumen environment supports the growth of various types of bacteria (Ruder *et al.*, 1981). Generally bacteria that contaminate the uterine lumen are removed by different types of uterine defense mechanisms. Under following normal condition cows eliminate these bacteria during the first 5 weeks after parturition, but in 10–17% of animal infection occurs which causes uterine disease (Olson *et al.*, 1984). It has been mentioned that bacterial load in uterus, bacterial metabolic products and the associated inflammation of uterine layers causes to suppress pituitary LH secretion that leads to disturbance postpartum ovarian follicular growth and function (Herath *et al.*, 2009).

Cows affected by metritis and endometritis with systemic symptoms require systemic antibiotic with sportive treatment because of severe illness and risk for death but criteria for assessing treatment success are inconsistent (LeBlanc, 2008). Thus, uterine infection ultimately leads to lower conception rates, increased intervals from calving to first service or conception and had to more cattle culled for failure to conceive (Kossaibati and Esslemont, 1997; Esslemont and Kossaibati, 2002).

## Risk factors affecting postpartum reproductive function

### Body condition score

There are practically very few reports on the direct relationship between body condition score at the time of calving and incidence of postpartum infection in dairy cows. Reports stats that the body condition of beef cows is related to many critical aspects of production such as conception rate, calving interval, days to estrus, and milk production. When cows are extremely thin ( $BCS < 4$ ), they are not only reproductively inefficient, but they are most susceptible to health problems (Beverly 1985; Selk *et al.*, 1986). On the other hand (Gautam *et al* 2010) found no significant effect of body condition score on the incidence of postpartum endometritis.

### Parity

Postpartum ovarian activity, days from calving to ovulation and the number of follicular waves to first ovulation may require longer interval in primiparous cows compared to in multiparous cows, somaybe it is a predisposing factor of post partum infection (Lucy *et al.*, 1992).

Cows in advance parity having more chances to develop uterine infections probably because of more relaxed birth canal and, delayed involution of uterus (Zezula *et al.*, 1990). Puerperal metritis tends to develop in cows having parity less than 3 because of uterine tissue damage during dystocia (Bruun *et al.*, 2002). Primiparous cows having higher risk of clinical endometritis compared to toward second-parity cows (Aghamiri *et al.*, 2014). Reports also support the risk of puerperal metritis was highest following first calving and lowest in second parity cows (Markusfeld, 1987). Thus the effect of parity on incidence of uterine infections to be inconsistent.

## Season

Calving season is known to affects postpartum reproductive function. Early involution occurs in dry season rather than in rainy season, dry season also having reduced number of pathogen in environment (Rekwot *et al.*, 2000). But some studies found no significant effect on uterine involution period due to calving season (Campo *et al.*, 2002).

Reports of some studies revealed positive association between retention of fetal membranes with a seasonal pattern that contributes uterine infections. During winter season reduced feed intake results in negative energy balance that leads to metritis and retention of fetal membrane (Buckley *et al.*, 2010). Immunosuppression and decreased leukocyte activity occurs in winter seasons increases the risk of uterine infection (Onyango, 2014). During winter months lack of grazing, thus increasing energy expenditure for maintenance, overcrowding, reduced exercise and less access to sunlight, stress increases the risk of postpartum uterine disease (Cady, 2010).

## Age

It is difficult to state any comment for metritis in relation with the age of animal. Cattle have most susceptible to uterine infection at early age (Brunn *et al.*, 2002). A study found lowest incidence of postpartum metritis in cows between 2 and 4 years of age and was highest in cows older than 7 years (Smith and Risco, 2002). Young cows have a small pelvis compared to older cows and thus are more prone to uterine injuries dystocia and thus predisposing them to uterine infections (Konyves *et al.*, 2009; Tsousis *et al.*, 2009; Potter *et al.*, 2010). Tsousis *et al.*, (2009) found out that cows in their first parity had more purulent discharge compared to older cows which could be a result of calving assistance.

