



The Impact of Endometritis on Reproductive Performance in Cattle: A Review

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ABSTRACT

Endometritis is a major postpartum serious uterine disorder in dairy and beef cattle that compromises reproductive performance. Endometritis is characterized by inflammation of the endometrial lining, which leads to delayed myometrial contraction, decreased conception rates, prolonged calving intervals, and higher culling rates, all of which adversely affect herd output and profitability. However, this review facilitates the understanding of etiology, pathogenesis, epidemiology, immune response, diagnosis, treatment, and methodologies to control endometritis. Meanwhile, endometritis is caused by polymicrobial infections; pathogens include *Escherichia coli*, *Fusobacterium necrophorum*, and *Trueperella pyogenes*, which directly suppress immunity and colonize the uterus. Both clinical and subclinical forms induce reproductive failures, with the subclinical form being more difficult to diagnose due to its asymptomatic nature. Early detection can be improved in diagnostics through the cytobrush-based cytology, ultrasonography, and microbial culture. Furthermore, treatment approaches include hormonal therapy, antibiotics, and alternatives involving phytochemicals, probiotics, and immunomodulators. This study aimed to identify control practices to maintain hygiene during calving, optimal nutritional support, and reduce predisposing factors. Current findings on the uterine microbiome and host genetic susceptibility suggest a new way to target the microbiome and prevention strategies based on selection. Moreover, accurate management and proper diagnosis and feasible therapies are mandatory to minimize the impact of endometritis and enhance fertility.

INTRODUCTION

Reproductive efficiency is an essential component of productive systems, directly affecting the profitability and sustainability of a herd (Lima, 2020). Endometritis, defined as inflammation of the uterine mucosa (endometrial lining), has a significant harmful impact on the reproductive tract and can result in delays in postpartum return to fertility, longer calving intervals, decreased conception rates, and increased culling of cows (Várhidi et al., 2024). The postpartum uterus is ex-

tremely susceptible to contamination because of cervical relaxation, lochial discharge, and a reduced immune system (Sheldon et al., 2008). However, microbial multiplication may result in clinical endometritis (CE) with the presence of purulent vaginal discharge or in subclinical endometritis (SCE), which lacks noticeable signs, but with high numbers of polymorphonuclear (PMN) cellular infiltrate (Pascottini et al., 2016b; Pascottini et al., 2017). Although retained placenta, dystocia, metabolic diseases such as hypocalcemia and ketosis, and negative energy balance (NEB) (Dubuc et al., 2010) adversely affect the processes of uterine in-

volution and immune suppression, thereby increasing the risk of the development of endometritis (Esposito et al., 2014). Similarly, endometritis is closely associated with repeat breeding syndrome (RBS), a condition in which cows fail to conceive after several inseminations, which increases the economic losses of producers (Pérez-Marín & Quintela, 2023). Modern diagnostic methods, including the Metrichick device, uterine cytology, and ultrasonography, are more accurate than traditional palpation and vaginoscopy (LeBlanc et al., 2002; Kumar et al., 2013). However, early detection can be difficult, especially in cases of subclinical infections. Various treatments are available, including systemic antibiotics, intrauterine antibiotics, NSAIDs, and phytomedicines like neem, garlic, and moringa (Rosmaidar et al., 2021; Paiano and Baruselli, 2022). In Pakistan, bovine endometritis is a common cause of infertility and repeat breeding due to the unhygienic handling of parturition, dystocia, and artificial insemination. Many handlers cull their animals because of a lack of awareness of endometritis and its control methodologies. Therefore, a systematic understanding of endometritis is necessary to know effective strategies for reducing the prevalence and impact of endometritis in cattle herds worldwide.

AETIOLOGY AND PATHOGENESIS OF ENDOMETRITIS

Endometritis in cattle is a multifactorial condition that is a combination of various pathogenic microbes, immune dysfunction, and environmental factors, all of which influence the uterine environment and have an adverse impact on fertility. Endometritis is primarily caused by both clinical and subclinical endometritis, which are caused by *Trueperella pyogenes*, *Escherichia coli*, *Arcanobacterium pyogenes*, and *Staphylococcus spp.* (Bicalho et al., 2012; Liu et al., 2024). Similarly, several anaerobes such as *Prevotella spp.*, *Fusobacterium necrophorum*, and *Fusobacterium nucleatum* are also involved in repeat breeding syndrome (RBS) (Jeon & Galvão, 2018). Meanwhile, bovine herpesvirus 4 (BoHV-4) is also associated with chronic uterine infection, particularly interaction with endometrial stromal cells (Donofrio et al., 2008). The present study has shown that environmental or opportunistic persistent vaginal flora leads to chronic inflammation or compromised immunity (Drillich and Wagener, 2018; Paiano et al., 2021).

Furthermore, the impact of endometritis on the uterus body is shown in Fig. 1, how microbes enter the uterus through anatomic barriers. While host

defense mechanisms, including mucus, antimicrobial peptides, and pH, protect the tissue lining from colonization by pathogenic bacteria or lipopolysaccharides (LPS), these pathogens can trigger an innate and adaptive immune response that leads to inflammation, infiltration of leukocytes, and synthesis of acute phase proteins; in more severe cases, tissue damage is modulated by microbial toxins such as pyolysin (PLO) (Sheldon and Owens, 2017). Although pathogenic microbes such as *E. coli* and *T. pyogenes* release virulence factors containing lipopolysaccharides (LPS) and pyolysin (PLO) that disrupt the endometrial barrier and trigger an inflammatory response (Jinagal et al., 2023). LPS from *E. coli* binds to toll-like receptors (TLRs) on endometrial cells, triggering the release of pro-inflammatory cytokines (IL-6, IL-8) and chemokines that attract neutrophils and macrophages to the site of infection (Goldstone et al., 2014; Turner et al., 2014; Jinagal et al., 2024; Jinagal et al., 2026). Additionally, bloodborne transmission of pathogens from the gut has also been hypothesized, emphasizing systemic microbial interactions in disease development (Jeon et al., 2017).

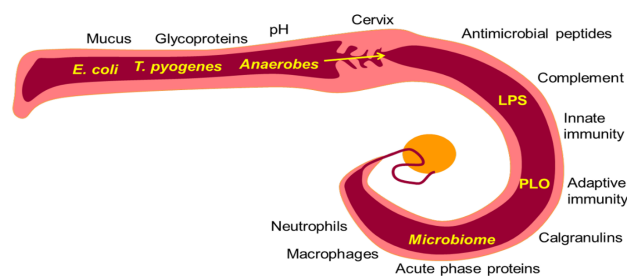


Figure 1: Schematic representation of the uterine microbial environment and host immune defenses, illustrating the interaction between the uterine microbiome, reproductive tract barriers, and innate and adaptive immune mechanisms. Key components include mucus, glycoproteins, pH, antimicrobial peptides, complement, acute-phase proteins, calgranulins, neutrophils, and macrophages, with bacterial components such as LPS and PLO contributing to host inflammatory responses (Sheldon and Owens, 2017).

