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Theriogenology
Theriogenology 66 (2006) 560–566
www.journals.elsevierhealth.com/periodicals/the

Pathogenesis and treatment of endometritis in the mare: A review

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Abstract

Inflammatory conditions of the uterus, collectively known as endometritis, can be classified as acute, chronic, active, or subclinical. This condition causes substantial reductions in mare fertility. To diagnose and treat mares with endometrial inflammation, it is imperative to identify predisposing factors and challenges to the reproductive tract of the mare in a chronological order; these factors change from those of the young maiden filly to the older, multiparous broodmare. This paper addresses predisposing factors, diagnostic procedures and therapy strategies for different mare groups.

Keywords: Endometritis; Post-mating endometritis; Endometrium; Uterus; Mare

1. Introduction

Endometritis is an important cause of reduced fertility in mares. Inflammatory conditions of the uterus may be categorized as acute, chronic, active, subclinical, post-partum, bacterial, fungal, viral, mating-induced, persistent, and others. Each of these classifications has validity in describing the infections and inflammatory insults to the uterus. When presented with a mare with uterine inflammation, the use of more than one of the above terms is usually appropriate. For the clinician, it is crucial that clients understand the apparently simplicity of uterine infections in mares, but also the complexity of endometritis. If clients have an appreciation of the pathogenesis of endometritis, they will understand not only the goal of prevention and treatment efforts, but also the treatment failures that occur.

2. The young mare

One approach to infertility in the mare is to analyze the predisposing factors and challenges to the reproductive tract in a chronological order. These factors change from those of the young maiden filly to the older, multiparous broodmare. Young mares are usually bred for the first time between 3 and 6 years of age. During the racing or performance careers of fillies, many fillies achieve a high level of fitness. These very fit fillies lose body fat in the perineal area. The rectum becomes displaced more anteriorly, allowing the vulva to be pulled above the pelvic brim. This altered perineal conformation allows repeated fecal contamination of the vulva and vestibule. During periods of exercise, muscular fatigue and estrus contribute to perineal relaxation. Aspiration of air, fecal material and bacteria into the vestibulum and vaginal cavity is common in performance fillies. This condition is termed pneumovagina. The above insults to the reproductive tract are further complicated by the frequent supplementation of performance fillies with altrenogest (an oral progestin) or injectable progesterone products.

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0093-691X/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.theriogenology.2006.04.006

Susceptibility to uterine infections is enhanced when the reproductive tract is under the influence of progesterone [1]. The innate resistance of young mares to bacterial endometritis can be compromised by pneumovagina and fecal contamination resulting in vaginitis, pneumouterus and endometritis. The above conditions are most common in racing Thoroughbreds. Perineal conformation can also be a heritable trait [2]. The conformational features of a recessed anus and horizontal angling of the vulva are most commonly observed in Thoroughbreds and Quarterhorses.

Vulvoplasty surgery, also known as a ''caslick procedure,'' can protect the reproductive tract from pneumovagina and fecal contamination. Caslick suturing the vulva in racing Thoroughbreds and other performance horses with compromised perineal conformation is recommended to prevent repetitive bacterial challenges to the reproductive tract and improve fertility of maiden mares their first year at stud [2].

Performance fillies are frequently given other medications, such as anabolic steroids. The influence of these medications on young mares' resistance to endometritis is unknown.

Although the fertility of young maiden mares is usually considered high, >20% of maiden mares fail to become pregnant. The cause of reduced fertility in maiden mares is not defined but is most likely related to estrous behavior for live cover and limited opportunities for mating as mares are retired from performance after the breeding season has started. Endometritis has not been identified as a substantial factor in lowered fertility of young maiden mares.

3. The older maiden mare

The fertility of older maiden mares is frequently compromised. Mares as young as 8 years, but usually >12 years, may be affected. Affected mares have an elongated, closed, fibrous cervix during estrus. The uterus is usually normal in size but it is common for affected mares to accumulate varying degrees of echolucent fluid in the uterine lumen, based on ultrasound evaluation of the uterus [3]. The development of uterine edema during estrus is usually very dramatic. When these mares are mated by natural cover, fertility is very compromised because semen is likely deposited in the vagina instead of in the uterus. Older maiden mares bred by artificial insemination of fresh or frozen semen, develop an acute inflammatory reaction; the inseminate is rarely bacteriologically sterile, resulting in an acute endometritis. Prior to breeding, bacteriologic cultures of uterine swabs are negative, although swab contamination is very common due to the extreme difficulty that can be encountered passing the swab through the cervical canal. Post-breeding culture of uterine swabs usually yield a wide range of bacteria originating from breeding or from the semen.