(LeBlanc *et al.*, 2002) found that endometritis is more prevalent in mature cows in their third or higher parity had a prevalence of 21% compared to 13% for cows in first and second parity. The frequency of postpartum metritis was significantly lower (21.42 per cent) in animals aged under 4 years as compared to 39.17 per cent in animals aged 4 to 8 years and 54.76 per cent in animals aged over 8 years (Somasekara, 2003).

## Dystocia

Assisted calving during parturition often results in postpartum uterine infections (Foldi *et al.*, 2006; Tsousis *et al.*, 2009) probably due to handling injuries or poor hygiene.

Dystocia also results in injury to uterine tissue due to oversized or malpresented calf can cause injuries to the genital tract during traction and retropulsion, which predispose it made it easy to invaded by pathogens and leads to uterine infection (Kim and Kang, 2003; Zaborski *et al.*, 2009). Multiple births increased the chances of dystocia which also contribute post-parturient infections (Hosseini-Zadeh, 2010). Dystocia results in delays the process of uterine involution by disturbing the hormonal events resulting in placental retention and predisposes cows for uterine infection (Smith and Risco, 2002). Injury during dystocia leads to release of heparin at the site of injury which inhibits collagenases and can also delay uterine involution and leads to retention of foetal membranes (Beagley *et al.*, 2010).

## Retention of Foetal Membranes (RFM)

According to many reports, there is a very close association between RFM and incidence of postpartum endometritis in dairy cattle. In cattle, failure to expel foetal membranes within 12 to 24 hours is considered as retention of foetal membranes (Drillich *et al.*,

2003). Contamination of this uterus by pathogens due to RFM affects animal fertility because it disrupts the normal endocrine control of ovarian activity, follicular development, and its lead to repeat breeding and makes it prone to higher risk of metritis and endometritis (Opsomer and Kruif, 2009). Retention of fetal membranes can also causes general health hazards that finally affect the reproductive performance of animal (Van Werven *et al.*, 1992). Decrease of the antioxidant enzymes secreting capacity of the placenta during pregnancy can also lead to the retention of foetal membranes. Dystocia and uterine trauma also have been associated with uterine atony that inhibits expulsion of membranes and lead to uterine infections (Au *et al.*, 1992; Eiler and Fecteau, 2007). Retention of foetal membranes causes delayed uterine involution, increased services per conception, longer time to 1st service, decreased pregnancy rates and increased days open. Including metritis RFM also have been associated with increased risk for endometritis, ketosis, and mastitis (McDougall, 2001; Bruun *et al.*, 2002). Animals with lower prepartum levels of placental superoxide dismutase and plasma estrogen level, subsequently developed retention of foetal membranes. (Gupta *et al.*, 2005).

### Milk yield

The milk yield for standard 305 days lactation was almost identical to healthy cows (Menadoric *et al.* 1979; Markusfeld, 1984). In uterine infection affected cow some studies found that high producing cows had a higher incidence of postpartum reproductive disorders including metritis than low producing cows (Buttler and Smith, 1989). But in other study found significantly higher incidence of chronic postpartum endometritis in animals with low milk yield as compared to those with high milk yield (Somasekara,

2003). So it is not to conclude that high productive cows did not necessarily show always higher incidence of postpartum disorders (Nakova *et al.*, 1992). In view of above and related other reports, it is difficult to assess whether the low milk yield is a risk factor for postpartum endometritis or the high milk yield itself.

### Miscellaneous factors

Several miscellaneous factors have been reported to predispose the development of postpartum endometritis in dairy cows. Parturient abnormalities such as still birth) have been identified as significant factors for postpartum endometritis in dairy cows (Markusfeld 1984; Correa *et al.*, 1993). The incidence of puerperal metritis was also reported to be higher in animals with short gestation length, following induction of parturition and multiple births (Muller and Owens 1974; Sandals *et al.*, 1979; Juchle 1981; Markusfeld 1984 and Erb *et al.*, 1985). Those animals suffering with post parturient metabolic diseases such as milk fever and ketosis are reportedly more prone for the development of puerperal metritis (Morrow 1969; Kendric 1980; Markusfeld 1984; Correa *et al.*, 1993).