Prevalence

Endometritis is a frequent reproductive disease in dairy and beef cattle around the world, with prevalence varying depending on management, location, and herd health (Khan et al. 2025). Studies have indicated that the incidence of endometritis (4%) in the Achai cattle breed is the lowest in the northern region of Pakistan (Sohail et al., 2018). More generally, about 40% of animals experience metritis in their first week after parturition, and about 10-15% of all these animals go on to

develop endometritis (Sheldon & Dobson, 2004). However, the occurrence of endometritis was 2.8% in the postpartum phase in Sahiwal cattle in the District of Faisalabad (Khan et al., 2020). By contrast, levels of disease during spring and winter months are comparable, but summer months are generally the most likely to have low disease levels (Pascottini et al., 2016a). In addition, there is variation in prevalence depending on geographic location and farm management practices, suggesting the need for targeted management strategies in various situations (Ferris et al., 2016). Meanwhile, detailed knowledge of endometritis is required to have effective prevention and control measures that bring about economic loss reduction in the cattle production system.

Immune Response

Immune response to endometritis is characterized by the movement and activation in the uterine lumen of polymorphonuclear neutrophils (PMN), required for tissue repair and elimination of the microbes (Sheldon et al., 2019). In the case of clinical endometritis, microbes cause dysbiosis, which leads to the destruction of endometrial stromal cells and results in a significant infiltration of PMNs attempting to control the bacterium but also likely contributing to tissue destruction if the PMNs are dysregulated (Pascottini and LeBlanc, 2020). In contrast, during subclinical endometritis, when immune dysfunction occurs, PMNs in the endometrium do not undergo apoptosis or necrosis, which inhibits the inflammation and leads to continuing endometritis with no convincing indication of microbial dysbiosis.

Furthermore, clinical and subclinical endometritis have unique pathological characteristics and outcomes because of this differential immune response. Additionally, the understanding of the immune response has been demonstrated in Fig. 2 (Lietaer et al., 2023). Clinical and subclinical endometritis in dairy cattle can be caused by post-partum physiological stress or by metabolic imbalance. Negative energy balance and systemic inflammatory responses inhibit rapid neutrophil migration into the uterus, which is necessary for uterine recovery. The clinical form is associated with dysbiosis and immune dysfunction, whereas the subclinical form can occur when there is a lack of clinical signs of infection but a metabolic stress (Pascottini et al., 2023a and b).

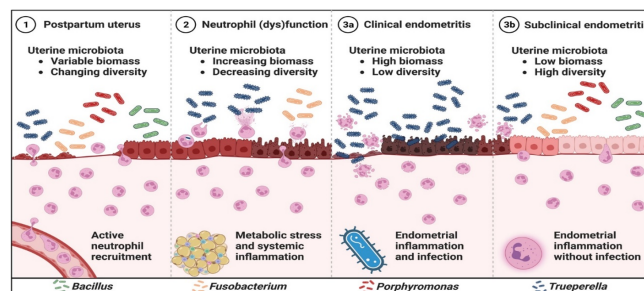


Figure 2: Schematic representation of postpartum uterine microbiota dynamics and their association with endometrial health and disease. The figure illustrates the transition of the postpartum uterus through four distinct states: (1) postpartum uterus, characterized by variable uterine microbial biomass and changing microbial diversity with active neutrophil recruitment; (2) neutrophil (dys)function, associated with increasing microbial biomass, decreasing microbial diversity, metabolic stress, and systemic inflammation; (3a) clinical endometritis, characterized by high microbial biomass and low microbial diversity, accompanied by endometrial inflammation and infection; and (3b) subclinical endometritis, characterized by low microbial biomass but relatively high microbial diversity, with endometrial inflammation in the absence of overt infection. Representative bacterial taxa are depicted by different colors: *Bacillus* (green), *Fusobacterium* (orange), *Porphyromonas* (red), and *Trueperella* (blue). Pink cells represent neutrophils and their recruitment/infiltration into the endometrium. The figure highlights the relationship between alterations in uterine microbial communities, neutrophil function, inflammation, and the development of clinical and subclinical endometritis.

RISK FACTORS OF ENDOMETRITIS

The occurrence of endometritis in cows is attributed to various intrinsic and extrinsic factors. These risk factors can significantly influence reproductive outcomes if appropriate preventive measures are not undertaken; therefore, it is important to identify and understand these factors.

Intrinsic risk factors

Postpartum endometritis is a multi-factorial disease, which occurs when there is a failure to cleanse the uterus, repair damaged tissue, or fail to achieve innate immunity due to contamination. Intrinsic risk factors are thus not always independent. Frequently, calving-related disorders interact with the unfavorable changes in metabolism, impaired uterine motility, tissue damage, and immune dysfunction, which together result in either elimination of normal bacterial contamination in the postpartum period or deterioration into metritis, clinical endometritis, and subclinical endometritis.

(Krasniqi et al., 2024; Várhidi et al., 2024).

Retained fetal membrane

Retained fetal membranes (RFM) are one of the most regular intrinsic risk factors for uterine disease in postpartum cows. If the separation of the placenta does not proceed normally, the placenta remains intrauterine, and the lochia undergoes changes that result in the formation of an attached placenta with nutrients and an attachment surface for opportunistic bacteria. If the separation does not occur normally, the placenta will remain in the uterine cavity, and the change in the condition of the lochia will form an adhered placenta with a nutrient supply and an attachment site for opportunistic bacteria. Retained membranes can also cause a delay of cervical closure, a decrease in uterine contractions, impaired drainage of uterine contents, and inhibition of endometrial repair. Damage to the caruncles can also occur if they are forcibly removed and bacteria are introduced if the operation is not undertaken in hygienic conditions. Neutrophil function is also compromised in RFM, and an inflammatory response swing around parturition is observed. Affected animals may then struggle to manage the growth of bacteria like *Escherichia coli*, *Fusobacterium necrophorum*, and *Trueperella pyogenes* in the womb during early involution. Puerperal metritis can occur at the beginning of the bacterial colonization and can later result in purulent vaginal discharge or cytological endometritis. There is recent field evidence on the importance of this association. The risk assessment of developing clinical endometritis for cows with RFM was found to be around 5.6 times higher for the cows than for cows without RFM in a study of 241 Holstein cows on family dairy farms (Valdivia-Navarro et al., 2025). Likewise, the investigation of 608 lactations on small-scale dairy farms associated subclinical endometritis with the main risk factors: RFM and other postpartum uterine diseases, at about 30 days of postpartum (Villaseñor-González et al., 2025). However, the interpretation of RFM must be coupled with other conditions, as it often is with dystocia, twin birth, stillbirth, hypocalcemia, and negative energy balance.

Dystocia and pro-longed parturition in cattle

Dystocia has several complementary mechanisms that predispose to uterine disease in cattle and buffaloes. Prolonged labor leads to delay of fetal expulsion, causes continued cervical dilation, and exposes the reproductive tract to the environment's microbes as well as causing myometrium depletion. Lochia, fetal membranes, bacteria, and inflammatory material are not expelled during the first 24 hours after difficult calving because

the uterine contraction has been reduced. Assisted delivery may result in abrasion to the vulva, vagina, cervix, and uterus, along with an edema and/or leakage from these areas. Excessive traction, repeated vaginal examination, fetotomy, fetal mutation, and cesarean section, if performed with poor obstetrical asepsis, can aggravate the trauma of tissues and bacterial contamination. Damage to the reproductive mucosa may disrupt the physical barrier, resulting in areas that can become colonized by bacteria and promote bacterial growth. It has been reported that vulvovaginal lacerations are associated with postpartum uterine diseases (Vieira-Neto et al., 2016). A recent prospective study of 496 Holstein cows showed that calving assistance and the factors related to the length of labor were linked to uterine health after calving, with a higher occurrence of metritis (Bauer et al., 2026). Otherwise, indirect risk factors for endometritis include the higher likelihood of occurrence as a result of RFM, poor feed consumption and low feed intake, hypocalcemia, systemic inflammation, and delayed uterine involution. The risk of endometritis is particularly high in cases of difficult calving, especially when there is significant obstetrical manipulation, fetal death, trauma, or placental retention.

