

Therapeutic considerations for mating-induced endometritis

M. H. T. Troedsson

Department of Clinical and Population Sciences, College of Veterinary Medicine, University of Minnesota

Summary

A transient mating-induced endometritis is most likely physiological in the mare, serving to remove excess spermatozoa, seminal plasma, and contaminants from the uterus. However, the inflammatory reaction has to be resolved and inflammatory products cleared from the uterus prior to embryonal descent into the uterine lumen. Mares that fail to clear a semen-induced inflammation from the uterus develop a persistent mating-induced endometritis which may result in infertility. If susceptibility to persistent mating-induced endometritis is suspected, the mare should be monitored by transrectal ultrasonography for intrauterine fluid accumulation at 6–12 hours intervals after breeding. Treatment should be aimed at assisting the uterus to physically clear contaminants and inflammatory products. Post-mating uterine lavage and/or the use of uterotonic drugs are recommended at 6–12 hours after breeding in mares susceptible to persistent endometritis.

keywords: equine, endometritis, treatment

Therapeutische Erwägungen zur equinen Endometritis, hervorgerufen durch die Belegung

Eine transiente, durch die Belegung hervorgerufene Endometritis ist bei der Stute ein physiologisches Ereignis. Sie dient der Eliminierung von Spermien, Seminalplasma und Kontaminationsprodukten aus dem Uterus. Die entzündliche Reaktion muß jedoch beendet und alle Entzündungsprodukte aus dem Uterus entfernt sein, bevor der Konzeptus das Uterustumen erreicht. Stuten, die nicht in der Lage sind, diesen Reinigungsprozeß zu vollziehen, entwickeln eine persistierende durch die Belegung hervorgerufene Endometritis, mit möglicherweise daraus resultierender Infertilität. Stuten, bei denen eine derartige Endometritisanfälligkeit zu vermuten ist, sollten in 6–12 Stunden Intervallen nach der Belegung ultrasonographisch in Hinblick auf eine intrauterine Flüssigkeitsansammlung überprüft werden. Die Behandlung besteht in einer Unterstützung der physiologischen Reinigungsmechanismen: chirurgische Korrektur von Defekten des äußeren Genitale, gezielte antibakterielle/antimykotische Behandlung, Minimierung der Kontamination durch möglichst präzise Terminierung der Ovulation und Reduzierung der Belegungen auf eine pro Zyklus. Zusätzlich sollte eine Uteruslavage 6–12 Stunden nach der Belegung möglicherweise in Kombination mit Oxytocin durchgeführt werden.

Schlüsselwörter: Pferd, Endometritis, Behandlung

Introduction

Endometritis is a major cause of subfertility in the mare and has a significant economic impact on the equine industry (*Dimmock 1939; Collins, 1964; Bain, 1966; Hughes et al., 1966; Ricketts 1975; Gordon and Sartin, 1978; Kenney, 1978; Doig et al., 1981; de la Conch-Bermejillo and Kennedy, 1982; Traub-Dargatz et al., 1991*). Based on the current understanding of its etiology and pathophysiology, endometritis should be considered as a multifactorial disease with at least four different causes: (1) sexually transmitted diseases, (2) chronic infectious endometritis, (3) persisting mating-induced endometritis, and (4) endometrosis (chronic degenerative endometritis). Sexually transmitted diseases and chronic infectious endometritis are often diagnosed first after the invading microorganism already has adhered to the endometrial epithelium and started its replication in the uterus. Similar to infectious diseases in other organ systems, infections in the female reproductive tract (sexually transmitted endometritis and chronic infectious endometritis) are most effectively treated with an appropriate anti-

microbial. In contrast to infectious endometritis, mating-induced endometritis has a known starting point and treatment can therefore, be initiated before the infection or inflammation has established itself in the endometrium. This report will review the therapeutic aspects and pathophysiology (as it relates to therapy) of mating-induced endometritis.

Pathophysiology of mating-induced endometritis

Regardless of if mares are bred by natural service or by artificial insemination, semen is deposited directly into the uterus. This provides an excellent opportunity for uterine contamination with bacteria. In addition, recent reports have shown that spermatozoa without bacterial contamination induce an uterine inflammatory response (*Kotilainen et al., 1994; Troedsson, 1995; Troedsson et al., 1995a*). Rather than considering a transient post-mating endometritis as a pathological condition, mating-induced endometritis is