### Diagnostic methods-

#### History and physical examination

The simplest approach for diagnosis of clinical endometritis is manual examination of vagina and expultion of the mucus from uterus for inspection. Such technique is considered inexpensive, quick and provides additional sensory information about such as detection of vaginal lacerations and detection of odor of mucus in vagina. (Sheldon *et al.*, 2002). Post partum endometritis is diagnosed as persistent purulent or mucopurulent uterine discharge after 26 days

in milking (LeBlanc, 2008). Hendricks *et al* (2006) found in there study clinical endometritis at days 50 of postpartum was suspected as 20% on the basis of purulent discharge detected by farmer by visual inspection of the prenum, vulva, tail, and further confirmed by clinician as trans-rectal palpation of uterus. Same as Somasekara (2003) states incidence of chronic postpartum metritis as 20.3% animals diagnosed on the basis of a history of mucopurulent discharge noticed by the animal attendant.

### **Vaginoscopy**

Visual inspection of the canal vaginal using a sterile metal or transparent barrel vaginoscopy with a light source (Vaginoscopy) has been used to inspect the presence of pus or abnormal accumulates (Runciman *et al.*, 2008a; Leutert *et al.*, 2012). Vaginoscopy has been considered as more sensitive method than simple external inspection for detection of purulent discharge (Dohmen *et al.*, 1995; Le Blanc *et al.*, 2002a). Vaginoscopy provides proper image of the all female animal reproductive organ to identify endometritis and metritis (Miller *et al.*, 1980; Dohmen *et al.*, 1995; Williams *et al.*, 2005; Leutert *et al.*, 2012) but vaginitis, cervicitis and cystitis may give false results. Vaginoscopy is convenient to use yet there is risk of disease transmission if not used with proper hygiene (LeBlanc *et al.*, 2002a).

### **Transrectal palpation of the uterus**

For clinical endometritis transrectal palpation is most common means of diagnosis but palpation correctly identified only 22% of cows predicted to have uterine infection, compared to uterine culture (Miller *et al.*, 1980). On perrectal palpation it is terribly subjective and it's going to be troublesome to differentiating the female internal reproductive organ undergoing involution

from postpartum endometritis, particularly within the initial two weeks of parturition. (Youngquist and Shore, 1997; Smith and Risco, 2002).

### **Transrectal ultrasonography**

Ultrasonography has become an important diagnostic tool for evaluating the female reproductive system. Its importance in diagnosis lies within the non-invasiveness of the instrument (Carriere *et al.*, 2002). Anechoic fluid found in cases of endometritis along with snowy echogenic particles observed (Lenz *et al.*, 2007; Barlunda *et al.*, 2008). More recently transrectal ultrasonography has been used to detect intrauterine fluid accumulation associated with endometritis or metritis (Lenz *et al.*, 2007; Oral *et al.*, 2009; Melcher *et al.*, 2014).

Ultrasonographic features also helpful in diagnosis of increased endometrial thickness (Lenz *et al.*, 2007; Oral *et al.*, 2009; Purohit *et al.*, 2013). In an attempt to increase diagnostic ability combined the results of endometrial cytology and an ultrasonographic evaluation of fluid in the uterus and could improve both specificity and sensitivity considerably (Kasimanickam *et al.*, 2004).

### **Uterine cytology**

Subclinical endometritis is known to occur beyond 8 week postpartum and hamper fertility. During recent years uterine cytology has been used to diagnose subclical endometritis in dairy cows. For cytologycal study different approaches for collecting sample viz. using uterine biopsy, uterine lavage and cytobrush were adopted (Kasimanickam *et al.*, 2005).

Endometrial cytobrush cytology was the most reliable method of diagnosing endometritis in cattle (Barlund *et al.*, 2008). The collected

swabs are rolled on glass microscopic slides and have been evaluated after staining with modified Wright or Giemsa staining. Prepared smear must contain epithelial cells (to confirm correct site of collection), if no epithelial cells are seen, there is no assurance that the sample was taken from the uterus (Azawi, 2008).

