Pferdeheilkunde 24 (2008) 1 (Januar/Februar) 56-60

Persistent breeding-induced endometritis

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Summary

Breeding-induced endometritis is a physiological reaction to semen. It is an important part of normal sperm transport to the oviduct as well as elimination of excess sperm from the uterus. In 10-15% of brood mares, the normal clearance mechanism fails resulting in a persistent breeding-induced endometritis with severe consequences on fertility. The cause of persistent breeding-induce endometritis is believed to be impaired myometrial activity in response to uterine inflammation. However, disruption of normal breeding activities may also contribute to the condition. Social interaction with a stallion appears to be important to normal uterine contractility after breeding. The presence of seminal plasma in an inseminate has also been shown to be of importance to normal sperm transport and elimination from the female tract, as well as in the modulation of the breeding-induced inflammation. Treatment of persistent breeding-induced endometritis has been focused on assisting the uterus to clear the inflammation in a timely fashion. Post-breeding treatments with oxytocin or prostaglandins and/or uterine lavage at 6-24 hours after breeding have been used by practitioners with good success. Alternative treatments such as the use of corticosteroids, immunostimulants, and acupuncture have recently been suggested to improve uterine clearance and fertility in mares that are susceptible to persistent breeding-induced endometritis. Regardless of the choice of treatment strategy, it is important to keep in mind that all mares develop breeding-induced endometritis after breeding, but only 10-15% of these mares develop a persistent form of the condition and would benefit from treatment.

Keywords: endometritis, equine, semen, inflammation, PMNs, reproduction

Persistierende belegungs-/besamungsinduzierte Endometritis

Die belegungs-/besamungsinduzierte Endometritis ist eine physiologische Reaktion auf den Samen und stellt einen wichtigen Bestandteil des normalen Spermatransportes zum Ovidukt sowie der Elimination überschüssigen Spermas aus dem Uterus dar. Bei 10-15 % der Zuchtstuten ist dieser Reinigungsmechanismus gestört und führt zu einer persistierenden belegungsinduzierten Endometritis mit schweren, erheblichen Konsequenzen für die Fertilität. Es wird vermutet, dass die Ursache dieser Endometritisform in einer beeinträchtigten myometrialen Aktivität infolge uteriner Entzündungsvorgänge besteht. Allerdings trägt eine Unterbrechung der normalen Zuchtaktivitäten ebenfalls zu diesen Veränderungen bei. So scheint die soziale Interaktion mit dem Hengst wichtig für eine normale uterine Kontraktilität nach dem Deckakt zu sein. Darüber hinaus konnte gezeigt werden, dass das Vorhandensein von Seminalplasma im Inseminat nicht nur für den Samentransport und die Elimination aus dem weiblichen Genitaltrakt wichtig ist, sondern auch an der Modulation der belegungsinduzierten Entzündung beteiligt ist. Therapien persistierender belegungsinduzierter Endometritiden konzentrieren sich bislang auf eine zeitnahe, den Uterus unterstützende Beseitigung des Entzündungsgeschehens. Der Einsatz von Oxytozin oder Prostaglandinen und/oder Uterusspülungen 6-24 Stunden nach dem Deckakt erzielten in der Praxis gute Erfolge. Alternative Ansätze, wie die Anwendung von Kortikosteroiden, Immunstimulanzien und Akupunktur wurden in jüngster Zeit für die Verbesserung der uterinen Selbstreinigung und der Fertilität von Stuten, die empfänglich für die Entstehung der persistierenden belegungsinduzierten Endometritis scheinen, diskutiert. Unabhängig von der Wahl der Behandlungsmethode sollte nicht außer Acht gelassen werden, dass alle Stuten nach dem Deckakt/der Insemination eine belegungsinduzierte Endometritis entwickeln., Nur 10-15 % dieser Tiere entwickeln jedoch persistierende Formen und würden somit von einer Behandlung profitieren .

