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Equine endometritis: An Update

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Endometritis is a major cause of infertility in mares and one of the most frequently encountered reproductive disorders in equine practice. It is characterized by inflammation of the endometrium and may be acute or chronic, infectious or noninfectious. Intrauterine inflammatory mediators, debris, and microorganisms compromise embryo survival and may induce premature luteolysis through prostaglandin F2α release, leading to early embryonic loss. Approximately 10–20% of mares are affected or predisposed to endometritis. The condition is classified as sexually transmitted, persistent mating-induced, chronic infectious, or chronic degenerative endometritis. Advanced age, poor perineal conformation, abnormal uterine position, and reduced endometrial quality increase susceptibility. Diagnosis relies on ultrasonography, cytology, bacteriological culture, and histopathology. Management includes uterine lavage, culture-guided antimicrobial therapy, ecbolic agents, immunomodulation, and adjunctive biological treatments. Rising antimicrobial resistance emphasizes the need for accurate diagnosis and targeted therapeutic strategies

Types of Endometritis

Sexually transmitted diseases (STD):

Contagious equine endometritis (CEM), caused by *Taylorella equigenitalis*, is a true sexually transmitted disease resulting in cervicitis, vaginitis, and endometritis. A copious mucopurulent vaginal discharge typically develops within one week after breeding to an asymptomatic carrier stallion.

Persistent mating-induced endometritis (PMIE):

Breeding-induced endometritis is a normal physiological response in mares and facilitates clearance of bacteria and excess spermatozoa (Troedsson, 2006). In healthy mares, inflammation resolves within 48 hours. However, mares with impaired uterine defense

mechanisms fail to resolve this response, leading to PMIE. Persistent inflammation beyond 48 hours compromises fertility and threatens embryo viability, as the conceptus enters the uterus approximately 5–6 days post-breeding (Oguri and Tsutsumi, 1972; Betteridge et al., 1982). Approximately 10–15% of broodmares retain intrauterine fluid 24–36 hours after breeding (Zent et al., 1998), making PMIE a major reproductive concern (Traub-Dargatz et al., 1991).

Chronic infectious endometritis:

Chronic infectious endometritis results from contamination by opportunistic fecal or genital flora in mares with compromised uterine defenses. Aerobic bacteria are the most common pathogens, with *Streptococcus zooepidemicus* accounting for approximately 65% of cases, followed by *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (~10%). Anaerobic bacteria, fungi, and yeasts are less frequently involved (Brito and Barth, 2003).

Chronic degenerative endometritis:

Chronic degenerative endometritis is characterized by severe, progressive, and irreversible fibrotic changes of the endometrium (Kenney and Doig, 1986). Histologic features include periglandular fibrosis, lymphatic stasis, and glandular dilation. Although often associated with repeated uterine inflammation, similar changes occur in older mares without prior endometritis, suggesting an age-related degenerative process (Allen, 1993).

Factors Affecting Susceptibility to Endometritis

Advanced age is associated with altered immune function and increased susceptibility to endometritis (Ricketts and Alonso, 1991; Zent et al., 1998). Poor perineal conformation significantly increases the risk of uterine contamination and endometritis (Hemberg et al., 2005). Additionally, mares with a pendulous uterus positioned below the pelvic brim demonstrate reduced uterine clearance (LeBlanc et al., 1994). Endometrial quality, assessed histologically, is a recognized indicator of uterine health and fertility (Kenney and Doig, 1986; Schlafer et al., 2007). Poor endometrial quality correlates with age, decreased fertility, PMIE, and chronic infectious endometritis (Carnevale and Ginther, 1992; Troedsson et al., 1993; Woodward et al., 2012).

Uterine Defence Mechanisms

Innate and adaptive immune responses:

Following breeding, the innate immune system provides the primary uterine defense through neutrophils, macrophages, and dendritic cells. Neutrophil migration begins within 0.5 hours post-breeding, peaking at 4–8 hours (Katila, 1995). These cells phagocytose spermatozoa and bacteria and form neutrophil extracellular traps (NETs) with bactericidal

properties. Humoral immunity contributes later, with elevated uterine immunoglobulins (IgA, IgM, IgG) observed primarily in mares susceptible to endometritis (Troedsson, 1999; Canisso et al., 2020).