A positive endometrial cytology having >18% neutrophils at 20-33 days postpartum or with >10% neutrophils at 34-47 days postpartum are considered diagnostic indication (Kasaimanickam *et al.*, 2004). Another technique is the low volume uterine flush to collect samples for endometrial cytology from cows between 40 and 60 days in milking (Gilbert *et al.*, 2005). Samples in this approach was only 2-5 ml fluid yet before staining it was suggested to be re-suspended and centrifuged by cytopsin centrifuge (Foldi *et al.*, 2006).

### **Microbial culture**

For definitive diagnosis of clinical endometritis microbiological examination of swabs collected from uterine lumen has been suggested, yet the difficulty in obtaining samples representative of the uterus limit the frequent use of such approach (Purohit, 2008). Swab is most accurate means of obtaining samples for identification of bacteria that cause infection (Olson *et al.*, 1986; Noakes *et al.*, 1991; Bonnett *et al.*, 1993).

Bacterial culture determine the microbes (Studer and Morrow, 1978; Olson *et al.*, 1986; Bretzlaff, 1987; Sheldon *et al.*, 2004) in the uterus causing the pathology. By swabs collected from uterine lumen of dairy cows 21 and 28 days after calving, purulent vaginal mucus was associated with growth density of pathogenic bacteria but not opportunist

contaminants (Dohmen *et al.*, 1995; Williams *et al.*, 2005; Westermann *et al.*, 2010).

### **White side test**

The coagulation of cervico-vaginal mucus on boiling with 5 percent NaOH with resultant appearance of yellow color was taken as positive indication of infection in uterus. On the basis of intensity of colour development, the degree of endometritis was classified as [1] No colour means absence of infection, [2] mild yellow colour change means mild infection), [3] intense yellow colour means severe infection (Anilkumar and Devanathan, 1996). However due to inconsistent results such test have not been validated (Purohit, 2008) and suggested (Raja *et al.*, 2012).

### **Endometrial biopsies**

Endometrial biopsy is highly diagnostic for pathology and has potential to generate extensive quantitative data on physiologic or immune mechanisms in cows.

The definitive diagnosis of clinical endometritis has been suggested based upon histological examination of endometrial biopsies (Bonnett *et al.*, 1993; Meira Junior, 2010; Dolatkhah *et al.*, 2013). Endometrial tissue is obtained with a biopsy punch by biopsy catheter, Ideal sample size of tissue is 10-20mm × 3mm (De Bois and Manspeaker, 1986).

Histologically endometritis is characterized by disruption of endometrial epithelium, infiltration of inflammatory cells, accumulation of lymphocytes, vascular congestion and stromal edema (Bonnett *et al.*, 1991; Bondurant, 1999; Meira Junior *et al.*, 2012). However uterine biopsy followed by histologic examination is costly, time consuming, and not clinically accessible under most situations. Moreover uterine

biopsy is an invasive technique and in cows has been associated with a detrimental effect on subsequent fertility (Miller *et al.*, 1980; Bonnett *et al.*, 1993).

## Hysteroscopy

It is a non-invasive, non-detrimental approach for the diagnosis of clinical endometritis in cows, (Madoz *et al.*, 2010). It is a very useful tool to diagnose, or interpretate physiological and pathological changes during the postpartum period in cow (Devine and Lindsay 1984; Metzner *et al.*, 1992).

However due to its high cost of the equipment and the problems encountered with passing the bovine cervix the prospects of such a technique are currently limited and suggested for specialized cases only (Milosh *et al.*, 2013).

## Therapy

Postpartum metritis is generally treated with antibiotics, hormones, alone or in combination. Antibiotics are used as systemically or locally into the uterine lumen. Animals with further health complications to suggested to be treated with anti-inflammatory agents with fluid therapy and other supportive therapy as priority basis (Pugh, 1994).

It is still controversial whether cattle without any signs of systemic illness should be treated with systemic antibiotics.

