

## Review Article

## Comprehensive Study on Endometritis in Dairy Cows with Special Focus on Recent Diagnostic and Treatment Approaches: A Review.

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## ABSTRACT

Inflammation of endometrial layer of uterus is termed as “endometritis”. Endometritis is one of the most common postpartum uterine diseases that influence animal’s profitability. The severity of a health issue is affected by bacterial load, pathogenicity, and cow immunological status. There are several risk factors responsible for the prevalence of disease, such as metabolism, abnormal calving, parity of cow and retained placenta. There are several techniques for diagnosis of endometritis including endometrial cytology, which is regarded as the most reliable approach for detecting whether a cow has clinical or subclinical endometritis based on presence of polymorphonuclear (PMN) cells. Also, negative energy balance (NEB) has been reported as a great threatening to animal’s health. Subclinical endometritis (SE) has been linked to an elevation in levels of non-esterified fatty acids (NEFA) and  $\beta$ -hydroxybutyric acid (BHBA) on comparing to healthy cows. Traditional strategies for treatment of endometritis include infusion of antibiotics, injection of hormones and using of povidone-iodine. However, Recently, scientists focused on developing alternative treatments to avoid the unnecessary prescription of antibiotics in treating dairy cows suffering from uterine infections. For example, using ozone for prevention of subclinical and clinical endometritis. In this review, we aimed to demonstrate the definition, causes, risk factors, pathogenesis, recent diagnostic tools and giving recommendation to the recent guidelines for treatment.

## 1. INTRODUCTION

Uterine disorders such endometritis and metritis, which have a severe detrimental financial effect on the animal's profit, may affect the reproductive health of female animals (Umer et al., 2022). *Escherichia coli*, *Streptococcus*, *Trueperella pyogenes*, *Bacillus licheniformis*, *Prevotella species* and *Fusobacterium Necrophorum* are the most prevalent microbes in uterine contamination in the days immediately after calving (Sheldon et al., 2006). It has been established that endometrial cells exhibit a distinct expression of genes during this time that code for several aspects of the inherent immune system functions, such as Type Toll receptors, inflammatory substances, and effector compounds (Sheldon et al., 2004). Additionally, a significant amount of Polymorphonuclear cells (PMN) also arrives. This inherent immune system capability in animals with good health can eliminate bacterial contamination. Therefore, the equilibrium between the immune system of the animal, the environment, and the bacteria that colonize the uterus decides whether clinical symptoms manifest (Potter et al., 2010).

## Definition and classifications of endometritis

Endometritis, which is the confined endometrial inflammation that lasts longer than typical uterine shrinkage, has been shown to be a serious obstacle to dairy cows' ability to reproduce at their peak capacity (Sheldon et al., 2006). Uterine inflammatory processes hinder the uterus' involution mechanism and postpones the beginning of ovulatory activity, which has adverse effects on the economy due to systemic illness, lower milk and meat output, and a major

impact on fertility (Deori and Phookan, 2015). Clinical and subclinical diseases have been further subcategorized under the term "endometritis." (Palmer, 2014). Clinical endometritis (CE) is an inflammation of the inner endometrial layer of the uterus that is followed by a pus-like or mucopurulent discharge from the vagina when there are no indications of a systemic sickness (Sheldon et al., 2006). Inflammation of the endometrium that is not immediately obvious is known as subclinical endometritis (SE) in cattle. It should be noted that both CE and SE occur  $\geq 21$  days in milk (DIM) (Yáñez et al., 2022).

## Risk factors incriminated in prevalence of endometritis.

As shown in (Figure 1), inadequate metabolism, unusual calving, and unsanitary barn conditions are some of the causes of long-term intrauterine inflammation (Osawa, 2021).

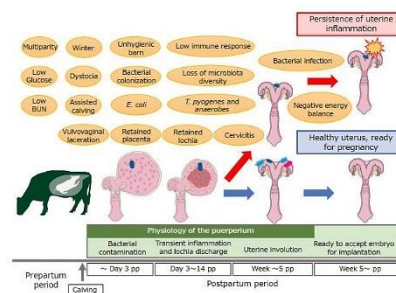


Figure 1 An illustration of the predisposing variables (yellow circles) for persistent endometritis in the cow, coupled with the prepartum and postpartum periods (Osawa, 2021).

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### Common causes of endometritis

Endometritis is commonly caused by mixed bacterial infection of the uterus. These include *E. coli*, *T. pyogenes*, *Prevotella melaninogenica*, *F. necrophorum* and *Proteus species* (Madoz et al., 2014). *E. coli* is the most common isolated bacterial species in the first week postpartum and is therefore the most common organism associated with metritis. *T. pyogenes* is the dominant bacteria associated with the uterus from week 2 onwards and is therefore most commonly associated with endometritis (LeBlanc et al., 2011).

