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Non-antibiotic treatment of equine endometritis

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Summary: Equine endometritis is an important cause of infertility, associated with major economic losses to the horse industry worldwide. An evolving understanding of the complexity of the disease has resulted in new treatment approaches to combat the effect on fertility through alternative non-antibiotic therapies. The objective of this article is to review some of the commonly used non-antibiotic treatment options for equine endometritis. The most recent literature on treatment options with non-antibiotic antimicrobials, immune-modulators, ecbolics and other treatments such as uterine lavage and stem cell therapy is reviewed. It is concluded that a great variety of treatment options are available to the clinician, but only a few have been tested and proven beneficial under controlled conditions. Fashionable treatments that are used without having been critically tested may represent a potential threat to the integrity of the veterinary profession, and the clinician should at a minimum have sufficient information to support the safety of the product, both for the horse and the health of the endometrium.

Keywords: endometritis, horse, equine, non-antibiotic, treatment

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Introduction

Equine endometritis is an important cause of infertility, associated with major economic losses to the horse industry worldwide. Past research has brought new information on the underlying causes of persistent inflammation and highlighted failures of the uterine defense mechanisms in horses that are classified as susceptible to persistent endometritis (*Troedsson* 1999). We have also learned that endometritis can be caused by either an infection with bacteria/fungus/ yeast, or semen associated with breeding. The two causative forms of endometritis require different treatment approaches. While local and/or systemic antibiotics based on microbial sensitivity may be the most effective treatment for infectious endometritis, this therapeutic approach is less likely to resolve a persistent uterine inflammation in mares with breeding-induced endometritis (*Troedsson* and *Woodward* 2016). Research data suggest that susceptibility to persistent endometritis involves a failure of uterine defense mechanisms at multiple levels (*Troedsson* and *Woodward* 2016). Anatomical defects of the perineal confirmation, the vestibule-vaginal fold, the cervix, and a tilted position of the uterus in the abdomen have all been associated with persistent endometritis (*Hemberg* et al. 2005). Without correction of physical defects, any treatment of endometritis would only represent a temporary solution. Insufficient physical clearance of the uterus caused by impaired myometrial activity in response to an inflammation has also been shown to cause susceptibility to persistent endometritis in response to bacterial contamination as well as semen during breeding (*Troedsson* 1999). Earlier research on the local uterine immune system produced conflicting and non-conclusive data regarding a possible involvement of a deficient cellular and humoral immune defense in the development of persistent endometritis (*Asbury* et al. 1982, *Troedsson* 1999). More recently, the innate immune system, particularly cytokine expression in response to bacteria as well as semen has been investigated by several research groups (*Fumoso* et al. 2003, *Christoffersen* et al. 2012, *Woodward* et al. 2013, *Marth* et al, 2015). The overall conclusion of this published data is that the development of persistent endometritis is associated with an imbalance of pro-inflammatory cytokines and inflammatory modulating cytokines in response to a bacterial or seminal challenge. A report by *Woodward* et al. (2013) suggests that the imbalance is present already within 3–6 hours after insemination in susceptible mares. The increased understanding of the pathophysiology of equine endometritis has resulted in new and suggested therapeutically approaches to the problem. While many treatment regimens have been, and currently are used in veterinary practice, there is limited data in support of efficacy as well as safety of these treatment options. The objective of this article is to review some of the commonly used non-antibiotic treatment options for equine endometritis.

Antimicrobial effects

While suitable antibiotics are the most effective treatment against infectious endometritis, recent research has been focused on situations where this treatment alone is not sufficient to eliminate bacterial growth from the uterus. Suggested presence of biofilms, dormant bacteria in the deeper layers of the endometrium, and other barriers may prevent antibiotics to reach their target and effectively eliminate bacteria (*Gores-Lindholm* et al. 2013, *Petersen* et al. 2015, *Ferris* et al. 2016). Although further evidence may be needed to conclusively confirm some of these hypotheses, their suggestive presence in the uterus have given rise to multiple treatment options to accompany or replace traditional antibiotics. The medical value of most of these treatments is often anecdotal, rather than evidence based.