Cytokine regulation:

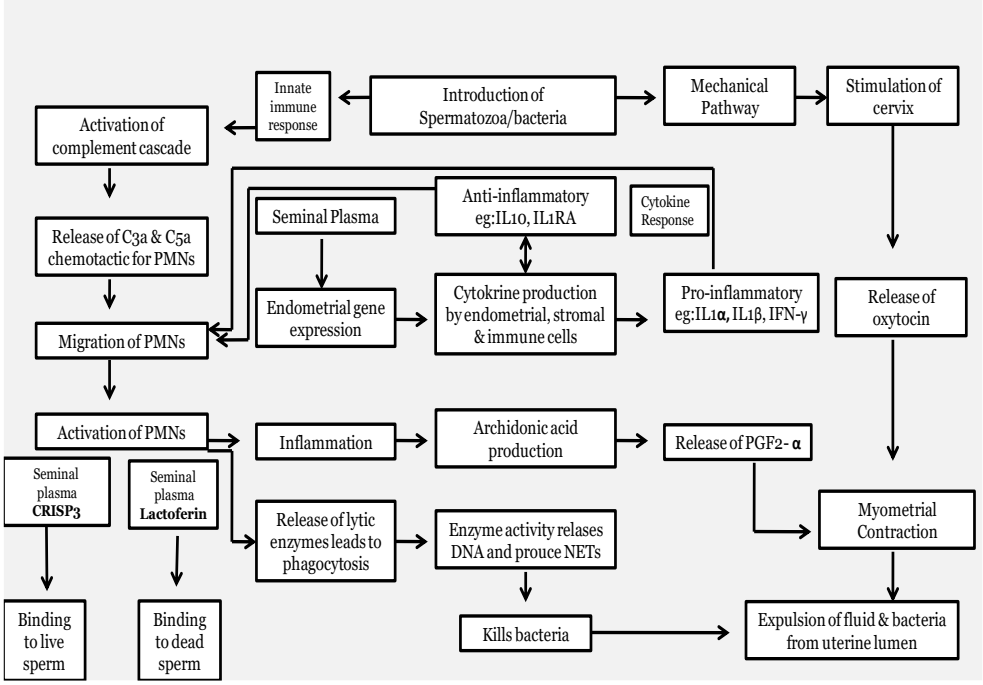
Pro-inflammatory cytokines, particularly IL1α, IL1β, and IFNγ, initiate and amplify uterine inflammation by promoting inflammatory cell recruitment and iNOS expression (Alghamdi et al., 2005; Woodward et al., 2013). Anti-inflammatory cytokines, including IL10 and IL1 receptor antagonist (IL1RA), regulate and limit inflammation, maintaining immune balance (Dinarello, 1991; Barnes, 1998).

Role of seminal plasma:

Seminal plasma modulates post-breeding inflammation by inhibiting complement activation, PMN chemotaxis, and phagocytosis. It selectively protects viable spermatozoa from PMN binding, while facilitating elimination of nonviable sperm (Troedsson, 2006). Proteins such as CRISP-3 and lactoferrin play key roles in this selective immune modulation (Doty et al., 2011; Troedsson et al., 2014).

Mechanical clearance:

Cervical stimulation during breeding induces oxytocin release, promoting myometrial contractions and uterine fluid clearance within 6–12 hours (Campbell and England, 2002).



Uterine Defense Mechanisms (Morris *et al.,* 2020)

Prostaglandin F2α produced during inflammation further enhances uterine contractions (Troedsson, 1999). Residual debris is cleared via lymphatic drainage following cervical closure.

Nitric oxide:

Nitric oxide (NO), produced primarily by inducible nitric oxide synthase (iNOS) during inflammation, contributes to pathogen elimination but may impair uterine clearance due to its smooth muscle–relaxing effects (Green et al., 1994; Liu et al., 1997). Excessive NO production has been implicated in the pathophysiology of persistent endometritis.

Patho-physiology:-

This physiological mechanism fails to be a several steps and causes to a development endometritis.