### Pathogenesis of endometritis

Disagreement exists regarding the pathogenicity of endometrial infection; virulent bacteria-related variables are what cause uterine disease. Additionally, immunological response exhibits strong pro-inflammatory cytokine concentration, and peripheral circulation exhibits acute phase proteins with few symptoms of systemic illness (Sheldon et al., 2006). The genital tract actually possesses innate immunity and depends significantly on pattern recognition receptors (PRRs), which it uses to identify pathogens through pattern-associated molecular patterns (PAMPs). Toll-like Receptors (TLRs) are a family that includes PRRs. These are capable to detect a wide range of PAMPs linked to bacteria, viruses, and fungi. Similar to this, the principal PAMP in the uterus for identifying harmful *E. coli* is the toll-like receptor 4 (TLR4), which is expressed by epithelial and stromal cells. TLR4 is a binding site for lipopolysaccharide (endotoxin, LPS) (Herath et al., 2006). Figure 2 illustrated the pathogenesis and the varied impacts on reproductive hormones (Umer et al., 2022). The degree of contamination, uterine defense mechanisms, and the presence of substrates (such as devitalized tissues) for microbial development determine the seriousness and longevity of infection in the uterus (Deori and Phookan, 2015). The cytokines and toxins that the bacteria release led to delayed ovulation. As a result, gonadotrophin releasing hormone (GnRH) is suppressed, preventing the production of luteinizing hormone (LH). Furthermore, inflammatory responses have a negative impact on the brain, which regulates ovarian processes like follicle formation, leading to lower fertility and conception rates in animals. The observation of decreased estradiol secretion has been linked to uterine infection, which inhibits follicular expansion and compromises its function (Sheldon, 2007).

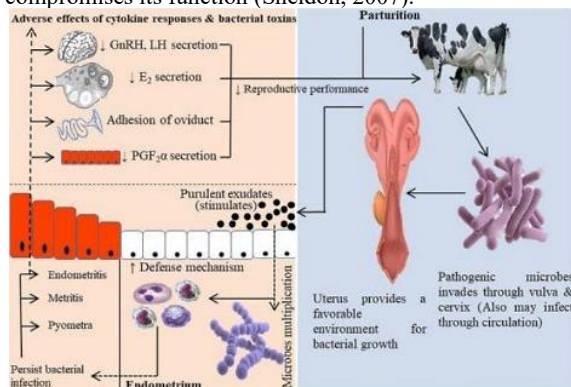


Figure 2. Pathogenesis of endometritis (Umer et al., 2022).

### Diagnosis of endometritis

#### 1) Ultrasonography

Ultrasonography is a straightforward, trustworthy, and non-invasive imaging method with low side effects. Real-time ultrasonography is now the most effective diagnostic technique for controlling reproduction in veterinary

medicine (Terzano, 2012). When assessing the presence and severity of inflammatory changes in the uterine wall, the diameter of the uterine horn and cervix as well as the quantity and type of accumulated fluid entering the uterus should be taken into account (Kasimanickam et al., 2004).

#### 2) Cytological examination

Currently, endometrial cytology is thought to be the most reliable method for determining if a cow has endometritis, both clinical and subclinical, based on the presence of cellular evidence of inflammation (Palmer, 2014). Kasimanickam et al. (2004) adapted the cytobrush (CB) by attaching it to a metal rod so that it could be used in bovine gynaecology. Similar to the artificial insemination (AI) procedures, a catheter protects the rod while it is transrectally inserted into the uterine body through the cervix. Wagener et al. (2017) demonstrated the shape of CB protected by catheter and plastic sleeve (Figure 3). According to Sheldon et al. (2009), the innate immune system is capable of recognizing bacterial infections that invade the uterus during the postpartum period, drawing inflammatory cells like neutrophils. A number of neutrophils in relation to endometrial cells becomes a sign of an inflammatory process and may be a significant feature of subclinical endometritis (Sheldon et al., 2009). Depending on the postpartum period, a threshold value of 5-18% is recommended for polymorphonuclear cells (PMN) as a diagnostic marker for subclinical endometritis (Wagener et al., 2017).