Clients need to be informed of the expected fertility and potential complications prior to breeding older maiden mares. Affected mares can usually be identified during reproductive examinations prior to breeding, especially when these exams are performed during the peak of estrus [4]. Uterine fluid may be present during diestrus or estrus, and the cervix fails to relax and dilate during estrus. When these mares are to be mated, clinical experience indicates that cautious but persistent digital dilation of the cervical canal is beneficial. The use of systemic or local medications to assist in cervical dilation has been attempted, but results were inconsistent. To my knowledge, the dosage and frequency of administration of PGE compounds have not been reported [5]. The goal of cervical dilation is not only to assist in proper placement of semen in the uterus, but also to allow the mare's post-breeding defense mechanisms to expel excess semen, extender, debris and bacteria from the uterus after mating. Oxytocin (5–20 IU) is frequently administered IV or IM to affected mares ≥4 h after breeding. Fertility is not compromised by oxytocin administration after breeding and prior to ovulation. Repeated injections of oxytocin or uterine lavage may be necessary to remove uterine fluid within 2–3 d post-ovulation. Because the uterus is frequently ineffective in clearing bacteria from these mares, intrauterine antibiotic infusions of the uterus in conjunction with uterine lavage are often necessary. Lavage fluids may include 500 mL of physiologic saline, lactated Ringer's solution, or embryo transfer flush fluids. The 500 mL lavage volumes are massaged throughout the uterus and are retrieved from the uterus by gravity flow. It may be necessary to instill and retrieve two or three volumes of lavage fluid until the retrieved fluid is clear. Uterine lavage is usually performed 4–24 h after mating. Following uterine lavage, oxytocin may again be given [6–10]. The mare's reproductive tract should be reevaluated 24 h later to ensure that fluid accumulation has resolved, signs of uterine infection are not present, and the mare has ovulated. The older maiden mare's compromised response to mating invariably recurs at subsequent matings. If these mares become pregnant and carry a foal to term, the foaling process appears to be normal.

Endometrial biopsy of the older maiden mare's uterus is characterized by mild to severe widespread dilation of the lumens of endometrial glands and

periglandular fibrosis that varies from slight to moderate in severity and scattered to widespread in distribution. Fibrotic and nonfibrotic endometrial gland nesting are common. Inflammation is not a salient feature in these endometrial biopsies unless there is fluid accumulation or the mare has been mated. Experience suggests that older maiden mares that become pregnant have a higher pregnancy loss rate than expected. Following foaling, some of the same complications are frequently encountered, such as pre- and post-mating accumulation of echolucent fluid and increased risk for post-mating endometritis, despite the substantially improved character of the cervix. Alteration of myometrial activity [11], vascular changes in the endometrium [12], poor myometrial response to prostanglandin [13], or altered mucus production [14], may explain delayed uterine clearance of bacteria, fluid and debris following mating.

4. The foaling mare

Foaling provides numerous challenges to the mare's reproductive tract. Mares foal in a variety of environments, all of which present a substantial bacterial challenge. During foaling, bedding materials (e.g. shavings, sawdust, straw, and soil) contaminate the perineum during foaling, and contusions and usually minor derangement of the reproductive tract lining occur. Prior to complete passage of the placenta, it can serve as a mechanism to contaminate the vaginal cavity. Relaxation of the vulva, vagina and cervix may allow substantial contamination by air, debris, fecal material and bacteria. Young healthy mares undergo involution of the uterus and cervix and reduce bacterial populations within 7–12 d after foaling [15]. Uterine involution may be delayed in foaling mares with delayed first estrus or in mares that are noncyclic after foaling.

The clinician needs to appreciate that when challenges to the reproductive system exceed resistance mechanisms, disease is likely. Post-partum disease may be manifest as acute endometritis, delayed or incomplete passage of the placenta, delayed uterine involution, and reduced fertility. The periparturient challenge to the mare may come in the form of nutritional imbalance, poor body condition, episiotomy, lack of exercise, foaling in dirty conditions (soil, shavings or sawdust), dystocia, fetal malposition, delayed placental expulsion, etc. Transient reflux of urine into the anterior vagina is not unusual in the immediate post-partum mare, also resulting in delayed uterine involution and an increased risk for endometritis.