Schlüsselwörter: Endometritis, Stute, Sperma, Entzündung, PMNs, Reproduktion

Introduction

In the past, endometritis was believed to exclusively be the result of bacterial contamination of the uterus (*Asbury* and *Lyle* 1993). Treatment strategies were focused on preventing bacteria from entering the uterus, and/or administration of antibiotics. *Hughes* and *Loy* (1969) demonstrated that young reproductively sound mares had natural resistance to an experimentally induced infection. They concluded that local components of uterine defense were responsible for the effective and rapid clearance of bacteria in mares with natural resistance to uterine infection. Mares that failed to spontaneously clear the uterus from bacteria were classified as susceptible to persistent endometritis. Subsequent research on uterine defense mechanisms has increased our understanding of the pathophysiology of equine endometritis. Causative agents have been identified, and we have learned to distinguish between uterine infection and a physiological breeding-induced endometritis resulting from uterine exposure to semen (*Troedsson* et al. 1995a, *Troedsson* 1999). Additionally, more effective management and treatment protocols have reduced the effect of endometritis on fertility. However, endometritis remains a major clinical problem in brood mare practice. The reasons for this may be that effective management/treatment of "susceptible" mares have resulted in maintaining these mares within our brood mare population, possibly also affecting the gene pool.

Breeding-induced endometritis

Intrauterine deposition of equine semen causes an inflammatory reaction resulting from spermatozoa (*Kotilainen* et al.

1994, *Troedsson* et al. 1995). This has also been described in other species with intrauterine deposition of semen (*Rozeboom* et al. 1998). The mechanism of the induced inflammation is similar to endometritis caused by bacteria, involving activation of the complement cascade (*Troedsson* et al. 1995a). The uterus responds quickly to an antigen with release of PMN-chemotactic mediators resulting in a rapid migration of PMNs (polymorphonuclear neutrophils) into the uterine lumen. Complement products as well as leukotriene B4 (LTB4), prostaglandin E (PGE), prostaglandin F2α (PGF2α), and IL-8 may all serve as chemoattractants for PMNs in the uterus. The complement cascade mediates a series of biologic reactions, all of which serve in the defense against a "foreign agent". They include increased vascular permeability, chemotaxis, opsonization prior to phagocytosis, activation of membrane lipases, and lysis of target organisms. Complement activity as well as isolation of complement cleavage products has been demonstrated in the equine reproductive tract (*Asbury* et al. 1982, *Watson* et al. 1987, *Troedsson* et al. 1993a).

Breeding-induced endometritis is a physiological transient reaction to semen, and it appears to be a normal process by which excess sperm and bacterial contamination is eliminated from the mares' reproductive tract (*Troedsson* et al. 1998, *Troedsson* 1999). Transport of spermatozoa from the uterus to the oviduct is completed within 4 hours after breeding, and only a small portion of the ejaculated or inseminated semen reach the oviduct (*Brinsko* et al. 1991, *Scott* et al. 1995). The rapid transport of spermatozoa to the oviduct coincides with an increased uterine activity (*Troedsson* et al. 1998). Increased myometrial contraction in response to breeding is also responsible for rapid sperm elimination from the uterus through the cervix (*Katila* et al. 2000). However, not all excess spermatozoa are removed from the uterus through this mechanism. The remaining spermatozoa are eliminated by means of other uterine clearance mechanisms, such as PMN-phagocytosis of spermatozoa (*Troedsson* et al. 1999). During breeding-induced inflammation, PGF2α is released from activated PMNs and maybe also the endometrium. The presence of PGF2α causes myometrial contractions, which aid in the removal of harmful inflammatory products that are released during PMN-phagocytosis and during programmed cell death of PMNs. This physical or mechanical uterine defense is a key factor in the prevention of persistent inflammation and endometrial damage. In mares with a functional defense system, the majority of inflammatory products are cleared from the uterus within 24 to 36 hours of contamination (*Katila*, 1995). However, in approximately 10-15% of Thoroughbred mares the system fails (*Zent* and *Troedsson* 1998). In these mares, the initial physiological inflammation becomes a pathological problem resulting in a detrimental effect on fertility (*Pycock* 1994, *Rausch* et al. 1996). If inflammation persists beyond the time when the embryo enters the uterus at 5 days after ovulation, embryonic loss will occur due to interference with the corpus luteum resulting from the inflammatory release of PGF2, or due to an incompatible inflammatory uterine environment (unpublished observations).