Uterine torsion

These results suggest that tissue damage resulting from obstetrical procedures and the potential for difficulty in calving both play a role in later uterine inflammation. Uterine torsion is a part of the obstetrical dystocia pathway as well as a subtle intrinsic risk factor for endometritis. Uterine rotation may block venous drainage and arterial perfusion, resulting in uterine edema and ischemic injury, with cervical non-dilation, longer labor, and fetal death in severe cases. Full manipulation may also be necessary, or it may be possible to auto-perform a cesarean section, thus increasing the potential for tissue injury and contamination. This condition may consequently lead to situations of abnormal retention or separation of fetal membranes or impaired uterine involution, which can predispose to chronic bacterial attachment and endometritis. Compared with unaffected dairy cows, time to conception was delayed by 27.6 days, and also the time from calving to the next ovulation was 25.5 days in affected cows with uterine torsion (Sickinger et al., 2020).

Twin birth, stillbirth, fetal abnormal size and fetal viability

Common problems for twins are reduced feed intake after weaning, hypocalcemia, reduced milk yield, dystocia, abnormal fetal positioning or secondary premature calving, and reduced incidence of retention of the placenta. Premature calving, abnormally situated fetuses, dystocia, reduced feed intake after weaning, reduction in milk yield, reduced incidence of placental retention, and hypocalcemia are common problems associated with twins. The overdistended uterus is likely to cause decreased uterine muscle activity after birth, which will prolong the duration of lochia, and the waste may increase the bacterial load introduced into the genital tract. Another theory is that there is an increased surface area in multiple pregnancies that causes abnormal separation of the placenta. The failure of a baby to move into the world has the potential to make the child's birth more complicated and time-consuming and may require obstetrical intervention. The bacterial load in the genital tract is increased by the autolysis of dead fetuses, contaminated fetal fluids, fetotomy, and difficulties in extraction. Likewise, cattle with large calves have a higher risk of a prolonged second stage, loss of traction, a risk of mucosal injury, and a risk of cesarean section. These fetal risk factors often work together with the dysfunction of labor (dystocia) and RFM and can be considered one of the clinical components of the overall fetal risk profile (Bauer et al., 2026; Várhidi et al., 2024).

The study did not examine torsion as an independent risk factor for clinical or subclinical endometritis; therefore, torsion should be considered a biologically plausible pathway for the development of clinical or subclinical endometritis, but it has not been proven to directly cause it. Additionally, the metabolic and immune status influence whether postpartum contamination resolves or progresses to a disease. Thus, hypocalcemia lowers the contractility of the myometrium, postpones placental removal and uterine involution, and decreases the migration and phagocytic activity of neutrophils. Ketosis and negative energy balance, evidenced by elevated levels of beta-hydroxybutyrate and non-esterified fatty acids, reduce the glucose administered to the immune cells and impair the ability to kill bacteria. The systemic inflammation and oxidant stress are also disturbed during transition. Low serum calcium has been related to obstruction of the placenta bed, so postpartum endometritis (Esposito et al., 2014; Ruiz-García et al., 2022; Yáñez et al., 2022) and poor postpartum metabolic status are related to subclinical endometritis. Therefore, multiple factors such as im-

paired uterine motility, delayed tissue repairs, and impaired innate immunity create an increased risk for metabolic disease. Age and parity may influence these intrinsic pathways. by age and parity. Stress on tissue during birth, repeated over the years, may cause delayed uterine involution or increased risks of concurrent metabolic diseases in older cows with high parity. However, all of these factors must be taken into account because they can also affect the response to the disease, with the exception of the ones relating to milk yield, calving difficulty, and herd management, which should be interpreted as susceptibility modifiers rather than as the factors themselves causing endometritis (Bruun et al., 2002).

Extrinsic risk factors

Extrinsic risk factors come from environmental conditions at the time of calving, human involvement, the housing system, climatic conditions, and transition-cow management. This factor is most important during and shortly after parturition, when the cervix is open, the endometrium is disturbed, and the lochia promotes bacterial growth. Thus, the magnitude and type of bacteria encountered by the reproductive tract during this process, along with the effects of management on immunity and uterine clearance, are, respectively, calving supervision and obstetrical practices, which are crucial factors in determining whether the uterus remains contaminated or develops persistent inflammation, particularly regarding calving supervision and obstetrical practices (Sheldon et al., 2019; Hermadi et al., 2025). The hygiene during calving, which includes calving supervision and obstetrical practices, is a key modifiable factor. Exposure can happen when the vulva and the birth canal come into contact with bacteria from the environment or feces. Exposure to other environmental or fecal bacteria can occur when the vulva and the birth canal come into contact with them. Exposure to other environmental or fecal bacteria can occur when the vulva and the birth canal come into contact with them. Although clean, dry bedding is sterile, it cannot prevent calving if there is any bacterial challenge but will help control it when calving supervision and obstetrical practices provide less protection to the mucous membranes. Data on the housing substrate are, respectively, calving supervision and obstetrical practices presented at the herd level, which also helps to demonstrate the complex relationship between housing cleanliness and dietary and environmental effects. Cheong et al. (2011) reported that 16.7% of herds with early postpartum cows in bedded packs had a higher herd prevalence of subclinical EPI than herds with early

postpartum cows in free-stalls, and a 10.7% lower herd prevalence of subclinical EPI was observed in herds that housed early postpartum cows in straw-bedded calving pens. These data highlight the importance of bedding dryness, regular renewals, manure removal, and stocking pressure, rather than the specific type of bedding material used. The external factors closely related to calving supervision and obstetrical practices include both calving supervision and obstetrical procedures. Prolonged second-stage labor duration may lead to increased tissue compression and prolonged retention of fetal membranes if they are not recognized until later, and excess or frequent vaginal exams might result in more contamination. If assistance is needed, washing the perineum, employing long clean gloves, disinfecting obstetrical chains or ropes, applying an appropriate lubricant, and avoiding unnecessary traction minimize preventable trauma and iatrogenic bacterial transfer. Routine removal of retained membranes should not take place, as the process of removing them in a forceful manner may injure the endometrium.

In the field study, the remote calving with the trained personnel present caused a reduction in the calving-related issues of fetal-membrane retention and postpartum uterine infection compared to unmonitored groups of cows (Palombi et al., 2013). But intervention should be timely and judicious—neither too early nor excessive—because delayed intervention is equally harmful. Postpartum housing can either sustain or decrease the exposure set up at calving. Lying space needs are more difficult to meet in fresh-cow pens due to overcrowding; more manure is deposited, and feed and water are more easily shared.

