Persistent Mating-Induced Endometritis

Lisa Metcalf, MS, DVM, DACT

Take Home Message: Persistent mating-induced endometritis in mares can often be managed effectively by using a combination of pharmaceutical agents, immunomodulation, and/or anatomical correction.

Author’s address—Honahlee, PC, 14005 S.W. Tooze Road, Sherwood, OR 97140; e-mail: honahlee@imagina.com

I. INTRODUCTION

Persistent endometritis in the mare has been categorized into the following conditions:1
1. Sexually transmitted disease
2. Chronic infectious endometritis
3. Persistent mating induced endometritis
4. Chronic degenerative endometritis (endometrosis)

Although the etiology may differ, all of the above conditions may contribute to persistent mating-induced endometritis (PMIE), which in turn, poses a significant threat to fertility.

Mares that suffer from persistent mating-induced endometritis are referred to as “PMIE mares”, “susceptible” mares, “fluid poolers”, and “DUC” (delayed uterine clearance) mares. This condition can be a result of either overproduction of intraluminal uterine fluid or inability to clear the fluid, or a combination of both. Unlike “resistant” mares that are capable of rapidly clearing inflammatory byproducts and fluid that result from insemination, these susceptible mares represent a population that fails to clear postmating fluid within the normal time period of 6-12 hours following breeding,2 thus leaving an unfavorable uterine environment for embryo survival.3

The etiology of PMIE is multi-faceted; impaired physical and physiological processes both play a role. Uterine defense mechanisms, endometrial histarchitecture and uterine anatomy are taken into consideration in management of the condition. All mares respond to the uterine deposition of spermatozoa and bacteria with the development of a physiologic endometritis, characterized by a rapid influx of polymorphonuclear neutrophils (PMNs). The activation of PMNs triggers the release of prostaglandin F2alpha that in turn causes myometrial contractions. The normal mare’s uterus responds by eliminating excess spermatozoa and inflammatory byproducts within 24 hours of contamination; the DUC mare’s does not. The DUC mare’s uterus often feels edematous and lacks tone. With age and repeated pregnancies, supportive ligaments of the reproductive tract weaken and some mares develop a heavy pendulous uterus that settles in a dependent position well over the pelvic brim. It appears that fluid is not as easily expelled under these conditions. As well, the myoelectrical physiologic process is impaired in susceptible mares and fluid is retained, thereby stimulating further influx of inflammatory cells. This defective myometrial contractility, coupled with poor reproductive conformation, age-related vascular, glandular and lymphatic changes to the endometrium, and weakened mucocilliary clearance of debris, contributes to both chronic endometritis and delayed uterine clearance in the susceptible mare.

Mares with pathological conditions of the cervix are also at risk of mating-induced DUC. Age or injury-related fibrosis, intraluminal adhesions or congenital abnormalities of the mare’s cervix can be associated with failure to clear fluid.

The diagnosis of DUC is based on an ultrasound exam that shows intraluminal fluid that persists in the uterus for > 12 hours following insemination. Mares that are predisposed to this condition may demonstrate an abnormal pattern of edema during estrus. Excessive edema (Grade IV on a scale of 1-IV) and/or hypoechoic intraluminal fluid visible on ultrasonographic examination prior to ovulation suggests that a mare is likely to experience DUC following mating.4

These DUC mares represent a considerable source of reproductive inefficiency and cost within the equine breeding industry. It has been estimated that as many as 10-15% of all broodmares develop this pathological response to the intrauterine deposition4 of spermatozoa.5 Many of these valuable mares face early retirement from the breeding population if they cannot be successfully treated.

The management of DUC depends on its etiology. Therapeutic options target improvement of reproductive anatomy, physiological function, immune defense and blood flow.
II. ANATOMICAL CORRECTION

Poor perineal conformation can be secondary to weight loss, age, parity or a low body condition score, especially in heavily lactating mares. Improved perineal conformation may contribute to optimized reproductive efficiency, especially in older mares.

There are means other than weight gain to improve conformation of the external genitalia of the mare. Placement of a simple Caslick’s procedure or reconstruction of the perineal body using a Gadd or Pouret technique may prevent repeated inoculation of the cervix and endometrium. However, these surgeries alone are not likely to correct DUC, for gravity still pulls the pluriparous uterus over the pelvis in affected mares.

