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# The Rising Impact of Endometritis on Infertility in Cattle and Other Large Ruminants

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## ABSTRACT

Endometritis is a significant cause of infertility in large ruminants, particularly in dairy cattle, leading to substantial economic losses in livestock farming. The condition, which is primarily caused by bacterial infections, retained placenta, and hormonal imbalances, disrupts reproductive health, resulting in prolonged calving intervals, reduced conception rates, and lower milk production. This review aims to provide a comprehensive synthesis of current knowledge on endometritis, exploring its epidemiology, pathophysiology, diagnosis, management strategies, and the impact on fertility. The review will also address emerging trends in the field, including molecular diagnostics, the role of the uterine microbiome, and the potential for vaccines and alternative therapies. Through a thorough analysis of the literature, the review identifies several key gaps in the understanding of endometritis, particularly regarding the molecular mechanisms behind bacterial infections and immune responses, as well as the broader microbial dynamics in the uterus. Furthermore, it highlights the need for more research on the economic impact of endometritis on herd productivity and sustainable management practices. The findings suggest that early diagnosis and timely intervention, along with improved farm management practices, such as better hygiene and nutrition, are essential for reducing the incidence of endometritis and improving fertility outcomes. It will also emphasize the role of precision livestock farming in the early detection and management of uterine infections. The review will conclude by recommending future research directions, including studies on the genetic and microbial factors contributing to susceptibility to endometritis, and exploring the development of alternative treatments that reduce reliance on antibiotics. These advancements are expected to contribute to more sustainable livestock farming practices and improved reproductive efficiency in large ruminants.

## INTRODUCTION

Endometrial infection (the inner lining of the uterus), known as endometritis, has recently become one of the major causes of infertility in large ruminants, especially in dairy cattle and beef herds. Metritis, a disease frequently caused by bacterial infections after calving or postpartum complications, is a serious threat to global livestock production (Sheldon et al., 2014). Endometritis remains a significant cause of reproductive failure in dairy cattle, with disease-causing conception rates decreasing by as much as 40% in affected herds (Carneiro et al., 2016). Management issues and environmental stresses aggravate the occurrence of this disease, as well as the growing fear of antibiotic resistance, which limits treatment effectiveness. Thus, endometritis affects the health and well-being of large ruminants and has serious economic consequences for agriculture by incurring high rates of culling, extending calving intervals, and reducing milk production (Horlock et al., 2020). This review paper addresses the increasing emergence of endometritis as a potential contributor to infertility in large ruminants, with emphasis on recent efforts to improve diagnosis, treatment, and prevention (Tasara et al., 2023).

Thus, despite important advances in the pathophysiology of endometritis, the underlying mechanisms remain partially understood. Bacterial pathogens that can cause endometritis to have recently received research interest, including Escherichia coli, Trueperella pyogenes, and Fusobacterium necrophorum (Ibrahim et al., 2017). Studies have also implicated uterine immune responses in disease progression, and an altered immune signaling balance may be a relevant contributory factor to chronic infections. Nevertheless, a significant knowledge gap exists regarding the molecular interactions between such pathogens and uterine tissues and how modern environments, such as heat stress and poor sanitation, intensify such diseases (Ferris et al., 2016). Furthermore, since antibiotic therapies and hormone injections are the most used treatments, the constant development of antimicrobial resistance tremendously complicates treatment protocols and raises concerns about future treatment plans. To address these gaps in knowledge, we synthesized the available literature aimed directly at addressing the relationship between high biomass biochar and terrestrial biodiversity (Carneiro et al., 2016).

The primary purpose of this review is to present a comprehensive overview of the relevance of endometritis in the infertility of large ruminants, recent progress, and directions for further research (Sheldon & Owens, 2018). This review provides new approaches to prevent and treat endometritis by overcoming the limitations of previous studies, particularly the limited holistic approaches that account for both the microbiological and immunological aspects of this disease. Its objectives were to consider the implications of our findings regarding livestock management practices and signal future research priorities. Such contributions from this review will be a significant step forward in magnetizing the attention of veterinary practitioners, animal health professionals, and farmers towards better and sustainable management approaches for treating endometritis in large ruminants, which will ultimately improve the reproductive performance and economics of sizeable ruminant farming (Cai et al., 2024).

## Epidemiology and Prevalence of Endometritis in Large Ruminants

Despite its well-documented role in reproductive inefficiencies, endometritis is an international burden on dairy and beef cattle populations, resulting in multimillion-dollar losses in the livestock industry (Kawashima et al., 2024). The incidence of endometritis varies greatly depending on geographical area, management, breed, and surroundings. Studies have shown that approximately 10%-40% of dairy herds have endometritis, although some high-production systems report an even higher prevalence of the disease. An estimated 30–40% of high-producing dairy cows are affected by subclinical endometritis, which is frequently associated with postpartum uterine infections (Sheldon & Owens, 2018).