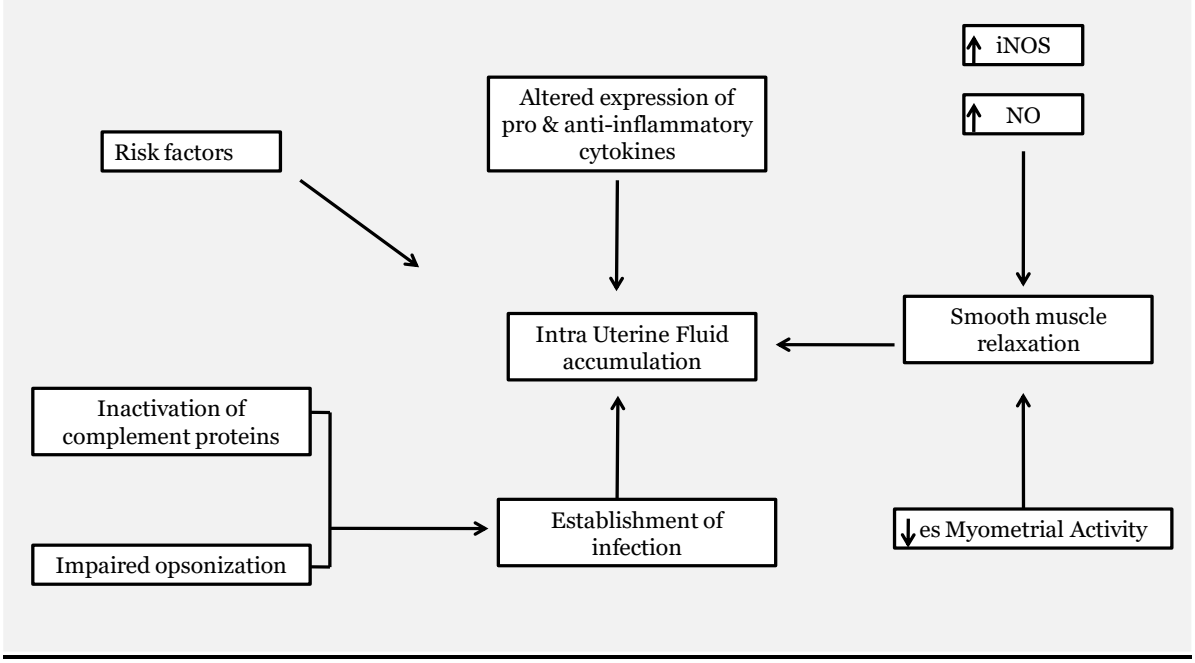


Figure: The pathogenesis of endometritis in the mare

Clinical Signs

Endometritis may result from bacterial infection or a post-breeding inflammatory response, with a common feature being endometrial inflammation characterized by polymorphonuclear neutrophils (PMNs) and intrauterine fluid accumulation (Troedsson, 2006). Clinical signs are often subtle or absent; however, vaginal discharge, shortened luteal phases, and reduced fertility may be observed (Caissie et al., 2020).

Diagnosis

The apparent prevalence of endometritis depends largely on the sensitivity and specificity of diagnostic methods. Diagnosis is based on a combination of clinical examination

and laboratory evaluation, including transrectal palpation, ultrasonography, vaginal examination, endoscopy, and uterine sampling (cytology, culture, and biopsy).

Transrectal palpation allows assessment of uterine size, tone, position, and cervical status. Findings may include a large, relaxed uterus with mild uterine wall thickening, and uterine massage may expel inflammatory contents through the cervix (LeBlanc and McKinnon, 2011; Brinsko et al., 2011).

Ultrasonography is widely used to evaluate uterine horn diameter, endometrial edema, intrauterine fluid (IUF), foreign material, cysts, and pregnancy (Ginther and Pierson, 1984). While endometrial edema is normal during estrus, excessive or persistent edema and increased IUF are associated with reduced fertility and increased susceptibility to endometritis (Allen and Pycock, 1988; LeBlanc et al., 1994; Cuervo-Arango and Newcombe, 2010). IUF ≥2 cm at any time during estrus is considered indicative of susceptibility to endometritis (Brinsko et al., 2003). Decreased myometrial activity is the primary cause of impaired uterine fluid clearance (Troedsson et al., 1993).

Vaginal examination, performed digitally or using a speculum, may reveal abnormal discharge, although many affected mares show no visible vaginal secretions (Greenhoff and Kenney, 1975).

Laboratory Diagnostics

Uterine samples are collected using guarded swabs, cytobrushes, low-volume lavage, or biopsy for cytological, bacteriological, and histological evaluation.