Uteropexy, on the other hand, lifts the ventrad-angled uterus dorsad and can be performed through laparoscopic imbrication of the mesometrium. Following this surgery on 5 pluriparous barren mares, the authors reported that the surgery was successful in returning the uterus to a normal horizontal position in all 5 mares and 3/5 mares became pregnant in the same year without receiving other treatment.6

Correction of cervical abnormalities can also improve pregnancy rates in these compromised mares. The use of a prostaglandin E1 analogue, misoprostol,4 has been shown to be effective,4 for 30 minutes-2 hours, for inducing mild cervical dilation. Tablet(s) (200ug) may be inserted directly into the distal cervical os, and/or pulverized and mixed into a sterile lubricant for application on the external cervix. There have also been anecdotal reports of improvement in cervical dilation using topical Buscopan8. In the author’s experience, patient and persistent manual dilation can be equally effective in cervical dilation. In mares that appear to have cervical incompetence and/or luminal adhesions (secondary to trauma during foaling, breeding or iatrogenic injury) surgical correction may be explored. In 2/3 mares undergoing a cervical wedge resection for correction of pyometra, not only did the pyometra resolve, but also embryos were later recovered.7

III. UTERINE LAVAGE

Dilution and physical removal of inflammatory byproducts can be accomplished with uterine irrigation, beginning as early as 4 hours after insemination, without deleterious effects on pregnancy rates.8 As well, uterine lavage can also be performed safely 1 hour prior to insemination.9 Serial liters of sterile fluid are introduced into the uterus through a Foley-type catheter and then immediately removed. This procedure is repeated until recovered effluent is clear. Lactated Ringers Solution (LRS) appears to be the fluid of choice, in comparison to other irrigation fluids, because it appears to be associated with significantly less neutrophil migration into the uterus following infusion (Miller, C unpublished).

IV. ECBOLIC DRUGS

By far, the most common treatment for DUC in mares involves the use of ecobic agents as early as 4 hours after breeding. Administration of these drugs has shown to be effective in promoting uterine clearance in compromised mares.10-12 Small doses of oxytocin (5-25 IU) increase intrauterine pressure and physical clearance of postbreeding uterine fluid and debris.13 Doses of oxytocin that exceed 25 IU have been associated with a decrease in pregnancy rate,14 possibly due to a change in the contractile pattern of the uterus, resulting in ineffective fluid expulsion.

In some affected mares, the recommended small doses of oxytocin are ineffective in uterine clearance. Explanations for the failure to respond to oxytocin may include the dependent position of the uterus relative to the pelvic brim, a closed or damaged cervix, oxytocin receptor unresponsiveness, and/or the short duration of effect of oxytocin. Treatment with a prostaglandin analogue, cloprostenol (250ug i.m.) has been shown to provide a significantly longer duration of uterine contraction16,17 and has been effective in some of these mares that fail to respond appropriately to treatment with oxytocin.4

However, the use of cloprostenol as an ecobic agent carries its own risks in mares. Some mares respond to even small doses of cloprostenol administration with side effects such as sweating, abdominal discomfort and diarrhea. Although these effects are self-limiting and of short duration, they are undesirable. More importantly, studies have shown that cloprostenol can be used only during a very small window of time in the periovulatory period without adversely affecting the size of the corpus luteum, progesterone levels, and pregnancy rates.18-20

Carbetocin, an oxytocin analogue with a half-life 4X as long as oxytocin, has been recommended as a treatment for mares with delayed uterine clearance that fail to respond to other ebolic agents.3,21 In women, carbetocin has been shown to be effective in both the prevention and treatment of postpartum hemorrhage. In horses, following IV administration of 0.175 mg carbetocin, Schramme et al22 reported that the half-life of carbetocin is greater than 2X the half-life reported for oxytocin (17.2 versus 6.8 minutes, respectively). In a study that compared administration of oxytocin (10 IU IV) and carbetocin (0.280 mg IM) in mares 7 days postovulation, it was reported that although plasma oxytocin concentration were not different between treatments, the peak concentration appeared almost 20 minutes later in mares that received carbetocin. Furthermore, the duration of peak concentration was almost three-fold higher in the mares that received carbetocin than those that received oxytocin.24