Poor ventilation, humidity, and wet bedding encourage microorganisms to survive, and moving several times and insufficient rest time during the transition period also bring physiological stress. These factors can indirectly influence health by decreasing dry-matter intake and increasing the production of ketosis or other coexisting lesions within the same herd, as well as by prolonging the time that bacteria are in contact with the vulva. However, these factors may be associated with farm size, bedding system, cleaning frequency, and nutrition, and the independent effects of these factors on the incidence of endometritis should not be assumed (Cheong et al., 2011). Risk is also influenced by season and thermal environment, although to a different extent in different production systems. In Florida, there were 3,507 calvings analyzed, with metritis found to be more prevalent during the warm season (24.2%) than during the cool season (21.1%).

The measured bacterial content of the vagina was

similar in abundance between the warm and cool seasons; however, persistent uterine infections, recorded on postpartum days 7 and 21, were observed more frequently in the warm season, indicating that bacterial numbers did not cause the difference in outcomes regarding the host's ability to resist infection (Molinari et al., 2022). A study of ultrasound samples from 1123 cows across two herds in Scotland, however, found autumn/winter calving was a risk factor for ultrasound-detected endometritis (McKay et al., 2023). Therefore, season is viewed as a context-dependent proxy measure of temperature-humidity load, housing, bedding moisture, exposure to pathogens, diet, and calving patterns. Practical strategies to mitigate thermal stress include providing shade, fans, and, where appropriate, sprinklers; adequate ventilation; and access to clean water. The extrinsic pathway is completed by the transition feeding and herd-health organizations. Negative energy balance, hypocalcemia, and ketosis also can arise from inconsistent ration mixing, rapid dietary change, denials of adequate bunk space, and inadequate supply of energy, calcium, trace mineral(s), and/or antioxidants and serve as intrinsic factors that may mediate impaired neutrophil function and uterine contractility. Evidence to support this association between transition management and uterine health is provided by the relationship between higher prepartum non-esterified fatty acids (NEFAs) and postpartum beta-hydroxybutyrate (BOHB) and clinical endometritis (Liu and Wang, 2026). Prevention should thus involve a combination of hygienic maternity pens, desired stocking density, timely but aseptic calving assistance, heat abatement, sale of a systematic transition diet, and fresh-cow surveillance. Many of these studies are observational and should therefore be viewed as part of a comprehensive endometritis risk-reduction program, rather than as evidence that any single environmental variable causes the development of endometritis.

DIAGNOSIS

The first step in making a proper diagnosis is to differentiate puerperal metritis from purulent vaginal discharge (PVD) from clinical (versus subclinical) endometritis, as the time of diagnosis, the disease history, and the type of diagnostic tool(s) used are different. Puerperal metritis typically strikes within the first 21 days after calving, when the uterus is enlarged and watery brown or red, and smelly fluid is streaming from the vulva accompanied by fever, depression, loss of appetite, or milk supply. Clinical endometritis is generally identified at 21 DIM or later as purulent discharge (usually) or mucopurulent discharge (usually) in a cow

without clinical signs of other illnesses, compared to normal cows. This classification is due to the fact that the discharge can come from the vagina, cervix, or uterus, and for this reason the use of the term “PVD” appears to be more preferred. Subclinical endometritis is characterized by a change in the percentage of polymorphonuclear neutrophils (PMN) in the endometrial biopsy, and it would be challenging to detect by simply looking at the clinical appearance of the discharge (LeBlanc et al., 2002; Pascottini et al., 2023b).

The first layer of diagnosis is provided by history and a general clinical exam. Factors that are relevant include dystocia, retained fetal membranes, twins, stillbirths, assisted calving, a fallow temperature, reduced feed intake, ketosis, and prior antimicrobial treatment. In cows with clinical cases, the uterus may feel asymmetrical and large and have reduced tone and fluctuant contents that can be palpated in the rectum. It has many benefits and features, including being quick, being inexpensive, and being available during a normal herd visit; on the other hand, its advantages and disadvantages are the uterine dimensions and tone that differ with DIM, parity, bladder fullness, and examiner expertise. Again, palpation is poor in identifying subclinical endometritis when there is little or no uterine fluid, meaning that a negative result does not rule out subclinical endometritis (Kasimanickam et al., 2004).

Discharge should be evaluated in a systematic way and not only by examination of the external surfaces. Vaginoscopy allows direct visualization of the vagina, the cervix, and the vaginal discharge and can detect purulent or mucopurulent material, malodor, vaginitis, cervical lesions, or obstetrical trauma. A clean gloved hand or a device for vaginal collection of discharge, like the Metrichheck device, can be used and is quicker in the field and allows for repeated herd-level screens. While there is less perfect agreement between the two methods, Metrichheck could recover more material and identify more cows with abnormal discharge than the gloved-hand method, as described by Pleticha et al. (2009). Vaginoscopy is very informative about anatomy but requires time, equipment, and cleaning and putting the patient in restraint. There is one common drawback to all discharge tests: they are testing for the presence of PVD rather than endometrial inflammation, and they sometimes show false-positive (Pus-sick) and false-negative (subclinical disease) results.

Endometrial cytology is the most common technique to establish a diagnosis of subclinical endometritis. The cells collected by means of a cytobrush, cytotape, or uterine lavage with a low volume of saline are stained and then counted under the microscope, and the per-

centage of PMNs is calculated. Even with normal vaginal discharge and/or rectal findings, a high proportion of PMNs are good indicators of active endometrial inflammation. It is important to take diagnostic cut-offs into account when considering the diagnosis when DIM is involved, as normal inflammation in the postpartum period decreases as involution progresses. Levels exceeding 18% PMNs from 20-33 DIM and >10% at 34-47 DIM were used to categorize clinically normal that had a lower subsequent pregnancy rate according to a single study (Kasimanickam et al., 2004). Lower thresholds have been used after postpartum or at insemination in other studies.

Therefore, a review is not a single universal PMN value but should include details about the sampling device employed, the staining method used, the number of cells counted, the DIM, and the cutoff. Compared to other cytological methods, the cytobrush usually produces a well-preserved, well-dilated but limited number of cells of almost monolayer quality, suitable for individual cow diagnosis after passing through the cervix, careful asepsis, microscope examination, and trained interpretation. Uterine lavage samples will sample a larger surface area within the lumen and may be used for cytology and culture; however, fluid recovery, dilution, sedimentation, and uneven cell sampling will decrease the repeatability.

Comparable field validation is less extensive, and Cytotape is a cost-effective option that could make the slide preparation more efficient. Relative sensitivity of lavage cytology was reported to be 92.3% and specificity 93.9% compared to 53.9% and 95.4% for vaginoscopy (Barlund et al. 2008). The results show the benefit of cytology for detecting subclinical inflammation, while discharge examination is more effective for detecting clinical disease (Barlund et al., 2008; Rana et al., 2020). Histopathology of the endometrial biopsy enables the evaluation of information that is not provided by cytology; these include epithelial disruption, stromal edema or fibrosis, vascular change, periglandular inflammation, glandular degeneration, and the depth and chronicity of lesions. A biopsy may identify recurrent or chronic endometrial damage even when the primary cytological finding is only suspicious, making it useful for research or when re-breeding investigations are pursued. However, biopsy is invasive; only a small area of tissue is being biopsied, requires laboratory processing and veterinary pathologist expertise, and can present inter-observer variation.