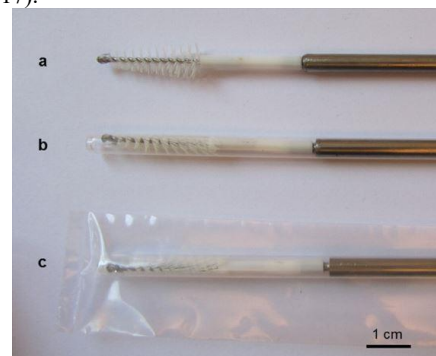


Figure 3. Cytobrush attached to metal rod (a) that was covered by a plastic catheter (b) and a plastic sleeve (c) (Wagener et al., 2017).

#### 3) Reagent test strips

##### 3.1. pH

Examination of cervical mucus for appearance, consistency, and pH may be helpful in the identification of subclinical endometritis since it alters the physico-chemical properties of the mucous. In repeat breeding cows, cervical mucus had a pH that ranged from 6.5 to 9.0, with a mean of 7.95 (Kumar et al., 2017). Manoj et al. (2014) stated that, the rise in pH (7.5–8.0) of vaginal discharge may be caused by bacterial contamination of uterine fluids, and the elevated pH makes it impossible for spermatozoa and embryos to survive in the uterus.

##### 3.2. Leukocyte esterase (LE)

Today's test strips can measure the LE enzyme's activity in specimens of urine, uterine flushing fluid, and uterine cytobrush samples. LE is an enzyme produced by neutrophils. Interesting research has suggested using LE activity as a cow-side test to identify postpartum SE (Cheong et al., 2012).

##### 3.3. Protein

Subclinical endometritis causes an increase in uterine fluid buildup, which could result in a rise in protein content and

be used to diagnose the underlying problem. In spite of this, there is a weak association between protein and SE (Cheong et al., 2012). This poor performance of the protein strip test could be attributed to the reagent strips' high sensitivity to albumin but much lower sensitivity to other proteins. Additionally, samples with high alkalinity may yield false positive results while samples with high specific gravity may yield false negative results (Sacks, 2001). This was also confirmed by Hajibemani et al. (2016) who reported that, although protein contents were higher in SE, protein assessment of discharges could not be advised for evaluation as a diagnostic tool for SE.

#### 4) Metabolic parameters analysis

Cows show signs of negative energy balance (NEB) within the first two weeks after giving birth, and it may last longer due to managerial, nutritional, or environmental problems. The accepted wisdom is that declining body condition score (BCS) and measuring serum levels of non-Esterified fatty acids (NEFA) and Beta-Hydroxybutyric acid (BHBA) are indications of NEB (Wagener et al., 2017). Cows release NEFA into the bloodstream as a result of NEB mobilizing their body stores. When the liver converts these NEFA molecules into ketones or stores them as triglycerides, it may result in fatty liver (LeBlanc, 2014). It was discovered that SE-affected cows had greater plasma NEFA values at 35 DIM than healthy cows (Galvão et al., 2010). It has been demonstrated that raised serum NEFA levels caused an elevation in Reactive Oxygen Species (ROS), which decrease neutrophil resilience and impair immune function (Scalia et al., 2006).

The well-known ketosis, with its ramifications for the animal's functionality and productivity, results from a simultaneous rise in serum levels of ketone bodies. BHBA is the most stable of these ketone molecules. Consequently, the most effective method for identifying ketosis is the measurement of BHBA concentrations (Oetzel, 2003). Yáñez et al. (2022) showed that the PMN% increased along with blood BHBA values, causing up to 60% of cows in clinical ketosis (BHBA > 2.4 mmol/L) to experience SE (PMN% > 8). These findings confirm the hypothesis that uterine infections are more likely to occur when animal is in ketosis. One theory is that peak amounts of BHBA disrupt PMN mission by decreasing chemotaxis and phagocytosis, which ultimately results in immunosuppression (Ingvarsen and Moyes 2015). However, Shin et al. (2015) found no connection between ketosis and SE. Although there were variations in management, the types of dwellings and the number of cows included across studies, further study is required to clarify this contentious subject (Yáñez et al., 2022).

Interestingly, Yáñez et al. (2022) said that albumin level might be helpful for the uterine problem. These results are consistent with those previously reported by Bogado Pascottini and LeBlanc (2020) who noted that 35 days postpartum, healthy cows had albumin concentrations that were higher than those of cows with SE. Furthermore, high serum BHBA and NEFA levels have been linked to low albumin levels, which may indicate poor liver function (Seifi et al., 2007). During NEB, the triglycerides stored in adipose tissue are converted to glycerol and NEFA through lipolysis. The latter are circulated after being non-covalently attached to serum albumin. Therefore, alterations in albumin levels could cause unbound NEFA to be stored in the liver as triglycerides, leading to fatty liver and worsening of NEB (Arfuso et al., 2016). Additionally, Schneider et al. (2013) discovered that since serum albumin levels were significantly lower three weeks before delivery in cows

subsequently diagnosed with uterine disease, suggesting that albumin's function as a negative acute-phase protein may help to detect cows which are vulnerable to uterine illness prior to calving.