Many of the above predisposing factors can be prevented by proper nutrition and management. Specifically, if mares have had vulvoplasty performed after breeding, an episiotomy should be performed prior to but as close to foaling as practical to minimize prefoaling contamination of the vaginal vault. This practice is particularly beneficial in thin, multiparous, and older mares. Once foaling has occurred, the vulva should be re-sutured as soon as practical. Even in mares with normal vulvar conformation, it is very common for air to be aspirated into the vagina. The clinician is frequently faced with a difficult decision. Many practitioners intentionally delay vulvoplasty in the older post-partum mare due to increased risk of post-parturient uterine artery rupture due to increased blood pressure caused by the excitement of restraint and a newborn foal [16]. This practice allows substantial pneumovagina and bacterial contamination of the reproductive tract for $\geq$2–4 d post-partum. Young healthy mares are usually capable of mounting adequate resistance to these periparturient challenges, but this resistance can be weakened or lost over time, with subsequent foalings, prolonged retained placenta, or an abnormal foaling.

Retained placenta can be a substantial risk factor for acute post-partum endometritis and delayed uterine involution. Most normal mares pass the placenta 30–90 min after foaling. Retained placenta is frequently defined as placental expulsion $\geq$3 h after foaling. Passage of the placenta occurs over a time continuum. It is not possible to impose a specific time limit on what constitutes delayed placental expulsion in a specific mare. Very rapid passage of the placenta, i.e. within 10–15 min, may also be considered abnormal. Many of these placentae have signs of substantial placentitis or premature placental separation. Adverse events that center around foaling and uterine involution are likely to contribute to acute and chronic endometritis, susceptibility to uterine infection and persistent post-mating endometritis.

During an uncomplicated foaling but more frequently during an aggressively assisted foaling or dystocia, the cervix may be damaged or lacerated. Cervical lacerations can range from minor to full-thickness, full-length tears. Regardless, there will be compromised tissue, potential tissue necrosis and inflammation. Post-partum cervical–vaginal adhesions may also develop. Furthermore, the vestibulovaginal sphincter may be damaged during foaling, particularly dystocia. The integrity of the vulva lips, vestibulovaginal sphincter and cervix are substantial barriers to uterine infection and contamination. When these structures are damaged, there is both increased microbial challenge to the reproductive tract and

increased potential for altered clearance of fluids and bacteria following foaling or mating.

Parturient insults to the reproductive tract not only allow establishment of acute endometritis, but their sequelae are also commonly noted in chronic endometritis cases. Mares with chronic endometritis have sporadic exacerbation of acute endometritis, such as following breeding or invasive internal reproductive examinations. The reproductive history, endometrial biopsy results and repeated reproductive exams during estrus and diestrus and before and after mating are extremely helpful in identifying mares with chronic endometritis. Therapy for mares with chronic endometritis needs to be directed at identified abnormalities. Physical abnormalities may need to be corrected by vulvoplasty, cervical laceration repair [17], surgery for prevention of urine pooling [18] or perineal body transection surgery [18]. Substantial weight gain may be necessary in thinner mares prone to pneumovagina, even though caslick suturing of the vulva has been done. Any fistulae in the sutured vulva need to be repaired.

Minimum contamination techniques for breeding mares by live cover or artificial insemination of mares with semen extended in an appropriate extender containing antibiotics should improve fertility in mares with chronic endometritis [19,20]. In mares with extensive vulvar suturing, it is helpful to pass a specialized catheter with an attached syringe into the vaginal vault and guide the pipette into and through the cervix by manual transrectal manipulation. This technique has been used for intrauterine antibiotic treatment and insemination of mares. Without this technique, it may be necessary to perform repeated episiotomies and vulvoplasties over a short interval.