N-Acetylcysteine (NAC)

This mucolytic substance has been used to reduce the viscosity of mucus in the uterus. In addition NAC has been suggested to have anti-inflammatory/ antioxidant and antibacterial activity (*Zuin* et al. 2005). Typically, 30 mL of a 20% solution NAC (200 mg/mL) is diluted in 150 mL of saline and infused into the uterine lumen during estrus, followed by ecbolic treatment or uterine lavage 12 hours after treatment. The treatment protocol has been suggested to be beneficial both 24–48 hours prior to breeding and 24 hours prior to antibiotic treatment. Repeated lavage may be indicated if the effluent fluid is cloudy (LeBlanc nad McKinnon 2011). When used together with antibiotics, the interaction with antimicrobials should be kept in mind. NAC enhances the efficacy of β-lactams, but reduces the anti-bacterial activity of aminoglycosides, fluoroquinolones and erythromycin. Oral treatment with NAC at 10 mg/kg did not reduce viscosity of uterine mucus; however an anti-inflammatory effect was observed in one study (*Witte* et al 2012). NAC was also suggested to decrease biofilm biomass and reduce bacteria within biofilms of E. Coli isolates in vitro (*Ferris* et al. 2016). The same effect was however, not observed for other bacteria. Intrauterine treatment with NAC is sufficiently proven to be safe, and has been suggested to improve pregnancy rates, although the pregnancy data was not supported by controlled experimental conditions (*Gores-Lindholm* et al. 2013).

EDTA-tris

Tricide® (a third generation chelator) chelates calcium and magnesium within the bacterial cell wall, which may potentiate the effect of antibiotics (*Lyle* et al. 2011). It has been suggested to potentiate the effect of antibiotics on some bacteria, but its effect to disrupt gram negative biofilms is less clear (*Ferris* et al. 2016). Treatment protocols often consist of intra uterine infusions of 500–1000 mL Tricide, followed by uterine lavage with a buffered saline solution the following day. The treatment is repeated until the effluent fluid is clear, at which time the mare is treated with local antibiotics for 5 days. Tricide can also be added to antibiotics, but is not recommended to be used together with ceftiofur, K-penicillin or Timentin due to precipitation in the solution (*LeBlanc* and *McKinnon* 2011).

Cationic Steroid Antimicrobial (CSA)

Ceragyn® belongs to a class of peptides that cause depolarization of bacterial cell wall membranes and activate apoptotic pathways. These peptides have been used for various conditions in human medicine because of their biofilm breakdown and broad spectrum anti-microbial activities. Ceragyn (60 mL; 1 vial) is labeled for use up to 24 hours before or 12–48 hours after breeding. The drug has become increasingly popular among equine practitioners but the authors have not been able to find conclusive data from controlled studies to support its effect on equine endometritis.

Hydrogen peroxide

H_2O_2 has a bactericidal effect on most uterine pathogens. A 1% solution [20 mL of a 3% H_2O_2 solution diluted in 60 mL lactated Ringer solution (LRS)] has been suggested to be effective on biofilms in vitro (*Ferris* et al. 2016). Information regarding the efficacy of H2O2 treatment is anecdotal, and needs to be supported by controlled in vivo studies.

bActivate

A proprietary substance marketed as bActivate® has been shown to activate dormant Streptococcus from the equine endometrium (*Petersen* et al. 2015). Dormant bacteria are not sensitive to antibiotics, but following confirmed activation with bActivate®, evident by a positive culture, mares can successfully be treated with intrauterine infusion of antibiotics. Fertility data from controlled studies are however, needed to confirm claims of improved fertility following treatment.

Immune-modulators

The immune response of the equine endometrium has been investigated following bacterial inoculation as well as following insemination (*Christoffersen* et al. 2012, *Woodward* et al. 2013). Treatment protocols aimed at restoring a normal immune response in susceptible mares after bacterial infection and/or breeding have been reported.

Corticosteroid

Several studies support a positive clinical effect of corticosteroids on persistent breeding-induced endometritis (PBIE). A single dose of dexamethasone (50 mg at the time of breeding) was found to improve pregnancy rates in mares with more than 3 risk factors for susceptibility to PBIE (*Bucca* et al. 2008). Researchers from Belgium did not observe a positive effect of treatment with 10 mg or 20 mg of dexamethasone 6–12 hours after AI in a large group of unclassified mares (*Vandaele* et al. 2008). However, mares with a history of excessive post-breeding inflammation had significantly higher pregnancy rates when treated with acetate 9-α-prednisolone (0.1mg/kg) twice daily when compared to control cycles (*Dell'Aqua* et al. 2004). An effect of corticosteroids on the innate uterine immune response as well as the uterine environment has been reported by several authors (*Woodward* et al. 2013, *Christoffersen* et al. 2012, *Arlas* et al. 2015). Although the immune modulation appears to favor resolution of inflammation, it does not mimic that of resistant mares.