Response to different therapies is variable because several factors like the differences in criteria used to diagnose metritis, the postpartum stage of the animals, the outcome variables that are being measured, and the route, frequency of administration of drug and different drugs used in each trial varies widely (Smith and Risco, 2002).

Uses of antibiotics in cases of retained placenta as prophylactic measure may be useful, but there are few studies evaluating their ability to prevent metritis, especially in relation to their cost and appropriate withdrawal times (Peters and Laven, 1996).

## Intrauterine infusions

A variety of agents, antiseptic or antibiotics have been infused into the uterus in an attempt to destroy the infection, enhance uterine defense mechanisms, and increase uterine tone and also blood flow.

The ideal antibiotic should have ability to eliminate harmful bacteria from the uterus without damaging the uterus and impairing uterine defense mechanisms. As reports shown, intrauterine antibiotic infusion are not so effective treatments for postpartum metritis (Smith and Risco, 2002). When intrauterine antibiotics used, it is unclear whether the drug is distributed throughout all layers of the uterus (Bar and Ezra, 2005). Since in metritis, the infection is present into the deeper structures of the uterus and possibly to the serosal surface, intrauterine infusion achieves higher drug concentration in endometrium as compare to systemic antibiotics, but there is little penetration to deeper layers of uterus and genital tissues (Masera *et al.*, 1980; Bretzlaff *et al.*, 1983).

Although neomycin only is labeled for bovine intrauterine therapy (Veterinary Pharmaceuticals 1988) but rather than it these Intrauterine agents used are Lugol's iodine (Callahan and Horstman, 1987), gentamycin, spectinomycin, sulphonamides, nitrofirazole, iodine and chlorhexidine (Gustafsson, 1984; Gilbert and Schwark, 1992), florfenicol (Li Yan and Ji Lian, 2008), ceftriaxone (Mahto *et al.*, 2012), Moxifloxacin (Purohit *et al.*, 2013), cefquinome (Amiridis *et al.*, 2003), cephalosporin (McDoughall, 2001; Runciman *et*

al., 2009; Kumar *et al.*, 2013; Zobel, 2013) Ciprofloxacin (Purohit and Sharma, 2007; Sunilchandra and Hiremath, 2004). Intrauterine therapy as combination of 2 or 3 antibiotics Gentamycin, Chloramphenicol and Enrofloxacin has also been reported (Sood *et al.*, 2002).

In cyclic cattle, use of irritable intrauterine drugs may induce prostaglandin release luteolysis and removal of the inhibitory effects of progesterone on the uterine defense mechanism (Paisley *et al.*, 1986). This might be a cause for use of irritating intrauterine agents, but it should be discouraged (Bretzlaff, 1987). Nitrofurazone, commonly available, has reduced effectiveness in the presence of pus, blood and necrotic debris and is also quite irritating to the endometrium (Gustafsson, 1998; Olson, 1985). The iodine solutions infusion with saline is most popular but studies have also proven that potential harmful effects of iodine infusion on future reproductive performance of animal. It has been studied that a single infusion of 50-100 ml of 2% polyvinylpyrrolidoneiodine (povidone-iodine) solution, as a routine therapy for 30 days postpartum, shown adverse effect on fertility in cattle treated with

endometritis compared to control group animals (Youngquist and Shore, 1997). Aminoglycosides are not effective as intrauterine infusion because it require aerobic environment to be effective (Olson *et al.*, 1985). Lugol's iodine, streptomycin and oxytetracycline are irritating and are reported to cause coagulation necrosis of endometrium (Gilbert and Schwark, 1992). Strong iodine solutions will cause endometrial necrosis and return to estrus within 4-7 days. The irritation caused by the disinfectant has been demonstrated to invoke a prostaglandin release with subsequent luteolysis and return to estrus (Sequin *et al.*, 1974). Oxytetracycline intrauterine therapy administration shown to very effective in treatment and prophylaxis of postpartum endometritis in cows (Singh *et al.*, 2001; Malinowsk *et al.*, 2004). Its antibacterial efficacy against almost infections caused by Gram-positive and Gram-negative bacteria are well-documented (Bretzlaff, 1986; Konigsson *et al.*, 2001). All intrauterine antibacterial have been negative effects on normal leukocyte function and their placement risks iatrogenic contamination and further injury to the uterus (Paisley *et al.*, 1986).