likely to be a physiological reaction that serve to remove excess spermatozoa, seminal plasma, and possible bacterial contamination from the uterus before the embryo descends into the uterine lumen. However, the uterus must be capable of clearing the inflammation within a few days after breeding/conception in order for a pregnancy to develop normally. Natural resistance to experimentally induced persistent uterine infections was demonstrated by *Hughes and Loy (1969)*. Others found that bacterial infusions with *Streptococcus zooepidemicus* or *Pseudomonas* organisms more often resulted in persistent uterine infection in multiparous and barren mares compared to nulliparous mares (*Peterson et al., 1969*). Based on these studies, mares have been classified as either susceptible or resistant to persistent or chronic endometritis. Mares that are susceptible to persistent bacterial endometritis are likely to be susceptible to persistent mating-induced endometritis (*Troedsson, 1997*). Local components of the uterine defense mechanisms are responsible for the rapid clearance of an infection or mating-induced inflammation in mares with normal resistance to persistent endometritis (Fig. 1; *Watson, 1988; Troedsson, 1994*).

Uterine defense mechanisms: Polymorphonuclear neutrophils (PMNs) are present in the uterine lumen within 30 minutes after mating (*Katila, 1995*). Both bacteria and spermatozoa stimulate PMN-chemotaxis into the uterus (*Blue et al., 1984; Pycock and Allen, 1988; Troedsson et al., 1993a; Troedsson et al., 1995a*). Several mediators, including

PGF_{2α} are released during the course of the inflammation (*Schalm, 1986*). In addition to being an inflammatory mediator, PGF_{2α} causes myometrial contractions. It has been suggested that PGF_{2α}-induced myometrial contractions are responsible for the rapid mechanical clearance of inflammatory products from the uterus (*Troedsson, 1995*). Mares that fail to clear a mating-induced inflammation from the uterus develop a persistent endometritis. An impaired physical clearance has been demonstrated in mares with increased susceptibility to persistent endometritis (*Evans et al., 1987; Allen and Pycock, 1988; Troedsson and Liu, 1991; LeBlanc et al., 1994a*). It has also been shown that delayed uterine clearance in these mares is due to an impaired myometrial activity in response to inflammation (*Troedsson et al., 1993b*). In contrast to the transient post mating endometritis, persistent mating-induced endometritis has severe consequences for the fertility of affected mares. A persistent inflammation often results in premature luteolysis and embryonic loss in response to increased PGF_{2α} concentrations. The inflammation could also interfere directly with the survival of an embryo (*Smith et al., 1971; Waites and Bell, 1982; Heuer et al., 1993*). Proteolytic enzymes, oxygen radicals and other toxic products are released during PMN-phagocytosis. These products must be eliminated from the uterus in a timely fashion in order to allow embryonic survival when the embryo descends into the uterus.

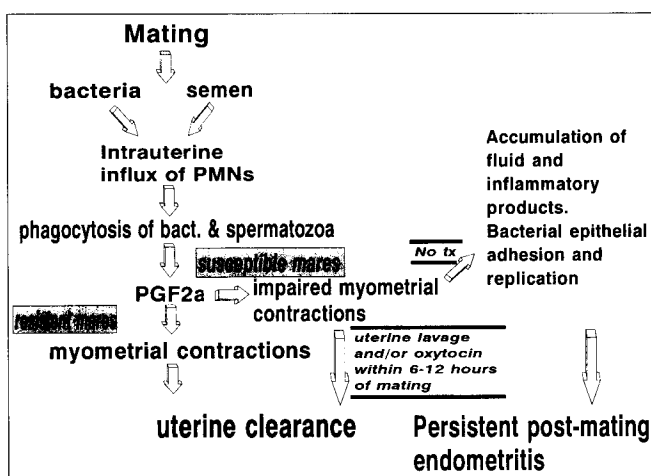


Fig. 1: Uterine response to semen and bacterial contamination during breeding. Dysfunctional uterine contractions in response to inflammation in mares susceptible to persistent endometritis result in an impaired uterine clearance. Treatments that assist the uterus to physically clear contaminants and inflammatory products may enhance fertility in affected mares.

Die Reaktion des Uterus auf Samen und bakterielle Kontamination nach der Bedeckung. Bei endometritisanfälligen Stuten resultiert eine gestörte uterine Clearance aus einer insuffizienten uterinen Kontraktion als Antwort auf die Entzündung. Behandlungen, die die physikalische Reinigung von Kontaminationen und Entzündungsprodukten unterstützen, können die Fertilität der betroffenen Stuten erhöhen.