In addition to its longer half-life, carbetocin may be an effective ecobic agent through other mechanisms. It appears to elicit a different contractile pattern than oxytocin in the mare. The pattern of propagation of uterine contraction in response to oxytocin has been shown to be different between reproductively sound mares versus mares with delayed uterine clearance.25
Carbetocin may induce contractions that are more effective in uterine drainage. In an unpublished clinical study that compared the effectiveness of oxytocin and carbetocin on the removal of uterine fluid in mares susceptible to persistent postbreeding endometritis, persistent fluid was successfully cleared from the uterus using oxytocin (10-20 IU IM) alone in 24% (9/37) of the estrous cycles examined. In those mares that failed to respond to oxytocin, uterine fluid was successfully cleared in 100% (28/28) of the cycles in which carbetocin (0.175 mg IM) was administered. Furthermore, in a group mares (n=15) that had a history of failure to respond to multiple doses of oxytocin to clear postmating fluid, carbetocin alone (0.175 mg IM) was effective in clearing the fluid on the subsequent cycle. In these studies, pregnancy rates were higher in DUC mares that were successfully treated with carbetocin versus oxytocin (51% and 19% respectively, P>.01).

V. MUCOLYPTICS/ BIOFILM DISRUPTION

The excessive production of mucus has been demonstrated to be detrimental to uterine defense mechanisms and mare fertility; it may be a component of the pathological processes in DUC. Common mucolytic therapy includes the use of either N-acetylcysteine (ACE) or dimethyl sulfoxide (DMSO). Researchers have reported pregnancy rates > 80% in a group of barren mares with a history of endometritis that were treated with an intrauterine infusion of a 0.6% ACE solution (30 ml 20% ACE solution diluted to 180 ml with sterile saline), followed 4-6 hours later by oxytocin. Improved pregnancy rates have been reported following 30% DMSO infusion. The mechanisms of action of these drugs may not be similar. And although the results look promising, they have not been well studied in a population of mares with persistent mating induced endometritis (PMIE) as opposed to chronic endometritis. Also, the production of endometrial biofilms by bacteria and fungi represents a method of antimicrobial resistance that is often difficult to detect and clear. Endometrial and aspirate swabs are often falsely negative and only molecular diagnosis through PCR amplification techniques have been reliable in the diagnosis of bacteria sequestered in biofilms. Although not directly causing PMIE, the production of biofilms may also contribute to chronic pathological conditions within the endometrium. The use of buffered chelating agents such as Tris-EDTA, either alone or in combination with antibiotics, have been shown, at least in vitro, to have the ability to disrupt the production of biofilms by certain bacteria associated with pathological conditions and chronic infertility in the mare.

VI. IMMUNOMODULATION-STIMULANTS AND SUPPRESSANTS

Although the immune system of mares susceptible to endometritis appears to function normally in the initial reaction to the presence of spermatozoa, the inability to physically clear postbreeding fluid ultimately leads to impaired phagocytic function of neutrophils, defective mucociliary function and compromised lymphatic drainage of the uterus. Immunomodulation has shown promising results. In a group of barren mares diagnosed with persistent endometritis, pregnancy rates were significantly increased after Propionibacterium acnes administration was incorporated into their conventional treatment. Another group investigating the expression of specific inflammatory biomarkers found that administration of mycobacterium cell wall extract 24 hours prior to insemination lowered the expression of IL-1B mRNA in the endometrium of susceptible mares in comparison to untreated mares. Along similar lines, Ferris et al reported that autologous conditioned serum and bone-derived culture expanded MSCs were capable of modulating the uterine inflammatory response to spermatozoa in normal mares, and suggested that this effect may prove beneficial in susceptible mares as well.

The use of intrauterine autologous plasma as an immunomodulator has also been investigated. Specifically it was predicted that plasma would enhance opsonization through the activation of complement, and thereby improve pregnancy rates in susceptible mares. Although some labs reported enhanced pregnancy rates with plasma treatment, others found no effect on pregnancy rates, and the treatment was no longer widely used.

However, platelet-rich plasma concentrates (PRP) have gained considerable attention in recent years, particularly in the fields of soft tissue injury, fracture and wound repair, and regenerative therapies, in that they appear to target specific inflammatory biomarkers to manage PMIE. The term, PRP, by definition, refers to an enriched concentration of platelets (2-10X above baseline) in autologous plasma. Platelets contain alpha-granules that, upon activation, secrete a variety of bioactive molecules with regenerative capacity in the form of growth factors, cytokines, and chemokines. These factors are responsible for recruitment, proliferation and maturation of cells in repair of damaged tissue.