Non-steroid anti-inflammatory drugs (NSAID)

Because of its modulating effect on inflammation, treatment of susceptible mares with NSAIDs has been studied (*Rojer* and *Aurich* 2010). Oral administration of Vedaprofen (2 mg/kg) the day before AI, and 1 mg/kg twice daily until one day after ovulation, had no effect on fluid accumulation or uterine cytology, but resulted in a higher pregnancy rates. It should be noted that the mares were also treated with oxytocin (20 IU) three times per day. More research is needed to determine the potential value of this treatment protocol.

Bacterial Cell-Wall Extracts

Cell wall extracts of Mycobacterium Phlei (MCWE) as well as Propionibacterium Acnes have been investigated regarding their effect on the uterine immune system as well as reproductive performance. *Fumoso* et al. (2003) found that MCWE treatment of susceptible mares at the time of breeding resulted in an endometrial immune environment similar to that of resistant mares at 24 hours after AI. In a follow-up study, the authors concluded that MCWE treatment was effective in eliminating inoculated bacteria from the uterus in 70% of treated mares at 7 days after infusion (*Rogan* et al. 2007). In another report by *Christoffersen* et al. (2012), studying the immune response between 3 and 72 hours after intrauterine inoculation of E. Coli, cytokine expression in MCWE treated mares was not different from untreated mares, but mRNA expression of SAA was suppressed in treated mares. Clinically, MCWE had a favorable effect in the clearance of pathogens and fluid retention (*Christoffersen* et al. 2012). Studying the immune response to semen, *Woodward* et al. (2013) found that MCWE down regulated mRNA expression of IL-1 in susceptible mares at 6 hours after AI, supporting previous observations by *Fumoso* et al (2007). A comprehensive clinical study suggested that treatment of problem mares with Propionibacterium Acnes extract (Settle®) resulted in a 10% increase in pregnancy rates compared to untreated controls (*Rohrbach* et al. 2006). However, the mares received additional treatments and the effect of stallion fertility was not considered under the condition of the study.

Plasma

Intrauterine infusion of autologous or heterologous plasma has been used in the past to treat mares with infectious endometritis (*Asbury* 1984). The rationale for the treatment was to add immunoglobulins and complement to assist the mares in eliminating pathogens from the uterus. Supplementation of fresh or cryopreserved PMNs into the uterine lumen in mares with persistent endometritis has also been proposed as an alternative treatment to antibiotics (*Zerbe* et al. 2003, *Mattos* et al. 1999, *Neves* et al. 2007). More recent use of plasma products has been directed towards immunomodulation rather than elimination of pathogens from the uterus. Platelet Rich Plasma (PRP) was shown to modulate the uterine inflammatory response to semen (*Reghini* et al. 2016, *Segabinazzi* et al. 2017), including mRNA down regulation of pro-inflammatory cytokines and NO in one study (*Metcalf* et al. 2012). The downregulation of NO was initially viewed as promising, since an upregulation of NO-synthase and accumulation of NO in uterine fluid in susceptible mares had been proposed as a possible mechanism for impaired uterine contractility in susceptible mares (*Alghamdi* et al. 2005, *Woodward* et al. 2013). However, subsequent studies could not confirm that PRP caused a consistent downregulation of the gene for NO-synthase or NO (*Reghini* et al. 2016, *Troedsson*, unpublished observation). Nevertheless, clinical reports have been encouraging, suggesting improved pregnancy rates in mares treated with PRP (*Metcalf* 2014, *Segabinazzi* et al. 2017). The protocol for treatment with PRP entails separation of 180 mL of whole blood by a special centrifugation system (Angel Cytomedix, Inc.; Gaithersburg, MD), followed by resuspension of the PRP in 10 mL plasma succeeding uterine infusion 24–36 hours prior to breeding.