Clinical signs of persistent mating-induced endometritis

Clinically, mares with mating-induced endometritis accumulate fluid within the uterine lumen following breeding. Mucrocrine endometrial secretion and edema is normal during estrus (*Tunon et al., 1995*), but the secretion should be effectively drained via lymphatics and the cervix. Both these draining mechanisms are dependent on functional myometrial contractions (*Guyton, 1991*). *LeBlanc et al. (1995)* observed that mares with delayed uterine clearance had dysfunctional lymphatic clearance. In addition, mares that fail to relax the cervix during estrus are likely to develop a persistent endometritis after mating. A diagnostic technique, using scintigraphy to monitor uterine clearance has been developed to identify mares with delayed uterine clearance (*LeBlanc et al. 1994a*). It was concluded that in order for a mare to be considered normal, >50% of inoculated radiocolloids need to be cleared from the uterus within 2 hours of the inoculation. Unfortunately, scintigraphy is not readily available in all brood mare practices, and many mares that develop a persistent endometritis after mating are free of uterine inflammation prior to mating. It may therefore, be difficult to identify susceptible mares before they have been bred. The presence of free intraluminal fluid prior to breeding strongly suggests susceptibility to persistent endometritis (*Pycock and Newcombe, 1996*). Furthermore, a detailed breeding history and a careful reproductive examination prior to breeding may reveal predisposing conditions. A mare with a history of chronic infectious endometritis is

likely to develop persistent mating-induced endometritis. A correlation between severe pathological findings on a uterine biopsy and susceptibility to persistent endometritis has been reported (Troedsson *et al.*, 1993c). Mares with delayed uterine clearance often suffer from visceroptosis with a significant forward tilt of the uterus when it expands over the brim of the pelvis (LeBlanc, personal communication). This may also contribute to accumulation of fluid and inflammatory products following mating. If susceptibility to persistent mating-induced endometritis is suspected, the mare should be closely monitored by transrectal ultrasonography for intrauterine fluid accumulation at 6–12 hours intervals after breeding. Normal mares may retain fluid in the uterine lumen up to 6 hours after mating. However, if intrauterine fluid is present at 12 hours or more after mating, the mare should be considered to have a persistent mating-induced endometritis.

Treatment of mares with persistent mating-induced endometritis

Treatment of mares that are susceptible to persistent mating-induced endometritis should be aimed at assisting the uterus to physically clear contaminants and inflammatory products (Fig 1). Before breeding a mare that is susceptible to persistent post-mating endometritis, the reproductive tract has to be free from predisposing factors and infection. This can be achieved by surgical corrections of defective external genital barriers and an effective treatment of existing bacterial or fungal endometritis. The uterus should be confirmed free from infection, based on cytology and culture before the mare is bred. Susceptible mares should, if possible be bred no more than once per cycle as close to ovulation as possible. Large-volume uterine lavage at 6 to 12 hours after mating will effectively aid the mare to clear inflammatory products from the uterus without interfering with conception (Brinsko *et al.*, 1991; Troedsson *et al.*, 1995b). Following thorough cleansing of the perineum, a uterine flushing catheter (30 French, 80 cm long, with a 75 ml balloon cuff¹) should be introduced through the cervix. Once the cuff is located in the uterus, it will be inflated until it effectively seals the internal cervical os. A total of 1 liter of buffered saline solution or lactated ringer solution should be infused into the uterus. Following brief transrectal massage of the uterus to ensure an even distribution of fluid in both horns, the fluid should be recovered in a bottle that allows visual examination. The lavage should be repeated until the recovered fluid is clear. A cloudy fluid is indicative of inflammatory debris. Measurement of the recovered fluid or ultrasonographic examination of the uterus will ensure that all fluid has been recovered. This is important, since the mare has an impaired ability to spontaneously clear the uterus. Uterine lavage should be performed after each mating to be effective.

¹ Bivona Inc. Gary, IN.

The use of uterotonic drugs that stimulate myometrial contractions can also assist in the clearance of inflammatory fluid from the uterus. The administration of oxytocin (20 U IM) at 4 to 8 hours after mating has been shown to effectively clear the uterus, resulting in improved pregnancy rates in susceptible mares (LeBlanc *et al.*, 1994b; LeBlanc 1994; Pycock, 1994, Rasch *et al.*, 1996). Prostaglandins have also been demonstrated to increase myometrial activity and assist in clearing the uterine lumen of contaminating products (Troedsson *et al.*, 1995b; Troedsson *et al.*, 1995c). Studies of the duration of myometrial activity following administration of oxytocin and PGF_{2α} show that 20 U of oxytocin causes 1 hour of increased myometrial activity, and that 10 mg of PGF_{2α} causes 5 hours of increased activity (Troedsson *et al.*, 1995c). However, both drugs also affected the oviductal smooth muscles in a similar way. Considerations of the duration of the effect of oxytocin and prostaglandins on both myometrial and oviductal activity should be made before these hormones are used in post-mating treatments. In a recent report, the investigators found that oxytocin was more effective than prostaglandins in clearing the uterus from radiocolloids (Combs *et al.*, 1996). Results from the study suggested that cloprostenol was more effective than PGF_{2α} and fenprostalene. However, susceptible mares responded to all uterotonins with increased clearance of radiocolloids. It appears that the efficacy and safety aspects favor oxytocin over prostaglandins in most cases. A combination of post-mating uterine lavage and oxytocin treatment is preferred by some practitioners.