### Intrauterine antibiotic dosages

Antibiotic	Dosage	Comments	Major Bacterial Susceptibility
Amikacin	1 to 2 grams	Buffer with sodium bicarbonate	Gram negative
Ampicillin	1 to 3 grams	Use soluble product, may be irritating when concentrated	Gram positive and <i>E. coli</i> Gram positive and Gram
Ceftiofur sodium negative	1 gram		
Chloramphenicol negative	2 to 3 grams	Can be irritating	Gram positive and Gram
Gentamicin	1 to 3 grams	Acidic: Need to dilute and/or buffer	Gram negative
Neomycin	2 to 4 grams		Gram negative
Potassium penicillin	5 million IU		Gram positive
Procaine penicillin	4.5 to 6 million IU	Concern about residue left in uterus	Gram positive
Ticarcillin	3 to 6 grams	Infuse with 150- to 200-mL solution	Gram positive, Gram positive,
<i>Pseudomonas</i>			
Ticarcillin with clavulanic acid	3 to 6 grams	Lactamase inhibitor	Same as ticarcillin plus more Gram positive ( <i>Staph</i> , . <i>Bacillus</i> , <i>Enterobacter</i> )
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Sulfonamide is a useless drug for intrauterine therapy. Necrotic tissue and purulent debris reduce the efficacy of sulfonamides, Pus and necrotic debris present in the infected uterus provide the metabolites needed by the bacteria to produce folic acid (Olson *et al.*, 1985). The penicillin family of drugs (Singh *et al.*, 2001; Smith and Risco, 2002) and the cephalosporin tend to perform poorly when infused in the first 30-days postpartum because there are a number of organisms producing inactivating  $\beta$ -lactamase enzymes (Smith and Risco, 2002). Moreover, because many agents administered into the uterus may be systemically absorbed to some extent, there are concerns about appropriate meat and milk withdrawal periods (Gustafsson, 1984).

### Systemic antibiotics

Systemic antibiotic therapy is having so many advantages. Withdrawal period of systemic antibiotic are well-known, distribution to all layers of the uterus is achieved, and systemic antibiotic appears to be less harmful to the uterine environment than intrauterine

antibiotics (Smith and Risco, 2002).

Penicillin is most common antibiotic for postpartum metritis because it penetrates all layers of the uterus, is inexpensive, (Smith and Risco, 2002) and almost of the bacteria penetrate the endometrium those are sensitive to penicillin. Withdrawl period of penicillin in Milk 96 hours and for meat 10 days after the last treatment (Ott, 1996).

Ceftiofur sodium at 1 mg/kg IM or SC administered for 3 to 5 days with there no withdrawal period required. It was found that Ceftiofur concentrate in uterine tissues at levels exceeding then the mean inhibitory concentrations for *Escherichia coli*, *Arcanobacter pyogenes*, and *Fusobacterium necrophorum* (Smith and Risco, 2002). In another study administration of ceftiofur (1mg/kg IM) for 3 days to cows having clinical endometritis at 21-27 days after calving resulted in clear vaginal discharge at 41-42 days of calving.(Kaufmann *et al.*,2010; Bartolome *et al.*,2014).