Persistent breeding-induced endometritis

Persistent endometritis has been shown to be the result of delayed uterine clearance of inflammatory products (*Troedsson* and *Liu* 1991, *LeBlanc* et al 1994). Using radioactive-labeled microspheres as markers, it was found that susceptible mares had an impaired uterine clearance compared to resistant mares (*Troedsson* and *Liu* 1991). Subsequent experiments that utilized electromyography (EMG) to register myometrial activity, demonstrated that the impaired uterine clearance in susceptible mares was caused by reduced myometrial activity in response to the inflammation (*Troedsson* et al. 1993b). Studies using scintigraphic measurements of intrauterine clearance of radioactive colloids further defined a delayed physical clearance in susceptible mares (*LeBlanc* et al. 1994a). Myometrial contractility was concluded to be an essential part of uterine defense mechanisms. In subsequent studies, the importance of physical uterine clearance was confirmed by the observations that administration of uterotonic drugs to mares with delayed uterine clearance resulted in normal clearance of colloids from the uterus, and treatments of mares with normal uterine clearance with prostaglandin inhibitors made them susceptible to delayed uterine clearance (*LeBlanc* et al. 1994b). Measuring isometric tension of the myometrium in normal mares and mares with delayed uterine clearance, it was suggested that mares with delayed uterine clearance have an intrinsic defect in myometrial function (*Rigby* et al. 2001). However, previous studies on uterine contractility in mares resistant and susceptible to persistent endometritis, found that the impaired myometrial activity was confined to the critical period following an induced inflammation (*Troedsson* et al. 1993b). No difference was found between susceptible and resistant mares in the absence of an inflammation. In addition, it has been shown that susceptible mares are fully capable of responding with normal contractility to ecbolic drugs such as oxytocin and PGF2α (*LeBlanc* et al. 1994b). *Alghamdi* et al. (2005) suggested that impaired uterine activity during inflammation in susceptible mares may be caused by an upregulation of inducable nitric oxide synthasase (iNOS) in inflammatory cells in the endometrium of susceptible mares. The authors also found a pronounced accumulation of NO in the uterus of susceptible mares. NO is an inflammatory mediator that moderates smooth muscle contractions. An up-regulation of NO could explain the relaxation of the myometrium that has been observed in susceptible mares in the presence of an inflammation (*Troedsson* et al. 1993b). Based on existing published data, our working hypothesis is that the presence of spermatozoa in the uterus induces an inflammation that is characterized by an influx of PMNs into the uterine lumen. Several inflammatory mediators are activated during the course of the inflammation. While PGF2α triggers uterine contractions, the presence of NO has the opposite effect. An imbalance between NO and PGF2α may be an important cause of impaired uterine activity and delayed uterine clearance in mares that develop persistent breeding-induced endometritis.

More recent observations suggest that individual stallions also could be a factor in the development of persistent breeding-induced inflammation (*Troedsson* et al. 2000, *Troedsson* et al. 2002). Support for this comes from observations that semen from some stallions is associated with an increased incidence of persistent breeding-induced endometritis (*Zent* and *Troedsson* 1998).

The role of seminal plasma in breeding-induced endometritis
In contrast to spermatozoa, seminal plasma has a suppressi-

ve effect on complement activation, PMN-chemotaxis, and phagocytosis (*Troedsson* et al. 2000). A function of seminal plasma may be to act as an inflammatory inhibitor or modulator in the uterus, which may be of importance for the transient nature of breeding-induced endometritis. The duration of breeding-induced uterine inflammation was shown to be shorter when seminal plasma was included in an insemination dose, compared to when all seminal plasma was removed and replaced by a commercial semen extender (*Troedsson* et al. 2002). Although the peak numbers of PMNs were the same for both groups, significantly fewer PMNs were recovered from the uterus at 24 hours, compared to 6 and 12 hours after insemination when seminal plasma was included. In contrast, there was no significant difference in the number of uterine PMNs at 6, 12, and 24 hours of insemination in the absence of seminal plasma. The role and mechanism of seminal plasma as an inflammatory modulator may be more complex than previously believed. In a recent report, it was found that seminal plasma alone caused an infiltration of PMNs in the stratum compactum of the endometrium (*Sieme* 2007). Furthermore, the residual PMN-infiltration was higher in mares inseminated with seminal plasma alone, compared to mares that were inseminated with spermatozoa alone, extended semen, and semen extender alone. Interestingly, clearance of PMNs from the endometrium was superior when seminal plasma was included in an insemination dose, compared to when spermatozoa or seminal plasma were used alone. Influx of PMNs into the uterine lumen was not evaluated in this study.