Post-mating infusion with antibiotics has been used in the management of mares with persistent mating-induced endometritis (Asbury and Lyle, 1993). Although spermatozoa, rather than bacteria have been implicated as the cause of mating-induced endometritis, it was recently suggested that seminal plasma suppresses both chemotaxis and phagocytosis of equine PMNs (Scheytt and Gilbert, 1995; Troedsson *et al.*, 1995a). An initial suppressive effect of seminal plasma on PMN function may predispose the mare to develop a bacterial uterine infection after mating since semen often is contaminated with a variety of potentially pathogen microorganisms (Kenney *et al.*, 1975). Treatment of susceptible mares with either intrauterine saline lavage, PGF_{2α}, or penicillin at 12 hours after an intrauterine infusion of *Streptococcus zooepidemicus* showed that saline lavage and PGF_{2α} were equally effective to eliminate bacteria from the uterus as penicillin treatments (Troedsson *et al.*, 1995b). These results suggest that antibiotics may not be necessary, even in cases of bacterial contamination, if mares are treated with uterine lavage or uterotonins within 12 hours after mating.

In conclusion, obtaining a current breeding history and the performance of an accurate reproductive examination prior to breeding is necessary to identify individual mares that are likely to develop persistent mating-induced endometritis. Once mares are identified to be at risk of persistent endometritis following mating, ultrasonographic monitoring of intrauterine fluid accumulation and treatments that aid in uterine clearance should be employed. A rapid uterine

clearance following mating is necessary in preventing a persistent inflammation. Uterine lavage and/or oxytocin treatments are recommended between 6 and 12 hours after breeding. It must be emphasized that the majority of mares that develop a transient inflammation after mating, are fully capable of an effective uterine clearance without any assistance. Only mares with delayed uterine clearance should be treated.

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Tagung über Labordiagnostik

Kurs über Entnahme und Bearbeitung von Muskelbiopsien beim Pferd
Arbeitsgruppe Pferd und Abbott Diagnostika

25.–26. Oktober 1997, Bonn

Programm:

Tagung am 25. Oktober, 9.00–18.30 Uhr

- ▶ Desmond Leadon (Irland): Bedeutung hämatologischer Variablen für die Diagnose von Krankheiten beim Sportpferd
- ▶ Arne Lindholm (Schweden): Polycytämie als Ursache mangelhafter Leistung des Rennpferdes
- ▶ Desmond Leadon: Einsatz der Labor-diagnostik vom Jährling bis zum Rennpferd zur Beurteilung der Leistungsfähigkeit
- ▶ Hans-Peter Sallmann (Hannover): Bedeutung des oxidativen Stresses von Pferden durch körperliche Belastung und Fütterung
- ▶ Peter Bauer (Neuruppin): Muskelbiopsische Untersuchungen bei Mensch und Pferd –

Bestandteil eines komplexen diagnostischen Systems

- ▶ José Luis López Rivero (Spanien): Möglichkeiten zur Leistungsdiagnostik durch Untersuchung der Muskulatur
- ▶ Arne Lindholm: Diagnose pathologischer Zustände der Muskulatur

Kurs am 26. Oktober, 9.00–15.00 Uhr

- ▶ Optimale Technik zur Entnahme und Aufbewahrung von Muskelproben zur Diagnose von Leistungsfähigkeit und pathologischer Zustände.

Kursleiter: José Luis López Rivero und Arne Lindholm

Teilnahmegebühr: DM 200,- für die Tagung (inkl. MwSt, Tagungsband und Kaffeepausen), DM 400,- für den Kurs (begrenzte Teilnehmerzahl)

Anmeldung: schriftlich unter Beifügung eines Verrechnungsschecks an Dr. Arno Lindner, Im Eichholz 10, 53127 Bonn

Information: Telefon (02 28) 29 92 59, Fax (02 28) 28 47 61, E-Mail <arnolindnerbonn@t-online.de>

ATF-Anerkennung: 12 Stunden

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Mats H. T. Troedsson, DVM, PhD

Department of Clinical and Population Sciences
College of Veterinary Medicine
University of Minnesota. St. Paul, MN 55108

Tel: 001-612-625 6733

Fax: 001-612-625 2743

email: troed001@maroon.tc.umn.edu