Lactoferrin

Infectious endometritis has been associated with endometrial expression of lactoferrin in broodmares (*Christoffersen* and *Nielsen* 2015). A recent study in our laboratory (*Fedorka* et al. unpublished) showed that human recombinant lactoferrin (hrLF), is safe to administer in the equine uterus and modulates breeding induced inflammation through a decreased in PMNs, as well as an upregulation of the modulatory cytokine IL-1RN and a down regulation of IFN . It was concluded that intrauterine treatment with 250 ug/mL hrLF may assist susceptible mares to resolve the breeding induced inflammation in a timely fashion. Clinical trials are needed to confirm this hypothesis.

Ecbolics

The administration of ecbolic drugs after breeding is effective in overcoming impaired myometrial contractility in susceptible mares (*LeBlanc* et al. 1994, *Troedsson* 1995, *Troedsson* et al. 2005).

Oxytocin

Generally, low doses of oxytocin appear to be more effective than high doses (*Campbell* and *England* 2002). A common treatment protocol is 10–20 IU of oxytocin 4–6 hours after breeding, repeated every 6–8 hours until the intraluminal fluid has disappeared. The half-life of oxytocin is relatively short, resulting in approximately 50 minutes of myoelectric activity after the administration of 10 IU (*Madill* et al. 2002).

Carbetocin

Carbetocin is a long acting oxytocin analogue with an extended half-life after intravenous administration of 0.175 mg IV (*Schramme* et al. 2008). Limited data is available on the efficacy of carbetocin versus oxytocin.

PGF2a

PGF2α has considerably longer duration on uterine contractility compared to oxytocin (*Troedsson* et al. 2001). Treatment is not recommended after ovulation, since PGF2α and its analogues can cause a delay in the formation of a functional CL when administered within 2 days after ovulation (*Troedsson* et al. 2001). It is the authors' observation that luteolytic doses of PGF2α are excessive and may cause myometrial "cramp" initially, rather than a physiological contraction that would be more suitable to remove fluid from the uterus. A suitable dose of PGF2α and its analogues for treatment of equine endometritis has not been established. In severe cases of persistent breeding induced endometritis, ecbolic treatment is often combined with uterine lavage with 1–2 L of buffered saline 6–12 hours after breeding (*LeBlanc* and *McKinnon* 2011).

Social interaction with a stallion: Social interaction with a stallion may facilitate normal uterine clearance following breeding. Audio, visual and physical exposure of mares to a stallion stimulated pituitary oxytocin release and caused uterine contractions (*Madill* et al. 2000). This observation has been confirmed in a subsequent report (*Lyle* et al. 2014). Housing susceptible mares close to a tease stallion after breeding may therefore enhance normal uterine activity and clearance.

Other

Uterine lavage

Infusion of 1–2L buffered saline solution or LRS at 6 hours after breeding, or prior to treatment with antibiotics in cases of chronic infectious endometritis, is effective in removing accumulated fluid and inflammatory products from the uterus. The uterine lavage is typically repeated until the recovered effluent fluid is clear. The treatment is often combined with an ecbolic drug in order to facilitate recovery of the infused fluid (*Troedsson* et al. 1995, *Mattos* et al. 1999, *LeBlanc* and *McKinnon* 2011).

Stem cells

The use of mesenchymal autologous stem cells and autologous conditioned serum has been explored in experimental models as potential treatment alternatives for susceptible mares and mares with degenerative endometrosis (*Ferris* et al. 2014, *Mambelli* et al. 2014, *Corradetti* 2014, Alvarenga et al. 2016). A modulation of the inflammatory response to semen has been reported as well as indication that regenerative treatment strategies have the potentials to restore degenerative changes to the endometrium. More research is expected in this area.

Additional

In addition to the mentioned treatments, numerous agents have been used to treat equine endometritis, including dimethyl sulfoxide (DMSO), kerosene, magnesium sulphate, Streptococcus filtrate, and dilute disinfectants (chlorhexidine, povidone-iodine). Reports on the efficacy of these agents is anecdotal, and it should be kept in mind that many are irritant to the endometrium and may cause more harm than good if not used with great restriction.

Conclusion

A variety of non-antibiotic treatment options are available to the clinician, but only a few have been tested and proven beneficial under controlled conditions. The clinician should at a minimum have sufficient information on safety of the treatment and its effect on the endometrium before implementing a treatment regimen. It should also be remembered that semen is the best single treatment of infertility, and only 10–15% of brood mares need help to assist the uterus to provide a healthy environment after breeding.

Conflict of interest

None

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