It is not recommended for routine herd screening due to factors such as cost, slow results, and fear of trauma. There is only partial agreement between the

two tests due to differences in measured properties of tissue architecture vs. inflammatory exfoliates (Pascotini et al., 2016b). TRU represents a quick, non-invasive adjunct that can record involution and can show an enlarged uterine lumen, echogenic/particulate fluid, excess fluid depth, asymmetrical horns, or a thick (but not necessarily) irregular endometrium. When these are found following the anticipated resolution of the lochia, they support clinical endometritis. Ultrasound also has a role in detecting pyometra and determining the ovarian status, particularly if a functional corpus luteum is present in the ovary, which will affect the choice of treatment. However, small amounts of fluid in the postpartum period are simply physiological; likewise, identifying a pathogen from echogenicity is impossible, and many cows with cytological endometritis have no visible fluid. In one study, endometrium thickness had 89.2% specificity and 3.9% sensitivity, as compared to cytobrush cytology, which had 30.8% sensitivity and 92.8% specificity (Barlund et al., 2008). Therefore, ultrasound can be beneficial for structural observations and for triage in cases but cannot supersede cytological reporting of the diagnosis of subclinical endometritis (McKay et al., 2023). Microbiological culture reveals the presence of living organisms, either aerobic or anaerobic organisms, and it can be used for antimicrobial susceptibility testing, which is helpful for severe, recurrent, unusual, and herd-level infections. An infectious diagnosis might be supported by the isolation of organisms like *Escherichia coli*, *Trueperella pyogenes*, *Fusobacterium necrophorum*, or mixed anaerobes. Moreover, bacterial exposure is likely to be encountered postpartum, and culture-negative inflammatory lesions are present, while a positive culture does not prove that the associated isolate is the causative agent in the lesion. The results are influenced by contamination of the sample, exposure to oxygen, conditioning prior to sampling or transport between samples, and the idiosyncrasy of some organisms. Molecular methods are more sensitive and quicker to assess selected targets; they can characterize members of the community that cannot be cultured; however, they may detect the presence of nonviable organisms and are unlikely to provide a level of susceptibility that is validated for routine clinical decisions, with the exception of molecular methods based on 16S rRNA sequencing (Jeon et al., 2017; Khan et al., 2020; Liu et al., 2024).

A combination of diagnostic tests is needed in each and every cow. Using a combination of DIM and clinical history, along with a general examination and discharge score for metritis and PVD, ultrasonography for evaluation of luminal contents, involution, pyometra,

and ovarian status, and cytology if there is suspicion of subclinical endometritis or unexplained reduced fertility is recommended. Molecular testing and culture should be reserved for select cases in which case management will be impacted by pathogen identification. A repeat equivocal exam at a reasonable time will differentiate between inflammation vs. ongoing disease. The combination of these approaches increases diagnostic specificity, reduces inappropriate antibiotic use, and allows the response to antibiotic treatment to be judged using the same case definition as before treatment.

TREATMENT

Treatment selection

The treatment recommended should be based on the postpartum syndrome, DIM, body condition of the animal, findings in the uterus, status of the ovary, and using any diagnostic technique. Acute puerperal metritis in cows or buffaloes when there is fever, toxemia, depression, reduced appetite, or dehydration should be treated with systemic antimicrobial and supportive therapy. These animals should not be treated in the same way as clinically healthy animals that have been diagnosed with purulent vaginal discharge (PVD) or cytological endometritis after 21 DIM. After giving birth, many animals may have bacteria in their uterus. Most postpartum animals can clear bacteria from their uterus without treatment. Thus, therapeutic goals must not only include the absence of vaginal secretion but also other goals. The treatment should address healing of infection and inflammation, return of the uterus to function, repair of the thickened endometrium, and stimulation of future fertility (Lima, 2020; Sheldon & Owens, 2017).

Treatment therapy

There is extensive field evidence in countries approved for this use of cephalosporins in the intrauterine space in suitably selected cows with clinical PVD or cytological endometritis. The local production by the local administration generates a high concentration of antimicrobial systemically, while at the same time it provides a high concentration of the antimicrobial in the uterine lumen. But only if the diagnosis is correct, treatment is timely, and the uterine content and extent of inflammation are correct. Based on a randomized field trial of 2259 cows examined at 35 ± 7 DIM, the incidence of cows becoming pregnant at their first service was significantly higher in those in the intrauterine cephalosporin treatment group (31.4% of cows in the group became pregnant at their first service) than in

the control group (15.4%). The percentage of cows that conceived at first service rose to 24.4% from 16.2% for cows with cytological endometritis. No benefit was seen in cows with either PVD or cytological endometritis (Denis-Robichaud & Dubuc, 2015).

Results of this study stress the need to target those cows that meet the following criteria for treatment in the intrauterine space and confirmed by diagnosis with intrauterine cultures only: 1) cows with negative cultures and therefore no reason for treatment; 2) cows that have a culture that the practitioner deems unsafe; 3) cows that present with inappetence or abnormal milk production. Assessment of clinical cure and restoration of fertility should be made separately. Forgetting to identify purulent vaginal discharge doesn't mean that all signs of endometrial inflammation are going away. Likewise, a decrease in inflammatory cells in the endometrium could not necessarily translate to a quick improvement in reproductive function. Therefore, the evaluation should consider vaginal discharge, uterine involution, endometrial cytology, and the potential for subsequent conception.

Systemic antibiotics selection

In puerperal metritis, especially, pathogenic bacteria and inflammatory mediators could be spread beyond the uterine lumen and cause systemic disease, so systemic antimicrobial therapy is crucial. Ceftiofur has been thoroughly studied for this use. It is better suited for treatment of cows with acute metritis, fever, toxemia, or other systemic symptoms than for clinically normal cows presenting with later PVD or cytological endometritis. Systemic or intrauterine treatment with penicillin and oxytetracycline was also used to treat bovine uterine infections. They are effective based upon antimicrobial susceptibility, the type of microorganisms, how the drugs are distributed in the uterus, amount of inflammatory exudate, and spontaneous healing potential. Therefore, the activity, label approval, response from previous herd treatments, and bacterial culture and susceptibility should be taken into account when selecting antimicrobial activity.

Limitations of antibiotic therapy

A large volume of uterine fluid, lochia with or without pus, and necrotic material can have an inhibitory effect on the effectiveness of intrauterine antibiotics. These materials may interfere with and neutralize the antimicrobial preparation and may prevent contact with the bacteria in connection with endometrial tissues and microbial biofilms. All other preparations could also irritate or harm the lining of the uterus. Systemic

treatment provides whole-animal antimicrobial exposure but is not necessarily associated with a sufficient concentration in the uterine lumen or endometrial tissue. Intrauterine therapy can therefore lead to high local (intrauterine) drug levels but low systemic (blood) drug levels in animals suffering from puerperal metritis and/or toxemia.