#### Prevention of endometritis

Prevention of endometritis is based around the promotion and support of the innate immune system. Management of nutrition in the early post calving period is critical to minimizing the negative energy balance and circulating NEFA concentration that inhibits PMN function. Proposed management practices include provision of bunk space for ease of feed consumption, provision of suitable; clean rest area so that fresh in milk cows can lie without excessive contamination of the reproductive tract. Regulate temperature so cows are comfortable and manage monitor methods and targets so that problems can be identified and managed early. Management of risk factors will also decrease the prevalence of endometritis such as retained placenta and all its underlying factors as well as the early resolution of dystocias and twinning (Madoz et al., 2014).

#### Treatment of endometritis

##### 1) Intrauterine infusion of antibiotic

Due to the presence of bacteria that generate penicillinase, penicillin may become ineffective. Since the uterine environment is anaerobic and the aminoglycoside group of antibiotics (Gentamicin, Kanamycin, Streptomycin, and Neomycin) need oxygen to function, they are useless. The most common treatment for the condition is intrauterine pessaries, which can be either antibiotic or herbal. Both oxytetracycline and cephalosporins are effective and broad-spectrum antibiotics that should be used as first-line treatments for uterine infections (Sheldon, 2004). Also, LeBlanc et al. (2002) revealed that the medicine of preference for uterine infusion is benzathine cephalirin (Metricure, Merck Animal Health), a first-generation cephalosporin with no withdrawal from meat or milk.

##### 2) Administration of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>)

The primary mechanism of PGF<sub>2α</sub> treatment is its luteolytic action, which is followed by the start of estrus. The myometrium contracts, and uterine contents such as pus can pass through an open cervix (Kasimanickam et al., 2005). On the other side, Stephen et al. (2019) recently asserted that ecobolic therapy has no influence on the rate of uterine involution.

##### 3) Using of Povidone-Iodine (polyvinylpyrrolidone iodine or PVP-I)

According to Ahmed et al. (2014), the repeat breeding (RB) syndrome in cross-bred dairy cows is most likely caused by subclinical endometritis of the reproductive tract as well as an Iodine deficit. In addition, intra-uterine infusion of 2% povidone iodine has been shown to boost the reproductive efficiency of RB dairy cows. Mido et al. (2016) also claimed that 2% PVP-I intrauterine infusion proved more successful than a 0.5% PVP-I infusion in treating severe clinical endometritis in dairy cattle. Interestingly, according to the results of uterine ultrasonography, Melia et al. (2020) demonstrated that, the 2% lugol's therapy had no influence on the healing process of endometritis in aceh cows. However, Wagener et al. (2017) stated that further research is needed before making a valid therapy prescription for SE. As a result, it is emphasized that medication is not a cure for endometritis disease, but that appropriate preventative and control strategies must also be implemented during the condition (Ganaie et al., 2018). Management interventions

(MIs) to avoid pathogen entry and minimize pathogen transmission in the herd are key components of successful herd management practices (Wolff et al., 2019). Alternative therapy for minimizing the adverse manifestations of uterine disease in dairy cows.

#### 1) Ozone

A study explored the effects of ozone on the prevalence of subclinical endometritis and reproductive function (Escandón et al., 2020). When compared to control cows, ozone therapy reduced the incidence of subclinical endometritis. However, first-service conception rates increased. Further research with a larger sample on ranches with conception rates closer to the actual state of the majority of farms is thus necessary (Lima, 2020).

#### 2) Probiotics

Intravaginal probiotics appear to be useful in lowering the prevalence of metritis and endometritis. Still, the mode of action needs to be clarified, and additional replication in large-scale field studies are needed to establish the advantages of this prospective therapy for uterine illnesses (Lima, 2020).

## 2. CONCLUSION

Endometrial cytology is the best method to identify cows with SE. Elevated NEFA & BHBA and low albumin levels are indicative biomarkers for SE. In spite of the good results of using cephalosporins antibiotic and PGF2 $\alpha$  in treatment of endometritis, medication alone is not a cure for endometritis illness; suitable prophylactic and control measures must be done as well. Among the recent alternative therapy strategies, Intravaginal probiotics appear to be beneficial in reducing the occurrence of metritis and endometritis.

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