During this period, as the uterus changes physiologically (with a further possibility of trauma at the time of parturition), cows become more prone to uterine infections. Retained placenta is another recognized risk factor for endometritis. Retained placenta is a known risk factor for uterine infection in cows because the retained tissue acts as a bacterial reservoir that can trigger endometrial infection (Sinchi et al., 2022).

Environmental factors and management practices also impact the incidence of endometritis. For instance, all badly nursed farms that lack the required strong sanitation or those that are overcrowded will likely have high infection rates of the disease (Sheldon & Owens, 2018). In addition, as temperature and humidity contribute, heat and humidity affect the ambiance, which creates stress and severity. Endometritis shows a noticeably higher frequency in tropical areas due to heat stress and its physiological consequences on the immune system. Heat stress increases the inflammatory response and impairs uterine defense mechanisms, ultimately increasing the risk of uterine infection (Ledgard et al., 2015).

Besides environmental and management issues, susceptibility to disease based on breed is another major factor affecting endometritis. Numerous studies have indicated that some cattle are more susceptible to endometrial infections than others, especially high-producing dairy breeds such as Holsteins, because increased milk yields may place considerable demands on the metabolic and immune systems (Rana et al., 2020). In contrast, endometritis appears to have little impact on beef cattle, although it is still reported to be an infertility factor in some herds (Ledgard et al., 2015).

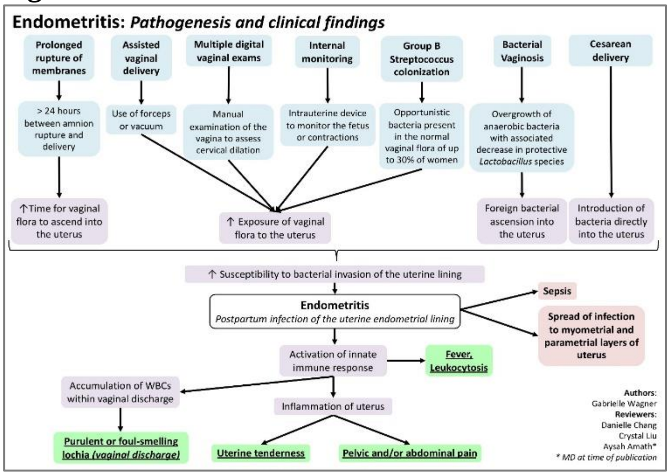
Endometritis is an economically important condition for livestock production. This condition is associated with longer calving intervals, lower pregnancy rates, and higher veterinary treatment costs (and culling of animals that fail to conceive). In addition to direct losses, endometritis also leads to diminished milk yield in dairy herds, resulting in further economic losses in dairy farms (Wang et al., 2018).

## Pathophysiology of Endometritis

Large ruminant endometritis is a predominantly inflammatory disease of the endometrium that occurs after infection, trauma/training, and other attacks that compromise the uterus. This disease mechanism involves a complicated interplay between pathogenic microorganisms, the uterine immune system, and the animal's physiological responses (Singh, 2023). Bacterial infection is a well-known factor in the pathophysiology of endometritis and is believed to be multifactorial (Sheldon & Owens, 2018).

The sequence of events triggered by bacterial pathogens, such as Escherichia coli, Trueperella pyogenes, Fusobacterium necrophorum, and Arcanobacterium pyogenes, are commonly associated with the development of endometritis as shown in **Figure 1**. These bacteria enter the uterus via the cervix, commonly following parturition when uterine defenses are compromised. The most frequent method of infection is the cervix during parturition or via the retained placenta, which is a source of bacteria. These pathogens may penetrate the uterine tissues and induce a local inflammatory response, causing uterine wall thickening, edema, and exudate accumulation (Adnane et al., 2017).

**Figure 1**

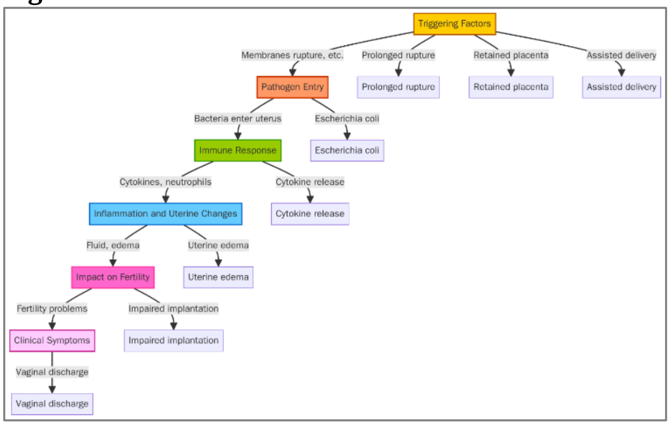



It shows the mechanism of endometritis in large ruminants. This includes how bacterial pathogens (E. coli and Trueperella pyogenes) invade the uterus through the cervix during parturition or via retained placenta, resulting in uterine infection and inflammatory response. The diagram also illustrates the immunological responses that lead to pro-inflammatory cytokine activation, neutrophil recruitment, and uterine tissue destruction. It also describes clinical manifestations like fever, leukocytosis, uterine tenderness, and sepsis, highlighting the multifactorial nature of the disease and how it affects reproductive performance.