Another function of seminal plasma in breeding-induced endometritis appears to be to protect spermatozoa from being phagocytozed and destroyed in an inflammatory environment. PMNs are present in the uterine lumen by 0.5 hours after breeding, but sperm transport is not completed until 3-4 hours later (*Brinsko* et al. 1991, *Katila* 1995). In addition, when mares are bred twice within a 24- hour period, semen from the second insemination is introduced into an inflammatory environment. This environment is detrimental to sperm motion characteristics, and motile spermatozoa appear to bind to PMNs forming large clusters of PMN and spermatozoa. Addition of seminal plasma reduced the binding between spermatozoa and inflammatory cells in vitro (*Alghamdi* et al. 2004). Data suggest that equine seminal plasma selectively protects viable, but not dead spermatozoa from PMN-binding and phagocytosis (*Troedsson* et al. 2005, *Troedsson* et al. 2006). We have recently identified a specific protein in seminal plasma that appears to be responsible for this function (*Troedsson* et al. 2006). The presence of this protein reduced binding of viable, but not dead spermatozoa in vitro. This effect was removed when antibodies against the isolated protein was added to test samples (unpublished observations). A selective protection of viable spermatozoa from PMN-binding and phagocytosis increases their survival in a hostile uterine environment and ensures that a sufficient number of spermatozoa reach the oviduct for fertilization. Effective sperm elimination of non-viable spermatozoa is also maintained. The biological function of seminal plasma should be considered when it is removed or reduced during preparation of an ejaculate for cryopreservation or cooled storage. Although fertility appears to be normal when mares are inseminated once without seminal plasma (*Katila* et al. 2005), fertility was significantly reduced when mares were inseminated in the presence of an existing breeding-induced endometritis without the inclusion of seminal plasma (*Alghamdi* et al. 2004). The addition of seminal plasma restored fertility to normal levels in this study. Additional research is necessary to determine which seminal plasma components are beneficial for sperm transport, elimination, and in the modulation of breeding-induced endometritis.

Diagnosis of breeding-induced endometritis

Persistent breeding-induced endometritis is characterized by delayed clearance of inflammatory products and fluid from the uterus. Diagnostically, it may be difficult to identify susceptible mares prior to breeding. However, distinguishing between these two populations of mares is critical to avoid unnecessary, and possibly detrimental, treatment of normal mares. Some susceptible mares have free fluid present in the uterine lumen prior to breeding, but most mares are not diagnosed until after they have been bred and intraluminal fluid is identified. Mares with poor cervical relaxation during estrus may accumulate fluid in the uterus after breeding as a result of compromised drainage through the cervix. If susceptibility to persistent breeding-induced endometritis is suspected, the mare should be monitored closely by ultrasonography per rectum at 6 to 24 hours after breeding. Resistant mares can retain fluid up to 6 hours after breeding with fresh semen and up to 12 hours after insemination with frozen/thawed semen. If free fluid is present in the uterine lumen after this time, the mare should be considered to have persistent mating-induced endometritis.

Clearance of charcoal particles from the uterus within 48 hours of inoculation and the use of scintigraphy to measure uterine clearance have been suggested to be useful when identifying mares that are susceptible to persistent breeding – induced endometritis (*LeBlanc* et al. 1989, *LeBlanc* et al. 1994). However, this may not be practical under field conditions.