Endometrial cytology is a rapid and inexpensive method for assessing uterine inflammation. It identifies epithelial cells, PMNs, erythrocytes, debris, mucus, fungi, yeasts, and bacteria (LeBlanc and McKinnon, 2011). Inflammation is assessed based on PMN counts or PMN-to-epithelial cell ratios, with diagnostic thresholds varying by sampling technique. Cytobrush samples have lower PMN thresholds due to higher cellular yield, while biopsy cytology considers ≥1% PMNs indicative of inflammation (LeBlanc, 2011; Kozdrowski et al., 2015).

Bacteriological culture is performed under aerobic conditions, as anaerobes are considered of minimal importance in equine endometritis (Ricketts and Mackintosh, 1987). Cultures are incubated on blood agar and evaluated based on colony morphology and growth patterns. Common pathogens include *Escherichia coli*, *Staphylococcus* spp., *Pseudomonas*, *Klebsiella*, fungi, and yeasts. Growth is classified as pure or mixed, with colony-forming units

(CFU) categorized from mild to heavy growth (Beehan and McKinnon, 2009; Reilas and Katila).

Histopathology remains the gold standard for assessing endometrial health. Biopsy specimens are evaluated for PMN infiltration, glandular and stromal changes, and fibrosis following Kenney's classification system. While any PMNs outside blood vessels may indicate inflammation, interpretation varies with estrous stage, with neutrophils considered more significant during diestrus (Kenney and Doig, 1986; Schoon; Rasmussen et al., 2015).

Scintigraphy

Scintigraphy is used to assess delayed uterine clearance by measuring the rate of elimination of a radio-labeled colloid infused into the uterus (Watson, 1988).

Technique	Approach and Applications	Limitations
Ultrasound	Used as a screening tool to detect the presence, amount, and appearance of IUF, which can be suggestive of endometritis.	Not all mares affected by endometritis, particularly chronic endometritis, accumulate IUF. The amount and echogenicity of fluid can be useful to direct the need for additional diagnostic techniques and therapeutic regimens.
Cotton-tip swab	Fast, user-friendly and inexpensive approach to collect samples for culture and cytology. Results in combination with cytology can be used to dictate therapeutic approaches.	Only a small segment of the uterus is sampled and thus, focal infections not generating a diffuse endometrial response can be missed. In comparison with cytobrush, fewer cells are recovered, and cells are slightly compressed, making the evaluation more diffcult.
Cytobrush	Fast,user-friendly, and inexpensive approach to collect samples for culture and cytology, although it is more commonly used for cytology.	Only a small segment of uterus is sampled, and thus, focal infections can be missed. Bacteria in biofilm may not be detected.

Low-volume uterine lavage	The whole surface of the uterus can be sampled for culture and cytology, and thus this technique is more utilized for the diagnosis of challenge and chronic endometritis. The recovered fluid can be centrifuged or allowed to decant before cytological evaluation.	There is a risk of contamination with commensal microorganisms of the caudal reproductive tract. It requires at least one well-trained clinician and an assistant. An excessive amount of fluid can overdilute the sample and cause a false-negative and may challenge the cytological evaluation. Mares with a pendulous uterus can have poor fluid recovery.
Endometrium biopsy	While this approach is primarily used for histological evaluation, endometrium biopsy is a sensitive and specific approach to diagnose endometritis in mares by histological evaluation and culture of the biopsy. Particularly useful for deep endometrium infection. Results may guide the treatment strategies employed.	It requires a biopsy, which is a minor procedure but still invasive. It also requires well-trained laboratory personnel capable of performing cultures and histological evaluations.

Treatment of Equine Endometritis

Traditionally, endometritis has been managed using uterine lavage, antimicrobials, ecbolics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), mucolytics, chelating agents, stem cells, and adjunctive therapies (Alvarenga et al., 2016). However, increasing antimicrobial resistance and poor response in a subset of mares with chronic endometritis have driven interest in alternative and adjunctive treatment strategies (Canisso, 2016).

Uterine Lavage

Uterine lavage was introduced based on the recognition of impaired mechanical uterine clearance in endometritis. It is recommended for mares with excessive intrauterine fluid accumulation (>2 cm) and increased fluid echogenicity. Typically, 1–2 L of crystalloid solutions (lactated Ringer's solution or 0.9% saline) are infused, often 6 hours post-breeding.

Lavage alone is insufficient for infectious endometritis and is commonly combined with ecbolic therapy. Additives such as antiseptics, vinegar (fungal endometritis), and biofilm-disrupting agents (e.g., N-acetylcysteine, dimethyl sulfoxide) may be used. Lavage is repeated until recovered fluid is clear and aids by removing microorganisms, debris, inflammatory cells, and dead spermatozoa (Troedsson et al., 1995; LeBlanc, 2008).