The diagram provides a visual representation of the key factors and mechanisms involved in the development of endometritis in large ruminants. It illustrates how bacterial pathogens, such as *E. coli* and *Trueperella pyogenes*, enter the uterus through the cervix during parturition or via retained placenta, leading to uterine infection and inflammation. The diagram also highlights the immune response, including the activation of pro-inflammatory cytokines, neutrophil recruitment, and the resulting uterine tissue damage. Additionally, it outlines clinical signs such as fever, leukocytosis, uterine tenderness, and complications like sepsis, emphasizing the multifactorial nature of the disease and its impact on reproductive health.

When bacteria invade the body, the immune system releases numerous pro-inflammatory cytokines (including interleukins and tumor necrosis factors) that initiate and propagate the inflammatory response as shown in **Figure 2**. These cytokines attract neutrophils and macrophages to the infection site, and while these immune cells are critical for eliminating pathogens, unregulated inflammation may cause tissue damage. Endotoxins from Gram-negative bacteria, such as E. coli, are present in the uterus and increase the inflammatory response by inducing the secretion of additional cytokines, leading to increased tissue damage (Monteiro & Faciola, 2020). Persistent inflammation may give rise to endometrial adhesions and fibrosis, which prevent the uterus from sustaining pregnancy (Adnane et al., 2017).

**Figure 2**




Pathogenesis of endometritis in large ruminants, illustrated in a flowchart indicating the main triggers initiating the infection, the entry path for pathogens to the uterus and in other the state of the associated immune response. Indicating the inflammation in the uterus, the impairment in fertility and the clinical signs like discharge and the tenderness of the uterus. The diagram shows the initial events contributing to endometritis beginning with precipitating factors such as prolonged rupture of membranes or manual intervention during delivery, followed by bacterial invasion, intense secretion of immune mediators, and the manifestation of infertility in the animals that succumbed to the disease.

In addition to bacterial infections, hormonal imbalances and uterine tissue remaining in the uterus after delivery also contribute to the pathophysiology of endometritis. Involution of the uterus occurs immediately after calving, during which time the tissue regresses, and the uterus returns to its preparation for another pregnancy (Adnane et al., 2017). An exception to this situation is if the placenta is retained, which delays the process of uterine involution and leads to prolonged exposure to bacteria and inflammation. Hormonal regulation (estrogen vs. progesterone) is another important factor that influences the immune status of the uterus. The uterine environment can be such that low progesterone levels or disturbances in the estrous cycle affect the ability of the uterus to resist infections (Fowden et al., 2015).

In recent years, the role of the uterine microbiome in endometritis has gained attention. Emerging evidence indicates that physiological uterine microbiota may provide a barrier against pathogenic overgrowth (Bicalho et al., 2017). Dysbiosis is an imbalance of the microbial community, predisposing animal to infections; hence, there is a higher risk of developing endometritis. Ongoing research on the interactions between the uterine immune system and microbial flora represents a potentially novel approach to preventing or treating this condition (Casaro et al., 2025).

These factors, together with the general health status of animals, can also affect the immune response to infection. This means that other factors, such as nutrition, stress, and overall immune function, can affect the severity of endometritis. Inadequate nutrition or stress can compromise a cow's immune response, resulting in persistent infections and an increased risk of chronic endometritis. The exact molecular pathways of these interactions are essential for understanding and creating targeted treatments and better diagnostics for early detection (Adnane et al., 2017).

## Diagnosis of Endometritis

The diagnosis of endometritis in large ruminants is complicated and multifaceted because the condition is often associated with subtle or non-specific clinical signs (Negasee, 2020). The application of contemporary reproductive technologies significantly impacts multiple at-risk species, but presenting clinical signs are variable, making timely and accurate diagnosis particularly difficult (Rinaudo et al., 2017). Many affected animals show no signs of illness (sub clinically), which poses challenges for the early detection of affected animals. Thus, accurate endometritis diagnosis requires clinical signs, diagnostic tests, and veterinary skills (Fuentes et al., 2018).

Assessment of vaginal discharge is one of the simplest and most reliable methods for diagnosing endometritis. Abnormal vaginal discharge, which can be purulent or mucopurulent, is commonly observed in cows with endometritis. It is often associated with uterine infection and inflammation (Brodzki et al., 2015). However, vaginal discharge is not a confirmatory factor in the diagnosis, as it could also be a result of other reproductive disorders, such as vaginal or cervical infection (Nithish et al., 2022). Consequently, abnormal discharge should be associated with other diagnostic methods to confirm the diagnosis (Mohamed Al-Absy et al., 2023).