5. The mated mare

Live cover matings or artificial insemination of mares during the foal heat may result in acceptable fertility. However, if involution of the uterus is delayed or varying amounts of fluid are present at the time of foal-heat breeding, fertility is substantially reduced and an acute endomentritis may result [21]. However, methods to evaluate post-partum uterine involution in a clinical setting are poorly defined and not effective. *Streptococcus equi zooepidemicus*, *E. coli* and mixed bacteria are frequently isolated from endometrial swab cultures [22–24]. If uterine fluid is present during foal heat, mating should be delayed. Affected mares can be treated with prostaglandin $\geq$5 d after foal-heat ovulation. Treated mares should return to estrus in 3–5 d, allowing a second estrus to improve uterine health prior to mating. Uterine lavage of the uterus of post-partum mares is commonly done between 3 and 10 d post-partum. Although this practice may be beneficial in cases of uterine infection or delayed uterine involution, the routine practice of uterine lavage of post-partum mares has failed to improve fertility in mares that are progressing normally through the post-partum period [23,25]. Oxytocin and prostaglandin have also been used to enhance uterine involution and reduce the potential for post-partum endometritis, with varying degrees of success [26,27].

If a mare is to be bred during foal heat, the mare's reproductive health should be evaluated 7–9 d after foaling. It is not unusual for the first estrus following foaling to be referred to as the 9-day foal heat. However, monitoring follicular development and ovulation in these mares suggests that ovulation may occur as early as Day 6 and extend to $\geq$15 d after foaling. There are indications that fertility following foal-heat breedings is substantially improved when ovulation occurs $>$10 d after foaling, compared to $\leq$10 d after foaling [28]. Delaying breeding until $\geq$10 d post-partum is commonly practiced. For mares that ovulate prior to 10 d post-partum, prostaglandin is administered to induce an early return to the second post-partum estrus.

This paper will not specifically address sexually transmitted infectious endometritis. However, following the identification of *Taylorella equigenitalis* in mares and stallions in the USA, many stallions were treated for the presence of the organism on the penis or were treated prophylactically. Treatment consisted of thoroughly washing the penis and prepuce with a 4% chlorhexidine solution, followed by application of furacin dressing to the penis and sheath for five consecutive days. Although this treatment was effective against the organism causing contagious equine metritis, it allowed the proliferation of *Pseudomonas species* and *Klebsiella*. Mares live-covered by these stallions had reduced fertility and frequently became acutely infected with *Klebsiella*, *Pseudomonas* or *Streptococcus* species [29]. Uterine infections were probably established due to substantial inoculation of the uterus and reproductive tract with pathogenic bacteria and the prolonged post-mating inflammatory reaction. Fresh, extended semen may also be heavily contaminated by *Pseudomonas*, *Klebsiella*, beta-hemolytic streptococcus, and other bacteria or viruses. A similar acute endometritis may follow artificial insemination of mares. Acute endometritis cases can be reduced by more appropriate hygiene of stallions at mating or prior to stallion collection. Current recommendations vary from washing and rinsing the stallion's

penis using clean water with no soap or disinfectant to rinsing the penis with clean water following live cover. The efficacy of these two management schemes should be investigated. In the case of artificial insemination, antibiotics are added to the semen extender. The antibiotics may have a broad spectrum of bacterial sensitivity or may be specifically selected for activity against specific bacteria. It should be noted that if the uterus is inoculated with a specific, pathogenic bacteria during estrus, this organism will not necessarily be the organism recovered days later when acute infection is established [1]. This phenomenon makes the study of bacterial endometritis difficult and justifies the frequent use of broad-spectrum antibiotics.

Following mating by live cover or artificial insemination, an endometrial inflammatory response occurs. There is an influx of PMNs, fluids, and proteins into the uterus, activation of uterine-derived complement, increased myometrial contractions due to prostaglandin release and evacuation of excess fluid, bacteria, debris, and sperm. The post-mating inflammatory response removes dead and abnormal sperm and seminal plasma. The neutrophils phagocytize bacteria, thereby assisting clearance of potential acute infection. Even though seminal plasma helps moderate the post-mating inflammatory response, excess seminal fluids are removed by uterine contractions. These uterine fluids are evacuated through the cervix or picked up via the lymphatic vessels. When the above-mentioned uterine response to mating is compromised, a persistent mating-induced endometritis can result [11,13,30–32].

Persistent mating-induced endometritis increases with mare age, bacterial contamination during mating, and other pre-existing clinical or subclinical abnormalities of the reproductive tract. Mares that have detectable fluid in the uterus during diestrus or estrus prior to mating are at increased risk of delayed clearance of fluid and bacteria following mating. If the fluid is not cleared within 1–2 d and the inflammatory response controlled by Days 2–4 post-ovulation, pregnancy rates are low and active endometritis may result [5,21]. Progesterone concentrations rise and the cervix closes rapidly immediately after ovulation; many of the mare's defense mechanisms are lost by 24 h after ovulation.