Recent research has shown that susceptible mares treated with an intrauterine infusion of PRP, show a down-regulation of mRNA expression of endometrial pro-inflammatory cytokines, IL-1b, IL-6, IL-8 and iNOS following semen deposition in comparison to untreated controls. Additionally, in PRP treated-vs-untreated mares, pregnancy rates were significantly higher (67% vs 19% respectively; p=0.004) and retention of intraluminal fluid was less (22% vs 100%; p=0.0001). It thus appears that, in mares susceptible to PMIE, intrauterine infusion of autologous PRP is associated with a lower incidence of delayed uterine clearance following insemination and improved pregnancy rates (in press). These initial results are promising and future investigation is currently underway.

Pharmacological agents that suppress the immune response have been shown to be beneficial in the management of DUC, but the type and amount of drug, as well as the timing of administration relative to ovulation, appear to be critical to their effectiveness.

The use of nonsteroidal anti-inflammatory agents (NSAIDS) in the moderation of DUC has not been well investigated, but it has been shown that mares treated with phenylbutazone have a decrease in uterine clearance. It is reasonable to suspect that
the suppression of cyclooxygenase enzymes by NSAIDS would negatively affect both uterine contraction and the ovulation cascade. In fact, periovulatory use of flunixin meglamine has been associated with anovulatory cycles in the mare. Therefore the use of NSAIDS in the periovulatory period should be limited.

On the other hand, the use of synthetic corticosteroids in the treatment of postmating endometritis appears more promising. Their effectiveness is dependent on type of drug, dose and timing of administration with respect to ovulation. Bucea et al reported that in mares with a history of DUC, a single dose of dexamethasone (50 mg i.v.) administered at the time of breeding, coupled with other postbreeding therapeutic regimens, resulted in significantly higher pregnancy rates. However, Vandaele et al found no difference in pregnancy rates in DUC mares following the administration of 10-20 mg dexamethasone i.m. 6-12 hours after insemination. Because dexamethasone has been shown to inhibit LH, suppress the LH-surge and result in significantly higher numbers of anovulatory cycles in the mare, many researchers recommend the judicious use of dexamethasone, at low dose and only postovulation. Prednisolone acetate does not appear to exert the same anovulatory effect as dexamethasone, and when administered for 4 days to mares with a history of endometritis, beginning 48 hours before breeding (0.1 mg/kg po q 12h), pregnancy rates were significantly improved in mares with a history of DUC.

Lastly, uterine lavage media, containing 10% DMSO, is recommended by many clinicians to combat fluid retention and endometritis. DMSO functions not only as a powerful antioxidant, but may have a mucolytic effect or provide a mild chemical curettage as well. For the treatment of DUC that does not respond well to ecobic drugs, this author recommends uterine lavage of 1-2 liters of 10% DMSO in Lactated Ringers Solution (LRS), followed by serial infusions of liters LRS until the recovered effluent fluid is clear.

VII. ADDITIONAL THERAPY AND MANAGEMENT TOOLS

The use of acupuncture in the management of DUC appears to be a popular adjunctive therapy among some practitioners but its effectiveness has not been evaluated in a controlled study. However, in a group of 44 barren mares with a history of DUC that were treated with acupuncture in combination with other conventional therapies, significant resolution of fluid was reported, as well as an 81% pregnancy rate. Although these results are encouraging, the well-known effect of acupuncture in stimulating B-endorphin, which in turn, may suppress LH levels, and thus elicit anovulatory cycles, warrants further investigation.

Exercise has also been reported to be beneficial to mares that retain fluid after breeding. Although it is well documented that postfoaling mares undergo uterine involution more rapidly if on pasture rather than stalled, the effect of exercise on fluid retention in DUC mares has not been scientifically evaluated. Moreover, exercise of mares has been reported to result in decreased embryo size, quality and recovery rate, as well as lengthening the interval between ovulations. Likely, the duration and intensity of exercise affects the outcome of studies.

Lastly, many breeders believe that the presence and use of a stallion in a breeding program not only enhances pregnancy rates, but also may be beneficial in treating mares that retain fluid. In one study, however, authors found that teasing failed to affect the number, amplitude or duration of uterine contractions in mares. Still another group reported that endogenous oxytocin is released in response to stallion teasing, which in turn, results in an increase in intrauterine pressure during the preovulatory phase in mare. An audiotape of stallion vocalizations has been found to be equally effective in inducing mares to demonstrate signs of estrous behavior as a live stallion. The effect of the taped stallion vocalizations on intrauterine pressure and contractility, however, has not been evaluated.

VIII. CONCLUSION

Although PMIE is a significant threat to mare fertility and a leading cause of economic loss within the equine breeding industry, there are many tools to manage this condition and prolong offspring production in susceptible mares.

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