Uterine cytology, the collection and cytological evaluation of uterine secretions is a more accurate method for diagnosing endometritis (Moscuzza et al., 2015). Infection and inflammation in the uterus are characterized by the infiltration of neutrophils into the uterine fluid. During the immune response to an infection, neutrophils are recruited to the site, so their presence suggests that the animal is trying to fight the infection. Clinical endometritis is usually defined as an elevated percentage (> 18%) of neutrophils in uterine fluid (Gahlot et al., 2017). Uterine cytology is commonly performed using a cytobrush or uterine lavage from the cervix or uterus. Although it is sensitive to identifying inflammation, it is not a specific test for a unique pathogen (Sofiane et al., 2020).

Bacteriological culture, which is like cytology, is another diagnostic adjunct. It facilitates identifying the pathogens causing the infection. Bacterial cultures are usually done on uterine lavage samples or cervix swabs (Ledgard et al., 2015). The primary bacterial species associated with endometritis, such as E. coli, Trueperella pyogenes, and Fusobacterium necrophorum, can be cultured and specialized so the veterinarian may prescribe rational treatment (Del Prete et al., 2024). Nevertheless, bacterial culture is a lengthy technique, and low-level infections may not always be detected, causing false-negative results, particularly in subclinical infections (Vallejo-Timaran et al., 2021).

The diagnosis of endometritis has increasingly utilized ultrasonography, especially for determining uterine damage severity and detecting intrauterine fluid accumulation. Real-time exploration of the uterus takes place using transrectal ultrasonography, and signs such as endometrial thickening, uterine edema, and uterine fluid can be recorded (Sharma et al., 2017). It is a beneficial, non-invasive method for diagnosing cases of chronic endometritis, which may exist without obvious clinical signs but affect fertility in the long term. Ultrasonography is also useful for follow-up of disease development and treatment efficacy (Nehru et al., 2019).

More sophisticated diagnostics, like PCR (Polymerase Chain Reaction (PCR) and Enzyme-Linked Immunosorbent Assay (ELISA), are gradually being studied with a focus on pathogen-specific molecular detection (Cecchini Gualandi et al., 2023). PCR is a very sensitive and specific method for identifying bacterial DNA, which allows the detection of pathogens, even at low bacterial loads. This can be used to diagnose endometritis, which could be subclinical when there are no visible signs of inflammation/infection but may still play a role in causing infertility (Hajibemani & Mirzaei, 2022).

Despite being powerful diagnostic tools, they face challenges for wider applications. However, more advanced diagnostic methods (such as PCR and ultrasonography) represent the gold standard for confirmatory testing. Their extensive use may be limited in low-resource settings owing to their high cost of use, which is prohibitive for small-scale farmers (Bukowska et al., 2020). Moreover, since the exact same diagnostic finding may be associated with different types of uterine inflammation and/or infection, expert veterinary training is required to interpret diagnostics effectively. Thus, the integration of different diagnostic tools together with clinical observation is usually the most reliable strategy to diagnose endometritis in larger ruminants (Virendra et al., 2022).

## Impact on Fertility

Endometritis is an important cause of infertility in large ruminants, mainly affecting dairy cattle, and is one of the most serious challenges for reproductive performance and efficiency. Not only does this result in lower conception rates, longer time between calving, and higher costs of veterinary intervention, but it can also be economically devastating for livestock keeping (Hossain et al., 2015). Endometritis hinders fertility mainly because it is an infection and inflammation of the uterus, which interferes with the uterus's role in the natural events of conception and pregnancy (Carneiro et al., 2016).

Endometritis directly affects fertility by disturbing embryo implantation bénieurs. A healthy endometrium is required for the embryo to attach and develop. However, when the uterine environment becomes inflamed during infection, appropriate hormonal signaling and immune responses are disrupted to maintain embryo survival (Paiano et al., 2023). Specifically, embryos may be implanted in a pro-inflammatory state with intricate levels of cytokines and immune cells within the uterus to produce possible hostile surroundings. Previous studies have reported that severe endometritis (clinical endometritis) in cows delays heat (oestrus) and subsequent conception. Severe cases can even lead to early fetal death, miscarriage, or infertility (Hossain et al., 2015).

Endometritis also extends the length it takes cows to return to heat following calving, resulting in longer calving intervals. Dairy cattle should calve every 365 days at most, implying a new pregnancy within 85–100 days after calving (Ghanem et al., 2016). In contrast, the interval from calving until conception is generally prolonged for cows with endometritis, resulting in impaired reproductive performance. This can be damaging, especially in high-producing dairy herds, because of the reduced capability to maintain sufficient calving intervals to support milk yield. Additionally, the duration of when cows are susceptible to mating or milking is missed due to extended calving intervals (Ribeiro et al., 2016).