Antimicrobials

Common uterine pathogens include *Streptococcus* spp., *Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp., and *Staphylococcus* spp. Frequently used antimicrobials include β-lactams (penicillin, ampicillin, ceftiofur) and aminoglycosides (gentamicin, amikacin). Notably, *S. zooepidemicus* and *E. coli*—the most common isolates—have shown increasing resistance to commonly used antibiotics, emphasizing the importance of culture and antimicrobial susceptibility testing.

Ecbolic Drugs

Ecbolics are administered post-breeding to improve myometrial contractility and uterine clearance in susceptible mares (LeBlanc et al., 1994; Troedsson et al., 2005).

- Oxytocin: Administered at 10–20 IU starting 4–6 h post-breeding and repeated every 6–8 h until fluid resolves; low doses are more effective than high doses (Campbell and England, 2002).
- Carbetocin: A long-acting oxytocin analogue with a longer half-life (Schramme et al., 2008).
- Cloprostenol: A PGF2α analogue inducing prolonged myometrial activity, beneficial in mares with pendulous uteri (Pycock, 2006).

Immunomodulatory Therapies

Corticosteroids:

Corticosteroids have demonstrated beneficial effects in mares with persistent breeding-induced endometritis (PBIE). Dexamethasone administered at breeding improved pregnancy rates in high-risk mares, while prednisolone acetate increased pregnancy rates in mares with a history of excessive post-breeding inflammation (Bucca et al., 2008; Dell'Aqua et al., 2004). These effects are attributed to modulation of the uterine innate immune response (Christoffersen et al., 2012).

NSAIDs:

Vedaprofen administered around breeding was shown to increase pregnancy rates in susceptible mares, likely due to its anti-inflammatory effects (Rojer and Aurich, 2010).

Bacterial Cell-Wall Extracts:

Mycobacterial cell-wall extract (MCWE) enhances innate humoral immunity and modulates cytokine expression. Treatment has been associated with improved pregnancy rates in mares with *Streptococcus zooepidemicus* endometritis (Fumuso et al., 2003; Rohrbach et al., 2007).

Mucolytic and Chelating Agents

N-acetylcystein(NAC):

NAC reduces mucus viscosity and exhibits anti-inflammatory and antibiofilm activity. It is infused intrauterinely during estrus, followed by lavage or ecbolic therapy. NAC may improve antibiotic efficacy but should be used cautiously due to potential interactions (LeBlanc and McKinnon, 2011).

Dimethyl sulfoxide (DMSO):

DMSO has anti-inflammatory and antimicrobial properties and penetrates tissues effectively. Intrauterine use has not been associated with adverse histological effects (Ley et al., 1989).

EDTA-Tris(Tricide®):

This chelating agent disrupts bacterial cell walls and may enhance antibiotic activity. Treatment involves intrauterine infusion followed by lavage and is repeated until effluent fluid is clear (Lyle et al., 2011).

Biological Therapies

Lactoferrin:

Human recombinant lactoferrin modulates post-breeding inflammation and has been shown to safely reduce prolonged uterine inflammation in mares with PBIE when administered intrauterinely (Fedorka et al., 2018).

Platelet-Rich Plasma (PRP):

PRP has immunomodulatory properties and enhances phagocytosis through opsonins. In mares with chronic endometritis, PRP administration at breeding reduced intrauterine inflammation and improved reproductive outcomes (LeBlanc and McKinnon, 2011).

Stem Cells:

Mesenchymal stem cells and autologous conditioned serum have shown promise in experimental models for modulating inflammation and improving degenerative endometrial changes, although further research is needed (Ferris et al., 2014; Alvarenga et al., 2016).

Acupuncture:

Acupuncture has been used as an adjunct therapy to promote uterine clearance by improving uterine tone and contractions (Scoggin, 2016).

Conclusion

Endometritis is a significant cause of infertility and economic loss in the equine industry. Although ultrasonography remains an indispensable diagnostic tool, microbiological evaluation is essential for identifying causative agents and guiding targeted antimicrobial therapy. Due to increasing antimicrobial resistance, empirical treatments should be avoided. While several non-antibiotic therapies show promise, only a limited number have been validated under controlled conditions, highlighting the need for further research.

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