Other important factors are antimicrobial-resistance selection, changes in the reproductive microbiota, milk and meat residues, treatment costs, and the restrictions in some countries. Oversowing or repeated and indiscriminate treatment can lead to greater selection pressure but not to a corresponding improvement in fertility. In such cases, recurrent infections, treatment failures, and problems with the antimicrobial susceptibility of animals should be kept in mind when considering culture and antimicrobial susceptibility testing for them. Almost all antimicrobial treatment should be in line with national legislation and under veterinary care (Kaufmann et al., 2010; Khan et al., 2020; Liu et al., 2024). Another constraint is the lack of clinical, bacteriological, cytological, and reproductive recovery. Persistent inflammation of the endometrium may decrease a cow's fertility and be present without any clinical signs of inflammation. In some cases, however, the inflammation of the tissue covers can last without any bacteria being present in the urinary tract. In those cases, antimicrobial therapy may be of little therapeutic effect, as continuous inflammation, rather than ongoing bacterial infection, may be the predominant pathological process.

Hormonal, physical and supportive therapy

Generally, hormones and physical therapies do not directly destroy bacteria but encourage uterine evacuation and restore reproductive function. If there is a functioning corpus luteum, prostaglandin F_{2α} (PGF_{2α}) might help if there is pyometra or persistent uterine fluid. PGF_{2α} leads to a drop in progesterone, resumption of estrus, relaxation of the cervix, and stimulation of myometrial activity, all of which can help aid in uterine clearance. The effect of PGF_{2α} cannot be determined in the animals in which the corpus luteum is absent. One controlled trial showed that the prevalence of subclinical endometritis and fertility in heifers with and without PGF_{2α} treatment were not different (Galvão et al., 2009). Examination of the ovaries, then, should be performed before deciding on the use of PGF_{2α}.

The action of oxytocin on the uterus is short and most effective in the early postpartum period when the uterus is still responsive to oxytocin. It is an unhelp-

ful test when endometritis is diagnosed several weeks after calving, both clinically and subclinically. Hence, oxytocin must not be used for the routine treatment of an endometritis that occurs following childbirth. SUL may be useful in removing a significant volume of feculent fluid, exudate, or debris in a select number of patients. Repeated instrumentation, however, can result in the entrance of microorganisms or trauma to the endometrium or disruption of defense factors. The procedure should thus be carried out aseptically and only in cases when clinically indicated. Disease of the uterus that involves systemic imbalances or metabolic stressors demands supportive treatment. Consideration can be given to fluid therapy, anti-inflammatory therapy, correction of hypocalcemia, providing nutritional support and energy supplementation, and treatment of any underlying diseases. Proper correction of metabolic and systemic disorders may take a while to achieve involution of the uterus and may decrease the effectiveness of treatment with antimicrobial drugs.

HERBAL THERAPY

Anti-microbial and anti-inflammatory potential

Bacterial membrane disruption, change in membrane permeability, interference with the metabolic pathways of microbes, and regulation of inflammatory responses are due to the action of phenolic contents and terpenoids from the products of herbs and essential oils. Cinnamon, oregano, thyme, clove, and eucalyptus, among other plant products, have therefore been assessed for use as alternative or complementary antibiotics. Essential oils of cinnamon, oregano, and thyme reduced *E. coli* and *Trueperella pyogenes* in vitro from dairy cows with clinical endometritis in vitro. The minimum inhibitory and minimum bactericidal concentrations of these oils were comparatively low, and therefore these oils manifested strong antimicrobial activity against the important uterine pathogens (Paiano et al., 2023). However, in vitro the activity of an antimicrobial is not necessarily meaningful in terms of efficacy in the clinic. The activity of the essential oils may be affected by conditions in the uterus, such as uterine mucus, the inflammatory exudate, tissue penetration, dilution, formation of uterine biofilms, and the chemical environment of the postpartum uterus. They can also differ in chemical composition by processing technique, storage, product formulation, geographical origin, and chemotype, depending on plant species. Essential oils with antimicrobial effects may harm the cells of the endometrium or sperm. Their pharmacokinetics, uterine tolerance, tissue irritation, residues, product stability,

and effects on conception should be determined prior to routine intrauterine use.

Evidence from standardized herbal products

Herbal medicines for dogs are no longer in laboratory testing. A formulation based on alcoholic extract of *Calendula officinalis*, *Melissa officinalis*, and *Origanum majorana*, plus eucalyptus oil, was tested in cows having clinical endometritis at 21 - 35 DIM. The efficacy was compared with intrauterine cephalosporin in a multicenter randomized field trial. The success rates were 61% for the herbal preparation and 67% for cephalosporin and were statistically indistinguishable at 14 ± 2 days after the first treatment. Only 82% of the cows treated with the herbal product were clinically cured, while 88% were clinically cured with cephalosporin. No significant differences were observed among the treatments (Menoud et al., 2024). These results are encouraging but cannot be generalized to all types of extracts, essential-oil formulations, severe puerperal metritis, chronic uterine disease, and cytological endometritis, respectively. More research is needed to assess herds' long-term fertility, reproductive safety, residues, product consistency, and product reproducibility.

Inflammatory therapy

Immunomodulatory therapy is designed to boost local uterine immune responses, enhance clearance of microflora and dysbiosis, modulate inflammation, and repair the uterus without using solely antimicrobial agents. Suggestions involve probiotics, some specific types of lactic-acid bacteria, stimulated innate immune pathways, platelet-rich plasma, and regulation of inflammatory mediators. Vaccination is primarily an immunomodulatory strategy of prevention. Machado et al. (2014) conducted a randomized experiment ($n=371$ heifers) that revealed vaccination containing bacterial components or virulence proteins of *E. coli*, *F. necrophorum*, and *T. pyogenes* decreased the incidence of puerperal metritis and increased subsequent reproductive performance. The results provide added confirmation of the possibility of preventing endometritis through vaccination and are not a treatment for already infected animals with either clinical or subclinical endometritis. Probiotics and certain lactic-acid bacteria can inhibit pathogens by preventing their growth, altering the colonization of adhesion sites, producing antimicrobial compounds, stimulating local mucosal immune responses, and modulating the reproductive microbiota. PRP can help to provide a variety of growth factors, cytokines, chemokines, and other biologically active compounds, which are usually involved in help-

ing to regulate inflammation and aid in the repair of the endometrial tissue. However, probiotics, platelet-derived products, and other immunomodulatory preparations have not been demonstrated to be successful in cattle and buffaloes. Strain and product identification, dose and route/s of administration, timing, sterility and contamination management, overstimulation of the immune system, and fertility improvement consistency are all important uncertainties. These methods are thus considered “emerging adjunctive” or alternative treatments, rather than proven alternatives to indicated antimicrobial treatment (Pascottini and LeBlanc, 2020).

Ozone therapy

Ozone therapy has an antimicrobial effect and oxidative signaling effects and may be administered as an oxygen-ozone gas mixture, foam, or ozonated oil. In a small randomized study involving 80 clinically healthy postpartum cows on four pasture-based farms it was found that by 72 hours after treatment with intrauterine ozone, the mean endometrial PMN decreased (from 3.7% in the treatment group to 7.6% in the controls), while the cows receiving treatment had a higher first-service conception rate (50%, compared to 16.2% in the 72 hours after treatment with intrauterine ozone, mean endometrial PMN decreased (3.7% of interesters, decreased to 7.6% in controls), while cows in treatment had a higher first-service conception rate (50%, compared to 16.2% of controls) (Escandón et al., 2020).