Chronic endometritis is another factor affecting herd reproductive efficiency. Cows with subclinical endometritis that do not show any signs of infection can experience a marked decrease in fertility (Pereira et al., 2020). Subclinical endometritis can reduce conception rates by as much as 20%, strongly suggesting a significant reproductive impact, even in the absence of overt clinical activity. Subclinical endometritis may be overlooked in cows, making them less likely to settle from AI or natural cover, thus contributing to herd infertility (Singh, 2023).

Fertility decline due to endometritis is also partly related to the increased risk of repeat breeding. For example, cows with a uterine infection are often bred, inseminated, and treated multiple times before becoming pregnant, incurring extra costs in insemination, veterinary services, and labor. In addition, repeat breeders not only have direct economic losses but also become an economic burden to the farm because of the time and effort that veterinarians and farmers spend to attend and perform fertility treatments. Additionally, cows that do not get in calves after repeated services may have to be culled, and consequently, farmers may lose even more money (Amin et al., 2022).

Not only is this disease responsible for reducing the probability of conception, but endometritis can also have a chronic effect on the reproductive system of cows. This can lead to scarring and adhesion of the uterus, causing it to stop functioning, which can lead to permanent infertility (Kimura et al., 2019). The severity of uterine damage may lead to culling of the animal, resulting in economic losses. Especially in dairy herds, large numbers of cows are expected to produce high milk yields throughout several lactations, and reproductive performance is both an essential and economical part of the total farm profitability (Song et al., 2023).

Endometritis can have acute effects on fertility in dairy cattle at the individual level. At the herd level, herd costs can be increased for the management, veterinary care, and replacement of non-breeding animals. Endometritis herd-level data collected from the literature has shown that herds, where endometritis is prevalent, produce less milk and have lower herd profitability (Pascottini et al., 2023). Endometritis is also an important disease in dairy cows, and more than $1 billion is lost to the dairy industry in the United States alone annually due to infertility, decreased milk yield, and veterinary costs. These financial consequences highlight the importance of adequate prevention, early detection, and management to minimize the adverse effects of endometritis on fertility and farm profitability (Bromfield et al., 2015).

**Management and Treatment**

Proper management and treatment of endometritis in large ruminants are key factors in enhancing fertility and reducing the economic impact of these disorders (Boudelal et al., 2022). Given the multifactorial nature of endometritis, its successful treatment may require a combination of antimicrobial, anti-inflammatory, and supportive measures. Treatment depends on the underlying cause, and the goals are to clear the underlying infection, reduce uterine inflammation, and restore the reproductive health of the affected animal (Giles et al., 2023). Nevertheless, management is limited because of antimicrobial resistance and the diverse nature of F. necrophorum between farms, meaning that unique management structures tailored to the animal and herd are needed (SATHIAMOORTHY et al.).

Antibiotic therapy is the mainstay of treatment for endometritis, especially if the cause is bacterial infection. Antibiotic selection was based on organism(s) and local antibiotic resistance trends (Iga et al., 2016). Intrauterine antibiotics (penicillin, cephalosporins, or tetracyclines) are often administered for the specific bacteria causing the infection. Such a treatment reduces bacteria and inflammation, increasing the likelihood of returning to normal uterine function. However, antibiotic overuse has raised concerns regarding antimicrobial resistance and challenging treatment (Neculai-Valeanu et al., 2024).

Hormone treatment is also a common supplement to antibiotic therapy in the management of endometritis. Uterine emptying due to prostaglandins (g., dinoprost or cloprostenol) stimulates uterine contractions to expel the retained placenta and uterine fluid. This facilitates the removal of residual tissues from the uterus, which may act as a bacterial reservoir and resolve the inflammation. They can also regulate the estrous cycle, which helps synchronize reproductive events and enhance fertility outcomes (Waheeb et al., 2017). Oxytocin, a hormone that stimulates uterine contractions, is also used along with prostaglandins to hasten the expulsion of uterine contents. That said, the use of hormone therapy needs to be performed very carefully, or there will be complications such as uterine damage or excessive inflammation if hormone therapy is performed incorrectly (Pal & Dar, 2020).

When endometritis is more severe or when other methods, including antibiotic and hormonal therapy, are ineffective, other treatments may be needed. One of these techniques is intrauterine lavage, which consists of washing the uterus with sterile solutions to wash infectious material and decrease inflammation. This is helpful in uterine-fluid or debris-accumulation situations (Buczkowska et al., 2015). This procedure can be performed with antimicrobial treatment as an adjuvant treatment. Nonetheless, it is imperative to manage this route with caution to prevent any new infections or trauma to the uterus (Hunt et al., 2020).