### Systemic Antibiotic Dosages

Antibacterial Antibiotics	Drug Dosage	Route, Comment
Amikacin	10 mg/kg q 24 h	IV or IM
Ampicillin	29 mg/kg q 12 to 24 h	IV or IM
Ceftiofur	2 to 4 mg/kg q 12 to 24 h	IV or IM
Doxycycline	10 mg/kg q12 h	PO
Enrofloxacin	5.5 mg/kg q 24 h	IV
	7.5 mg/kg q24 h	Per os
	4.0 mg/kg q 12 h	Per os
Gentamicin	6.6 mg/kg q 24 h	IV or IM
Metronidazole	15 to 25 mg/kg	PO
Oxytetracycline	6.6 mg/kg q 12 h	IV, dilute and give slowly
Potassium penicillin	22,000 IU/kg q 6 h	IV
Procaine penicillin	22,000 IU/kg q 12 h IM, only 10 mL	per injection site
Trimethoprim sulfa	30 mg/kg q 12 h	PO

IV, intravenous; IM, intramuscular; PO, per os; IU, international units

Parenteral oxytetracycline is an appropriate treatment for postpartum metritis. Oxytetracycline is also a very commonly used for the treatment of postpartum metritis, especially in cattle even only mild signs of systemic involvement (Malinowsk *et al.*,

2004). Intravenous administration of oxytetracycline @ 11 mg/kg twice in a day, maintain mean tissue concentration >5  $\mu$ g/g in the uterine wall for the first 4 hours after the first treatment and reaching a maximum of 9 hours by the 5th day of treatment. Slightly higher and more persistent concentrations of

oxytetracycline were found in the caruncles and endometrium for a long periods of time. Concentrations in the uterine wall were far below those of blood (Bretzlaff, 1983). The minimum inhibitory dose for *Arcanobacter pyogenes* in uterine isolates is reported to be 20.4 µg/mL. A single IM administration of oxytetracycline has been reported to improve fertility as well as to treat subclinical endometritis (Tek *et al.*, 2010).

### Hormone therapy

Hormone therapy is another good alternative optional treatment protocol. The therapeutic action of hormone is to increase expulsive uterine contractions or to induce an estrus (Laven, 2003; Heuwieser *et al.*, 2000).

Therapeutic action of estrus are well known during this increase neutrophil function under the influence the estrogen, makes uterus resistance to infection (Smith and Risco, 2002) and increase myometrial contractility are all reduced under the influence of progesterone (Frazer 2001).

Induction of estrus is the effective treatment for metritis (Heuwieser *et al.*, 2000; Laven, 2003). During estrus there is naturally effective expulsion of uterine contents and in this state stimulate the uterine defense mechanisms to a very high level. The benefits of estrus are well-recognized since neutrophil function, uterine resistance to infection (Roberts, 1986; Bretzlaff, 1987). The corpus luteum destroyed by the action of estrogen or prostaglandin, leading to estrus induction. Prostaglandin F<sub>2α</sub> and various analogs have been widely used for the treatment of postpartum metritis. The uses of prostaglandin F<sub>2α</sub> and its analog in the immediate postpartum period, attempt to increase uterine tone to induce estrus (Bretzlaff, 1987; Hussain, 1989). However, it is proven that PGF has effect if there is luteal

tissue present on the ovary and progesterone level is high (Le Blanc *et al.*, 2002). Use of cyclooxygenase inhibitors (NASADS) reduces the PGF production, but it don't effects on the rate of involution in size of the uterus and cervix is unaffected by 80% decline in PGF production (Steffan *et al.*, 1984; Frazer, 2001). Intramuscular injection of PGF at high dose 50 mg has not had any apparent effect on uterine tone. Other hand Intravenous injection in lower doses have been much more effective, but only up to 4-days postpartum (Laven, 2003; Frazer, 2001). This may due to IM injections are absorbed more slowly and, once absorption occurs, PGF is metabolized on a single pass through the lungs. The benefits of prostaglandin in the postpartum cow may relate to its role in the inflammatory process, but this hypothesis has yet to be validated (Frazer, 2001; Sheldon and Noakes, 1998). Estrogens, more commonly estradiol cypionate, have been used to formation of oxytocin receptors in the postpartum uterus. It has been proven that estradiol will speed up the process of oxytocin receptor expression in cyclic cattle, but it is not always essential for the process for all times postpartum (Hixon and Flint, 1887).