Transrectal palpation and ultrasound examination of the uterus should be done to determine the presence of uterine fluid following mating. Uterine fluid should not be present 6–12 h after mating in normal mares. Oxytocin (10–20 IU) is frequently administered IV or IM to mares that have detectable uterine fluid 12–24 h after mating. Oxytocin induces a rapid onset of myometrial contractions. The excess fluid is usually removed within hours. In more refractory cases, oxytocin may be given repeatedly at intervals of $\geq$2 h to promote removal of uterine fluids. Oxytocin probably assists in fluid removal through the cervix and by absorption of fluid by the lymphatic system. Some mares seem refractive to exogenous oxytocin treatment; in these mares, treatment with prostaglandin or cloprostenol may be indicated [6–8,10]. At the post-breeding evaluation, the presence of echodense uterine fluid or purulent vulvar discharge suggests the onset of bacterial endometrititis. These mares may benefit from the intrauterine infusion of a broad-spectrum antibiotic such as timentin, chloromycetin, ampicillin or ceftiofur [4,10,19,33,34]. The infusion volume may range from 60 to 250 mL, depending on uterine size. Mares that have accumulated a substantial amount of uterine fluid or in cases where the uterine fluid cannot be evacuated using oxytocin therapy, lavage of the uterus using one or more 500 mL volumes of saline or lactated Ringer's solution may substantially improve endometrial health. A broad-spectrum antibiotic may be infused following lavage. However, if oxytocin is administered following lavage (to help assure clearance of residual fluid), the antibiotic infusion should be delayed for 2 h. The uterus should be re-evaluated 24 h after the lavage procedure or antibiotic infusion to determine the persistence of uterine fluid. Additional uterine lavages or treatments are frequently needed in persistent mating-induced endometritis cases. There is a high frequency of persistent mating-induced endometritis in affected mares from cycle-to-cycle and even year-to-year. Affected mares have an elevated incidence of early embryonic death in spite of post-mating treatments. The causes of the pregnancy losses are most likely related to mare age, a high prevalence of periglandular fibrosis, abnormal lymphatic drainage, cervical laceration, or other pre-existing conditions. In spite of the mating-induced inflammatory reaction, mares may need to be bred 6–48 h after initial mating if ovulation has not occurred. The interval between matings will vary due to stallion fertility and mating method such as live cover, AI with fresh semen, or AI with frozen semen. Seminal plasma appears to have a protective mechanism to sperm in the face of an inflammatory reaction [35]. If mares are re-mated, treatments for persistent mating-induced endometritis will need to be repeated. Fertility does not appear to be compromised in these mares if mated two or three times [35,36]. Housing susceptible mares near a stallion or breeding activity may also induce endogenous oxytocin release and assist in the clearance of fluid and debris from the uterus [37].

Embryo transfer is a management technique that has been invaluable as a method of obtaining foals from mares with persistent chronic endometritis, repeated early embryonic death or abortion, and non-responsive, persistent mating-induced endometritis. These conditions are usually complicated by cervical laceration, advanced mare age, and bacterial or fungal endometritis. The use of uterine lavage, ecbolics and artificial insemination before and after ovulation may allow the uterus to support embryo development for 7–10 d. Uterine lavage of the uterus to recover one or more embryos is usually done 7 or 8 d after ovulation; therefore, the embryo needs to survive the uterine environment for only 2–3 d. Embryo recovery rate is usually in the range of 70–80% in normal mares bred to a fertile stallion. By comparison, the embryo recovery rate for chronically infected mares, intensively managed and bred to fertile stallions, is usually 25–40% [38,39]. The pregnancy rate following transfer is somewhat reduced for embryos transferred from chronically infected mares. In order to avoid the hostile uterine environment for mating or embryo transfer, oocyte transfer may be another management technique to obtain pregnancies from these difficult cases [40].

The treatment of endometritis in the mare is based primarily on minimizing the predisposing factors associated with at-risk mares and understanding the mare's innate resistance mechanisms. Endometritis is very difficult to study because of the wide array of variables associated with each affected mare. It is not prudent to assume that cases of acute, chronic, or persistent mating-induced endometritis can be treated in standardized protocols. Furthermore, all of the above discussions are complicated by a lack of uniformity and precision in diagnostic methods and agreement on the interpretation of clinical findings.

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