Although treatment is essential for controlling endometritis, the pre-existing disease can be controlled through prevention, reducing endometritis, and making the herd more fertile. Preventive measures are based on reducing the risk factors predisposing cattle to endometritis, such as poor calving hygiene, retained placenta, and environmental stressors (Rabindra Kumar & Sudeep Solanki, 2017). The key here is to manage the calving conditions, as appropriate calving and postpartum management; that is, cows should lie in a clean and dry-bedded area free from stress during the postpartum period, which not only lowers the incidence of metritis but also reduces the spread of infection. Strict biosecurity practices, such as disinfectants and gloves used during the calving period, would be beneficial for the safer surroundings of the animals (Muchtaromah et al., 2018).

Nutrition is an integral component of the prevention and management of endometritis. When provided with proper nutritional support, cows are better able to sustain a functioning immune system, which is essential for fighting uterine infections. Moreover, sufficient energy supply is fundamental to maintain immune and reproductive function, and deficiencies in nutrients, including vitamins A, selenium, and zinc, can suppress immune responses and increase the risk of infections (Feng et al., 2024). Appropriate nutritional support during the postpartum period can also lower the risk of retained placenta (an important risk factor for endometritis) (Serbenyuk, 2023).

Timely management practices, such as finding sick and regularly checking herd health, are important integrated parts of good treatment. Routine veterinary gallants, including uterine palpation, ultrasonography, and uterine fluid azimuth, aid in the early detection of endometritis, even when bruiser signs emerge (Serbenyuk, 2023). Timely treatment with antimicrobial and anti-inflammatory agents through early intervention may halt the development of the disease, thus preventing the establishment of chronic stages that irreversibly damage the uterus. In addition, monitoring reproductive performance (pregnancy rates and calving intervals) should help identify subclinical forms of the disease (Bhat & Dhaliwal, 2023).

**Preventive Measures**

Endometritis in large ruminants must be avoided to maximize reproductive health and productivity (Parmar, 2021). Given its negative effect on fertility and considerable economic losses, appropriate preventive strategies should be implemented to reduce its prevalence and impact. Preventive approaches target risk factors, farm management practices, and animal health issues. These approaches not only decrease endometritis but also improve herd reproductive performance (Mohamed Al-Absy et al., 2023).

Prevention is undoubtedly one of the best approaches, with a key role in the management of the calving process itself. Calving is a period in which cows are very prone to developing endometritis, especially when born because the act of parturition is physical trauma that gives them the risk of a retained placenta (Faradillah & Agustina, 2023). Hygienic calving is important for reducing the risk of uterine infection. This involves providing clean and dry calving areas, as pathogens are more likely to survive in wet, dirty environments. Farms must have sanitary practices for cow management during calving, cleaning calving areas with saints, and cleaning equipment, including calving-related instruments. This prevents bacteria or dirt from entering the uterus, as it can cause infections and uterine inflammation (Wu et al., 2022).

Retained placenta is another important factor that must be handled in time. Retained placenta is a potential cause of endometritis because it provides an environment for bacteria to colonize the uterus. This must be prevented, and cows must be closely monitored for 24–36 h after calving to ensure the placenta is passed in that time frame. When the placenta is retained, quick intervention by a veterinarian is necessary to remove the tissue, as delaying this process can lead to septic complications (Livani et al., 2023). In certain instances, hormone treatments such as prostaglandins may be administered to facilitate the removal of the retained placenta. Adequate nutrition and good calving management to prevent retained placenta represent the best preventive strategies for endometritis (Muiño et al., 2024).

Another key aspect of endometritis prevention is the management of postpartum uterine health. After giving birth, a woman can rest assured that her body was designed for normal involution of the uterus during the postpartum period. This can take longer for cows that are stressed, underfed, or sick. Particularly in the transition period from late pregnancy to early lactation, nutrient provision is crucial for maintaining cows' good reproductive health status (Mirzaei et al., 2023). Adequate energy and protein intake and essential vitamin A, selenium, and zinc status promote immune function, such that uterine infections are less likely. Provided with optimal nutrition, cows can prevent infections better and recover from uterine infections faster (Oladejo et al., 2020).

Heat stress is a serious risk factor for endometritis. Similar to hot weather, consuming excessive amounts of moisture reduces the body's immunity, making it more susceptible to uterine infections. Farmers can reduce heat stress by providing cooling methods such as shade, airflow, and fresh water. This ensures the animals' overall health and immunity and helps them avoid infection (Tsolakidis et al., 2021). Another way to improve the overall well-being of cows is to manage herd density and ensure that they have ample space to roam freely (Dai et al., 2023).