Breeding management and treatment

Management of mares susceptible to persistent breeding-induced endometritis should include limited uterine exposure to semen, and assisting the uterus to physically clear contaminants and inflammatory products after breeding. Pre-existing uterine infections should be resolved before the mare is bred. Exposure to semen should be limited to a single breeding per cycle, if possible. This can be accomplished by closely monitoring follicular development and hormonal treatment to induce ovulation of mature follicles. Physical clearance can be assisted by the use of uterotonic drugs. Oxytocin or PGF2α treatment at 4-8 hours after breeding has been shown to aid in uterine clearance, resulting in improved pregnancy rates in susceptible mares (*Pycock* 1994, *Rausch* et al. 1996). Data suggest that a lower dose of oxytocin (5-10 IU) may be more effective than higher doses, in promoting uterine clearance (*Madill* et al. 1997, *Madill* et al. 2002, *Campbell* and *England* 2002). Care must be taken with regards to the timing of PGF2α treatment, since PGF2α and its analogues can cause a delay in the formation of a functional CL when administered within 2 days after ovulation (*Gunthle* et

al. 2000, *Troedsson* et al. 2001, *Nie* et al. 2002, *Brendemuehl* 2002, *Mocklin* et al. 2006). This was associated with pregnancy failure in two of the reports (*Troedsson* et al. 2001, *Brendemuehl* 2002). Large-volume uterine lavage at 6-12 hours after breeding will also effectively assist in clearing the uterus from fluid and inflammatory products (*Troedsson* et al. 1995b). Because sperm transport to the oviduct is completed within 4 hours after breeding, uterine lavage between 6-12 hours after breeding will not have any negative effect on fertility. It is not recommended to treat mares prior to this time, since it may interfere with sperm transport to the oviduct and fertility. Manual dilation of the cervix, or local administration of PGE in mares with poor cervical dilation may help these mares to more effectively clear the uterus from fluid.

Social interaction between mares and stallions may facilitate normal uterine clearance following breeding. Audio, visual, and physical exposure of mares to a stallion stimulated pituitary oxytocin release and myoelectrical activity (*Madill* et al. 2000). The authors suggested that the contractile response may be mediated neurogenically, with a concurrent oxytocin release augmenting the myometrial response. These observations are interesting, since social interactions between mares and stallions often are minimized when assisted breeding is implemented. When possible, housing a mare close to a tease stallion after breeding may enhance normal uterine activity.

Several alternative treatment regimens for susceptible mares have been suggested. The use of mycobacterial cell wall extract (MCWE) to modulate the uterine immune system in susceptible mares has been reported. *Fumoso* and co-workers (2003, 2006) investigated the effect of MCWE on pro- and anti-inflammatory cytokines in susceptible mares. They suggested that treatment with MCWE can help restoring homeostatic immune system when disrupted. *Rohrbach* et al. (2006) found that mares with endometritis were more likely to become pregnant if treated with MCWE when compared to non-treated controls. The study did however, not consider the effect of stallion fertility and the cause of endometritis. In a recent study, *Rogan* et al. (2007) found that mares with experimentally induced bacterial endometritis cleared the inflammation more rapidly after treatment with MCWE, compared to untreated mares. These results are interesting, and warrant further research on the mechanism by which a modification of the immune system may help resolving breeding-induced inflammation in susceptible mares.

The use of corticosteroids in mares with excessive inflammation in respond to breeding has been suggested (*Dell'Aqua* et al. 2004, *Dell'Aqua* et al. 2006). The authors administered acetate 9-alpha-prednisolone (0.1 mg/kg) twice daily during estrus, starting when a follicle >35 mm was detected and ending when ovulation was confirmed. Preliminary results are encouraging and further research is needed to clarify the mechanism of action for this treatment alternative.

Electro-acupuncture has been used clinically to increase uterine contractility in mares with delayed uterine clearance. Anecdotal reports are encouraging, and research is needed to confirm the efficacy of this treatment alternative.

It is important for the clinician to keep in mind that a transient inflammatory response to semen is normal and required for normal fertility. Post-breeding treatments of these normal mares will most likely not improve fertility and may even cause further contamination and interfere with pregnancy. Only 10-15% of all brood mares develop a pathological persistent form of breeding-induced endometritis (*Zent* and *Troedsson* 1998). Attention should be given to identify these mares, distinguish them from normal mares, and to manage them appropriately in order to optimize the reproductive efficiency. Normal breeding physiology should also be considered when assisted reproduction is used.

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