The use of ozone is being studied to treat bovine uterine infections without antibiotics or as a treatment that does not require them. Ozone is highly oxidizing and causes reactions with membrane lipids, proteins, enzymes, etc., which are vulnerable to the effects of microorganisms. Microbial membranes: Such oxidative damage can harm microbial membranes and disrupt metabolism. Such oxidative damage can affect metabolism. Ozone exposure that can be controlled also elicits the production of ROS and lipid oxidation products, which could potentially affect local antioxidant, immune, and inflammation pathways. But high levels of ozone, or if it is released for too long, can cause oxidative damage to host tissue. Thus, the biological effects of ozone can be very dependent on the concentration, volume, pharmaceutical preparation, and contact time (Sciorsci et al., 2020; Đuričić et al., 2026). In bovine reproductive practice, ozone has been used as an O₂-O₃ gas mixture (directly in the uterus), ozonated water, foam (directly in the uterus), and ozonated water-oil (also directly in the uterus). Although these formulations are similar, none can be substituted for another

due to differences in the stability of the ozone in the formulation, distribution throughout the uterus, and length of time that the tissues are in contact with the ozone.

Laboratory evidence

Under laboratory conditions, the direct antimicrobial effect of ozone on bacteria related to bovine uterine diseases has been shown. Lillo et al. (2023) assessed the performance of the oxygen-ozone mixture against reference strains and triggered acute metritis in cows, bacteria collected from the cervicovaginal mucus. *E. coli* and all other tested bacteria and *Mycoplasma bovis* were highly vulnerable to exposure to ozone. No bacterial growth was observed when tested at 20 µmole/mL for 1 minute; bacterial growth was significantly reduced at the lowest concentration tested for *M. bovis*, and none of the bacterial growth was observed in the case of both reference and clinical isolates of *M. bovis* at the lowest concentration tested for *M. bovis*, i.e., 20 µmole/mL for 1 minute. However, this represents in vitro results and should not be read as proof of efficacy in vivo, as the in vivo activity of ozone could be reduced or altered by the presence of uterine mucus, inflammatory exudate, tissue penetration, and microbial biofilms. (Lillo et al., 2023) Escandón et al. (2020) assigned 80 clinically healthy, 40 dairy cows on each of four pasture-based farms to either an intrauterine ozone treatment or a control that was not treated. Ozonated solution was given 35 days postpartum. After 72 h the level of endometrial polymorphonuclear neutrophils decreased in ozone-exposed cows compared to controls (3.7 ± 1.4% vs. 7.6 ± 1.1%, respectively). Also, the absence of sub-clinical endometritis in treated animals (5.0%) was observed to be lower than in the controls (50.0%).

In addition, treated cows had a higher first service conception rate (50.0% compared to 16.2%) and fewer services per conception (2.1 ± 0.3 compared to 3.1 ± 0.2). Therefore, the original text should read “3.7% of the cows that did subsequently receive ozone had their PMNs reduced to 7.6%, as opposed to the controls” (Escandón et al., 2020). Patra et al. (2023) examined intrauterine ozone insufflation in 14 clinical endometritis cases of cows. Seven cows were available for each treatment of ozone alone or ozone plus cephalixin. Ozone alone and in combination reduced the counts of bacteria by 99.60 and 99.72%, respectively. The first insemination conception rates were 42.85 and 71.42 percent, respectively. The findings presented do suggest potential antimicrobial and fertility benefits for ozone treatment when compared to control; however, as this study

involved a limited number of cows, treatment with antibiotics alone and an untreated control group were not included, so it is difficult to compare ozone treatment and antibiotic treatment (Patra et al., 2023). Evidence has also recently become available in buffaloes. Dutt et al. (2025) investigated 31 reportedly normal cervico-vaginal discharge in Murrah buffaloes. A threshold of $\geq 5\%$ PMNs on cyto-brush was used to diagnose sub-clinical endometritis. The other 25 buffaloes received intrauterine normal saline with an oxygen-ozone gas mixture (55 $\mu\text{g/mL}$; 60 mL) on day 1 and day 2 during estrus, while 06 control buffaloes received intrauterine normal saline. 68% (17/25) of the buffaloes treated with ozone presented cytological recovery (defined as PMN proportion $< 5\%$). The 17 recovered buffaloes that had some pregnancy diagnostics appeared in 6 animals, yielding a pregnancy rate of 35.29% for the recovered animals. There was no significant difference in PMN percentage in the saline-treated group.

Furthermore, the small number and uneven distribution of the groups, along with the limited reproductive follow-up, indicate that the findings require further analysis since the results are preliminary (Dutt et al., 2025). Carbonari et al. (2026) screened 156 repeat-breeder cows and found 57 cows to have cytological subclinical endometritis. Intrauterine oxygen-ozone treatment had 30 cows, and the control group consisted of 27 cows. The number of cows receiving intrauterine oxygen-ozone treatment (OPT) was 30, and the untreated control group was 27 cows. One minute of continuous flow of oxygen-ozone with an ozone concentration of 20 $\mu\text{g/mL}$ was provided during estrus. After 12 hours, no bacteria could be cultured from any of the 12 treated cows that had been culture positive, but positive bacteria were cultured from all 14 of the culture-positive control cows. Treated cows had a 30% pregnancy rate while controls had a 7% pregnancy rate after the first artificial insemination. The pregnancy rates in the second inseminations were 43% and 4%, respectively, in cows inseminated twice. There were no clinical adverse effects reported at sites or in the body after treatment. Nevertheless, the data from this randomized study should be viewed as preliminary, and the 12-hour bacteriological evaluation does not prove a long-term bacterial or histological (cytological) cure (Carbonari et al., 2026).

Taken together, these studies suggest that in utero ozone has antimicrobial, anti-inflammatory, and fertility-enhancing effects in cows and buffaloes. Even with all of these trials, however, there is significant variation among all studies in the choices of animals, definition of endometritis, method of preparing ozone,

ozone concentration, the amount of ozone administered, the timing of treatment, and evaluation of the outcome. Some small sample sizes and less often a direct comparison with licensed antimicrobial treatments are also included in several studies. As a result, ozone should really be considered a promising complementary or antibiotic-reducing treatment, but as of now, it is not a recognized alternative treatment for traditional treatment methods. To determine what is optimal, the optimal concentration, formulation, and exposure time must be investigated in multi-center randomized trials, in comparison with the standard treatments, using cytological cure, bacteriological cure, conception rate, calving-to-conception interval, recurrence, and adverse effects as outcome measures.