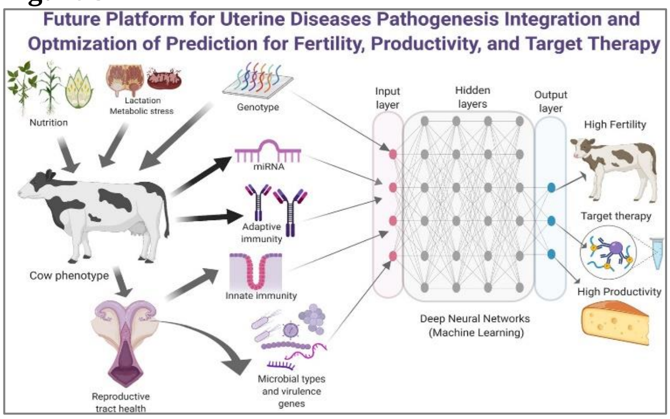
Regular checks for reproductive health are also important to avoid endometritis. The accurate and timely identification of subclinical endometritis is critical for intervention and management. Frequent veterinary examinations (uterine palpation, ultrasonography, uterine flushing, etc.) can diagnose the condition (Gautam et al., 2023). Although subclinical endometritis does not display visible signs of infection on the part of the cows, the increase in insemination-to-conception intervals and extension of the calving interval are symptoms of the disease. Identifying these animals and treating them will help farmers prevent the disease from reaching a crucial stage, thus decreasing the effect on fertility (Fatwaddin et al., 2022).

In addition to the farm-level practices, vaccination may also be effective in preventing endometritis. Vaccines directed against specific pathogens (e.g., Escherichia coli, Trueperella pyogenes, and Fusobacterium necrophorum) associated with uterine infections are under investigation. Although not presently used to treat endometritis, vaccines may be an important tool in the future to decrease the number of uterine infections. As progress is made with developing vaccines, they have the potential to play an important role in large ruminants' reproductive disease management (Khan et al., 2021).

## Emerging Trends and Future Directions

This novel information on the diagnosis, treatment, and prevention of endometritis in large ruminants has recently received attention as the understanding of endometritis continues to be elucidated (Rashid Dar et al., 2019). New diagnostic technologies, molecular understanding of pathogenesis, and novel treatment options can potentially enhance the management of endometritis and fertility outcomes as shown in **Figure 3**. Further research should investigate the uterine microbiome and the use of vaccines and precision livestock farming to develop better prevention and treatment strategies (Hemphill et al., 2016).

**Figure 3**



It provides an overview of a possible basis for prediction and management of uterine diseases in ruminants, with main relevance to fertility and productivity. Nutritional-Factor-based Interactome (NFI) is a composite of factors including nutrition, metabolic stress, genotype, innate and adaptive immune responses, and microbial environmental exposure which integrates those factors and can be studied by machine learning and deep neural networks. Using the skeleton of this model, it shows (i) how factors co-contribute to cow phenotype, reproductive tract health, and performance, (ii) how data can be layered onto factors to create a data-driven picture and targets for improving predictions of disease and targeting therapy. This combination will change how we manage uterine diseases, as it can now be more accurately referenced and utilized to improve cattle fertility and productivity on an individual basis.

Identifying specific pathogens at the genetic level through molecular techniques, such as polymerase chain reaction (PCR), is one of the latest trends in endometritis diagnostics. PCR-based strategies allow PCR to detect the presence of the pathogen even at very low levels of pathogenic bacteria in the sample, offering high levels of specificity and sensitivity. These techniques can detect several pathogens simultaneously and increase the potential for recognizing subclinical endometritis through non-specific clinical signs (Russell, 2015). Additionally, point-of-care PCR devices and diagnostic kits are the next considerable step that can help veterinarians and farmers diagnose endometritis at an early stage, especially in remote areas where laboratory facilities are limited. This instant and accurate identification would allow swift treatment, and thus, chronic infections would cover less, and fertility rates would rise (Maiden, 2019).

In addition to molecular diagnostics, ultrasonography is becoming an increasingly important tool for the diagnosis and follow-up treatment of endometritis. The introduction of real-time assessment of uterine wellbeing with high-resolution portable ultrasound devices has advanced the assessment of uterine wellbeing and allowed for the refinement of subtle changes in uterine structure (fluid or endometrial thickening), an indicator of inflammation. Serial ultrasound can help determine disease progression and can be used to evaluate the response to treatment. Advancements in technology and cost will likely be part of routine herd health management shortly, helping us find and manage reproductive diseases sooner (Nakaya & Pulendran, 2015).

Another significant interest is determining how the uterine microbiome contributes to endometritis (Holyoak et al., 2022). Recent studies have indicated that the uterus hosts a community of microbes as a barrier to pathogenic bacteria to maintain uterine health. Dysbiosis of the uterine microbiota can render animals susceptible to infections, including endometritis. Advances in metagenomics and microbiome sequencing have provided insights into the composition of this diversity, and other advances in linking functions with the host immune system level are of great value to this nascent field. Such an understanding may open avenues for new treatment approaches for endometritis, such as probiotics or prebiotics, to restore normal uterine microbiota. These approaches can be used to improve standard antimicrobial therapies and provide a more sustainable and less resistance-prone strategy for treating uterine infections (Virendra et al., 2024).