Estradiol at doses of 5-10 mg per animal has been used as treatment for postpartum endometritis and is almost effective as PGF2 (Pepper and Dobson, 1987; Sheldon and Noakes, 1998). But as the adverse effect of it to lactating cows can suppress milk production and can also result into formation of ovarian cysts (Roberts, 1986; Jeengar *et al.*, 2014) and so that the use of estrogens is not advocated on a wider scale and should be limited to a short term therapy only under specific circumstances. Estrogen may be used alone for metritis treatment. Recommended doses of estradiol range from 3-10 mg and doses may be repeated twice at 3 day intervals. Furthermore, the use of 5 mg of ECP IM 18-hours post-partum was found to

negatively affect the frequency and duration of uterine contractility for at least 5 days (Wiltbank *et al.*, 2000).

Oxytocin is inexpensive drug, but is thought to be useless to uterine clearance after long period in postpartum cow. It is well known that there is a loss of oxytocin receptors in the myometrium effective till 48-hours postpartum. Problem with oxytocin is its short duration of therapeutic action so repeated doses required for desirable action (Gustafsson, 1984). Repeated daily dosing of oxytocin following the single estrogen injection did not produce a demonstrable benefit. It has been demonstrated that uses of estrogen causes, uterine contractions are toward cervico-tubal. It may be a reason for the high incidence of salpingitis in a study where cows with metritis were treated with 10 mg of estrogen IM. With ECP treatment there is increased incidence of cystic ovarian degeneration (Smith and Risco 2002). Oxytocin used in post-dystocia or post caesarean to treat uterine atony, placental expulsion, and to prevent uterine prolapse. To till date, it is has been not clear to determine the most appropriate dose, A study evaluate oxytocin dose as a treatment for Retention of fetal membrane, 60 IU oxytocin IV was found to result more effective (Frazer, 2001).

Continuous slow IV infusion of oxytocin in saline over 6 hours would may be more appropriate, but this difficult to maintain such a period in large animal (Gilbert and Schwark 1992). The increased frequency of uterine contractions has been to be similar to as in early stage II of parturition in cattle. Most of the studies used IV route of administration for oxytocin. Same responses have been also found following IM or SC uses with different doses. However critical, scientific evaluation has yet to be done to determine its effectiveness (Frazer, 2001). Ergonovine is a fungal derivative and not actually a hormone.

It is known for uterine contraction stimulation, otherhand controlled trials have shown little or no effect on myometrial contraction (Gustafsson 1984).

### **Alternative treatment**

Vitamin E and selenium increase chemotaxis and leukocyte numbers at the fetomaternal junction, thus contributing to the normal expulsion of fetal membranes, ultimately reduces the chances of infections (Bourne *et al.*, 2007).

Calcium is an essential trace-element that results smooth muscle contraction of the uterus. Immediately after calving most of the high yielding cows becomes deficienct in calcium leading to atonicity of the uterine musculature which ultimately causes retention of fetal membranes and metritis (Al-Eknah 1989; Whiteford, 2005). Therefore, prescribing oral calcium during this period may be beneficial to prevent metritis. Sometimes after calving, cows loss their appetite and there are many chances of developing ketosis in such animals which causes displaced abomasums or metritis. In such conditions supplementation with propylene glycol or propionate is beneficial (Littledike, 1981).

In conclusion, uterine infection after calving is the most important cause of infertility in dairy animals. Predisposing factors for establishment of uterine infections are RFM dystocia, caesarean section, still birth. Severity of uterine infection depends totally on the immune response of the animal and the types and load of bacteria. Bacteria multiply and penetrate the mucosal epithelium, release bacterial toxins that causes to establishment of uterine infection. Postpartum uterine infections disturbs the normal cyclicity of animal, intrauterine transport of sperm and embryo implantation these factor leads to

delayed calving to first service interval and reduced conception rates finally economic losses to the owner. Treatment with intrauterine therapy alone in case of endometritis may gives a good result but in the case of metritis parental antibiotic infusion only gives results. Ceftiofur is good treatment of choice for metritis. Provides proper nutrition during pregnancy, hygienic conditions during calving and immediate veterinary care in case of dystocia to reduce the postpartum uterine infections.

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