The therapeutic effectiveness of intra-uterine ozone was studied by Dutt et al. (2025) in 31 repeat-breeding Murrah buffaloes. All of the remaining buffaloes received repeated artificial insemination after three consecutive cycles of normal cervico-vaginal discharge and were unable to become pregnant. The cytobrush method was used to obtain samples of the endometrium during estrus. The smears were air-dried, fixed in the methyl alcohol, stained in the modified Giemsa stain, and examined under the microscope at 400 $\times$. In each specimen, at least 100 endometrial cells were counted, and buffaloes were considered to have subclinical endometritis when $\geq 5\%$ of the cells were polymorphonuclear neutrophils (PMNs). The buffaloes were divided into control and ozone-treatment groups; 60 mL of normal saline was infused into the uterus of the control group, and 60 mL of the ozone gas at 55 $\mu\text{g/mL}$ was infused into the uterus of the ozone-treatment group on the first and second days of the estrous cycle. After treatment, buffaloes with an $< 5\%$ PMN proportion in the endometrium were treated as cytologically recovered and were inseminated during subsequent spontaneous estrus. No significant difference was found in the percentage of PMN in the endometrium of the control group. On the other hand, 68% (17/25) of the buffaloes that were treated with ozone attained cytological recovery. Of the 17 animals recovered, six were pregnant (with a pregnancy rate of 35.29% among the recovered buffaloes). Overall, the pregnancy proportion was 24% (6/25) when considered for all the animals that underwent ozone treatment. The study results indicate that the intrauterine administration of O_3 can help diminish the inflammatory response at the endometrium level and improve fertility in subclinical endometritis-affected repeat-breeding buffaloes. It acts as an antioxidant that also has an oxidative antimicrobial activity, which could minimize the levels of microorganisms in

the uterus, and a controlled oxidative signaling might activate local immune and antioxidant responses. The use of ozone could thus serve as a potential treatment to reduce the reliance on antibiotics for managing subclinical endometritis in buffaloes. The findings should be taken with some caution, as this study included a small and disproportionate control group, failed to compare ozone with a standard intrauterine antibiotic, and had limited information on blinding, recurrence over the long term, and subsequent reproductive performance. Standardized ozone levels, uniform group sizes, and head-to-head comparisons with the traditional treatment methods are needed in larger randomized controlled trials to justify ozone as a standard alternative to antimicrobial treatment.

While promising, the short interval between the cytology tests, the small sample size, and the specific production system limit the procedure's effectiveness; additionally, including a sham procedure this time would further enhance its effectiveness, but it also introduces limitations regarding generalizability. There is a lack of standardization in ozone concentration, ozone exposure to the operator, the delivery method, and oxidative tissue injury in addition to residue or regulatory considerations. Ozone is recommended for routine therapy until independent multicenter trials with appropriate blinding are completed.

Treatment should be based on an appropriate diagnosis, judicious antimicrobial use, and correction or improvement of predisposing factors in general. Prompt evidence-based systems care should be given to cows with systemically ill metritis, while clinically stable cows with PVD or cytological endometritis should be treated selectively according to a locally licensed treatment protocol for which there is a fertility benefit. In the future, the use of antibiotics could be decreased using herbal formulations, immune modulators, and ozone, but these are partially indicated by *in vitro* activity, up to small, formulation-specific field trials. Follow-up should repeat the same type of results as those obtained at diagnosis, either discharge or cytological or ultrasonographic, and should include reproductive endpoints like first-service conception, days open, and pregnancy by a defined DIM.

Overall therapeutic evaluation

Systemic antibiotics are still very significant when a puerperal metritis is associated with fever or systemic illness. There is relatively strong evidence supporting the use of intrauterine cephalosporins for cows that are appropriate candidates after experiencing early postpartum purulent vaginal discharge and cytological en-

dometritis. Potential treatments such as herbal remedies, immunomodulators, platelet-rich plasma, probiotics, and ozone have reductions in antimicrobial use, although the majority need further standardization and larger controlled trials. Vaginal discharge, as a standalone diagnosis, is not the determinant of a treatment's success. Vaginal discharge alone should not be used to determine a treatment's success; that should be defined by restoration of uterine health and fertility.

CONTROL

Preventative management is the key to control of bovine, especially during the calving period, when the uterus is at its most vulnerable to microbial invasion. However, maintenance of appropriate hygiene is important during the calving period. When a cow is calving, poor hygiene can also let bacteria or debris into the uterus, which can lead to infection (Wu et al., 2022). Although preventive measures to limit risk factors such as retained placenta, environmental stresses, and poor calving conditions are important for controlling bovine endometritis and improving herd fertility, they must be accompanied by appropriate hygiene practices to control bovine endometritis and improve herd fertility. Adequate nutrition is also crucial for sufficient energy, vitamin A, selenium, and zinc levels to ensure a strong immune system to resist infections (Feng et al., 2024). Furthermore, proper nutrition during this period reduces the risks associated with retained placenta, a significant predisposing factor for endometritis (Serbenyuk, 2023).

INNOVATIVE STRATEGIES AND FUTURE DIRECTIONS

Management of bovine endometritis has been rapidly changing over the past years with technological innovation and knowledge of the biology of the uterus. The use of ultrasonography is an expanded diagnostic tool, especially high-resolution portable ultrasonographic devices. These tools allow for the visualization of uterine changes, such as the presence of uterine fluid and thickening of the endometrium, in real time, with increasing importance for monitoring and evaluating treatment efficacy (Nakaya & Pulendran, 2015). The detection of endometritis introduces new concepts regarding deep networks as a potential approach for managing multiple factors, including nutritional status, metabolic stress, genotype, microRNA expression, reproductive tract health, and microbial virulence factors. Alongside, machine learning algo-

rhythms can detect complex, non-linear relationships among variables and generate predictions that are not possible by traditional statistical models, such as high fertility, increased productivity, and the development of therapeutic strategies (Fig. 3) (Lima, 2020). Furthermore, the current models of fertility management are increasingly incorporating immunomodulation approaches, such as vaccines and immunostimulants, to support both innate and adaptive immunity against uterine pathogens (Choudhary et al., 2023).

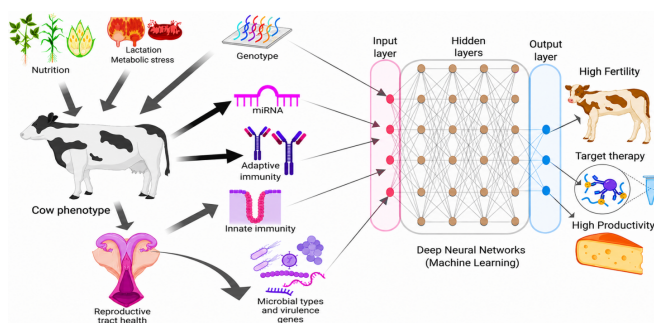


Figure 3: Schematic representation of an integrated multi-omics and deep learning framework for predicting cattle fertility and productivity. Nutritional status, lactation-associated metabolic stress, and genotype influence the cow phenotype and reproductive tract health through miRNA, adaptive and innate immune responses, and microbial types and virulence genes. These biological and phenotypic inputs are integrated using deep neural networks (machine learning) to predict fertility, productivity, and potential target therapies, supporting precision management and therapeutic interventions in cattle.

CONCLUSION

Endometritis is one of the significant causes of infertility and economic loss in dairy and beef cattle due to its multifactorial interaction with microbes, immune dysfunction, metabolic imbalance, and postpartum risk factors. However, diagnostic approaches, including molecular microbiology and understanding of the uterine microbiome, have improved early detection and provided opportunities for targeted, non-antibiotic therapies. Additionally, control strategies should incorporate accurate diagnosis, effective herd management, optimal nutrition, proper sanitation, and immunological support to enhance reproductive performance while reducing antibiotics and hormonal dependency. Such versatile approaches will be necessary for a sustainable productive system.

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ETHICAL CONSIDERATIONS

This article is a review and meta-analysis and did not involve any new experiments on humans or animals. Therefore, informed consent was not applicable.

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