Another promising avenue of research for the prevention of endometritis is vaccination (Pezeshki et al., 2019). Although vaccines against pathogens implicated in uterine infections are not yet available, several such candidates are being developed. Vaccines to guard against E. coli, one of the significant bugs responsible for endometritis, are in early trials and appear promising. In addition to pathogen-specific vaccines, which have been more frequently studied, other vaccines that modulate the immune system within the uterus to decrease inflammation and provide a better uterine milieu for embryo implantation are being researched. Successful vaccination against endometritis may significantly change prevention strategies, lessen dependence on antibiotics and other chemical treatments, and promote better long-term functional fertility in large ruminants (Vetter et al., 2018).

Precision livestock farming is another emerging trend with great potential for managing endometritis and fertility in large ruminants (Vasoya et al., 2021). Farmers can track the health status of individual animals in real-time using advanced technologies, including sensors, wearable devices, and automated monitoring systems. Such systems can assess temperature, activity, and uterine health and identify early indications of disease or infection. Combining this information with artificial intelligence (AI) algorithms may help predict the time of endometritis and reproductive diseases, thus allowing early intervention and easier herd management. Precision farming techniques can also help increase animal welfare while improving endometritis detection and management by allowing for a more tailored approach to care for individual animals (Poland et al., 2018).

The worldwide movement toward antimicrobial stewardship drives the future management of endometritis. Given the growing threat of antimicrobial resistance, studies are searching for alternative treatment strategies to limit the use of antibiotics. This also involves investigating the potential use of immunomodulatory agents, such as cytokines or growth factors, to modify immune activity and facilitate the resolution of uterine infection. Other treatments are also being explored for endometritis, such as herbal therapy or antimicrobial peptides, which could provide a direct antimicrobial effect while avoiding difficulties related to antibiotic resistance (Shah et al., 2023).

In summary, managing endometritis in large ruminants requires a combination of improved amendatory measures through advanced diagnostic matrices, an ever-expanding awareness of the uterine microbiome, and the use of vaccines and alternative therapies. Recent research regarding the underlying pathophysiology of disease will ultimately begin to translate into methods of prevention, diagnosis, and treatment of endometritis and will undoubtedly impact veterinarians and farmers alike. Ultimately, developing these technologies will help ensure that livestock becomes more fertile, herds are easier to manage, and the livestock sector is more sustainable (Vordermeier et al., 2016).

## CONCLUSION

This review highlights the role of endometritis as one of the major causes of infertility in large ruminants and its effects on reproductive health, fertility, and productivity of farmers. Endometritis, mainly caused by a bacterial infection (e.g., Escherichia coli and Trueperella pyogenes), retained placenta, and hormonal disorders, are significant problems in the dairy and beef cattle industries. This emphasizes the necessity for early detection and prompt measures to avoid chronic cases of pathology in the uterus, which would otherwise cause extended calving intervals, lower pregnancy rates, and economic losses in livestock farming. Prevention and management involve managing the cow properly from calving (hygiene, nutrition, and uterine health checks very early) through day 28 post-calving before cystic ovaries/follicles become a problem to manage, and fertility has its origins in cow management. These results are relevant to enhancing herd management and fertility outcomes. With advanced diagnostic tools, including but not limited to PCR, ultrasonography, and precision livestock farming, the detection of subclinical endometritis becomes more accurate so that farmers and veterinarians can treat the disease at an early stage, preventing potential infertility. Furthermore, a robust immune response is the cornerstone of effective defense against uterine pathogens; hence, optimized herd health status via improved nutrition and lower stress status will reduce endometritis incidence at the herd level. Nonetheless, the literature is still limited in several ways. The molecular mechanisms involved in uterine pathogen-immune system interactions are not entirely understood, and the role of the uterine microbiome in preventing infections needs to be further investigated. In addition, most research has been conducted on high-producing dairy cattle, indicating that further cross-species studies among ruminant species need to be undertaken. Additionally, the genetic predisposition and microbiome involved in endometritis susceptibility need to be explored, and alternative treatments to antibiotics (e.g., probiotics or vaccines) should be evaluated in the future. Future needs will be essential in furthering the sustainability of livestock systems through the long-term economic effects of endometritis on herd productivity and sustainable management practices. Conclusion Endometritis remains a significant challenge in the reproductive efficiency of large ruminants. By closing the knowledge gaps identified here, better prevention and treatment strategies can be developed to enhance livestock production systems' fertility and economic sustainability.

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