The diagnosis, causes and treatment of persistent endometritis in the mare

Endometrite persistente na égua: causas, diagnóstico e tratamento

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Introduction

Published reports in the literature on the diagnosis and treatment of endometritis in the mare are exhaustive and at times, controversial. Opinions vary considerably among individuals. Herein, the author has formulated his own opinions based on the available literature and is not to be considered as generally accepted among all individuals.

Endometritis has been over the past 40 – 50 years, and continues to be, one of the major causes for infertility in the mare. Prior to the use of ultrasound, methods for detecting endometritis in the mare ranged from solely, the observance of inflammation of the cervix with a speculum examination and observance of cervical and/or vaginal discharge, to methods for culture (Dimock and Edwards, 1928), and cytological examinations [Knudsen, 1964). The combined use of cytology and bacteriological culture as an aid to the diagnosis of endometritis was initially eluded to, almost 20 years ago (Shin et al., 1979) and is currently the most used procedure for the diagnosis of endometritis in the mare. Our methods for diagnosing endometritis in the mare have not changed (with the exception of instrumentation) since these early investigations, but with advancing knowledge of the pathophysiology of endometritis, our methods for treatments have. Therefore, it may be prudent to spend more of this discussion on the varying methods for treatment rather than on the diagnosis of endometritis. Standard doses and protocols for the various treatments can be obtained from excellent texts and reviews available on line. A summary of key events in the literature on the diagnosis and treatment of endometritis will be mentioned in this discussion with hopes that those not mentioned will not be construed as unimportant.

It was not until the late 60's and early 70's when it became clear that endometritis in the mare was observed to occur in two forms…. the acute phase and the chronic phase. In 1969, Hughes, JP and R Loy demonstrated that following the inoculation of *Streptoccocus zooepidemicus* into the uterus of both, young, maiden and older, multiparous and barren mares, a large inflammatory response was generated by the young mares and little visual changes were noted in the older mares [Hughes and Loy, 1969). However, within a few days the young mares were no longer observed to have evidence of inflammation or infection, whereas the older barren mares became chronically infected with obvious visual vaginal discharge. After spontaneously resolving the inflammation, the young mares were mated in the following cycle and all became pregnant. From a practical viewpoint, this made a large difference in our diagnostic ability to determine which mares with endometritis required treatment and which do not. Hence, it is the persistence or the prolonged presence of endometritis that is responsible for subfertility/infertility in mares, and those that require treatment

Diagnosis and pathophysiology of endometritis

Prior to the use of ultrasound it was difficult to determine the presence of, let alone the character and amount of fluid present in the uterus of mares. Since its inception, the use of ultrasound in reproduction has made a strong impact on our ability to detect its presence as well as the volume and severity of fluid present in the uterus of mares. This modality has increased our awareness and observations of endometritis at perhaps earlier stages of infections and compromised clearances in mares. Retention of fluid in the uterus alone does not comprise contribution to our diagnostic ability to detect endometritis. However, being able to notate the character of the fluid and the volume of echogenic fluid accumulation gives us a good clue of the presence and severity of endometritis. We continue to use culture, cytological and histological specimens to assist us in the diagnosis of endometritis in the mare. These methods continue to be standard operating procedures in many broodmare practices yesterday and today. An important complication observed over the years using standard practices (use of guarded swabs of the endometrium) of culture and cytology has been the presence of false positive and false negative results. For barren and subfertile mares, low-volume uterine flushes have been proposed as an alternative to the use of guarded swabs in diagnosing endometritis in the mare. Although large-volume uterine flushes of the endometrium have been used in the identification of various proteins, bacteria and chemical components of the uterus (El Sanousi and El Tayeb Amna, 1979; Williamson et al., 1983; Slusher et al., 1984; Stremienski and Kenney, 1984), Dr. Barry Ball and his colleagues first reported the use of low-volume uterine flush and its potential inclusion as a more effective method for the identification of bacterial pathogens and inflammatory response, with emphasis on the barren and subfertile mare [Ball et al., 1988). Recent reports

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confirm the use of low-volume lavages in a large number of mares as a useful diagnostic method in detecting chronic endometritis (LeBlanc et al, 2007). Low-volume lavage, although more cumbersome than standard procedures used for obtaining cultures and cytology with guarded swabs, may prove valuable for conditions of subclinical endometritis in the chronically infected mare. Further improvements in obtaining more representative samples of endometrial contents have been suggested by Dr. J. Steiner, 2007 (personal communication) using a cervical brush adapted from instrumentation used for cervical cytology procedures in women. Clinicians having the opportunity to using this instrumentation (Minitube of America, Verona, WI 53593), indicate that this procedure has valuable potential as an alternative to currently used cotton-tipped swabs. Recently, Dr. Nielsen from Denmark compared and evaluated the endometrial swab and endometrial biopsy procedures for obtaining cytological and culture results for diagnosing endometritis in the mare [Nielsen, 2005). The results suggested that endometrial biopsy was a more sensitive and specific method in diagnosing endometritis in the mare than the use of endometrial guarded swabs. The study did not distinguish the differences between mares with acute or persistent endometritis. Since persistent endometritis (clinical and subclinical) is a more important issue to the practitioner, investigations may be required to evaluate its effectiveness solely under these conditions.

It has been proposed that endometritis, both acute and chronic is initiated by two distinctly separate origins. One is by bacterial contaminants and the other is sperm- induced (Troedsson, 2006). 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 and manage these mares appropriately in order to optimize the reproductive efficiency. The inflammatory response to either antigen is similar in that an acute or persistent inflammatory response may ensue. Hence, treatment strategies may be somewhat different based on the origin of the disease. While other currently unknown factors may also be involved in the development of persistent endometritis, it is clear that the major factor influencing the retention of endometrial inflammatory responses, whether they are bacterial or sperm-induced, is based on delayed uterine clearance as a result of compromised myometrial function (Troedsson and Liu, 1991; Troedsson et al., 1993; LeBlanc et al., 1994) For many years investigators hypothesized the importance and studied the role of immunoglobulins and polymorphonuclear leukocytes as they relate to persistent and reccurring endometritis. Although evidences were provided that immunoglobulins and PMNs played key roles in persistent uterine infections, a few notable studies demonstrated that compromised uterine clearance and myometrial contractility played a major and perhaps a more important role in the pathophysiology of mares affected with chronic uterine infections. Using chromium51 labeled microspheres, it was shown that mares potentially susceptible to chronic uterine infections failed to clear the microspheres adequately when compared with mares with normal uteri (Troedsson and Liu, 1991). Studies using electromyographic recordings by these investigators further provided direct evidence that the cause for poor uterine clearance was due to compromised uterine contractility (Troedsson et al., 1993). Similarly, Dr. Michele LeBlanc and her group in Florida, in their elegant study using radioactive colloids and scintigraphy also demonstrated that mares with histories of chronic uterine infection have compromised uterine clearance (LeBlanc et al., 1994). While the underlying cause for compromised myometrial contractility and delayed uterine clearance remains unknown, these studies made a strong impact on our current treatment strategies of persistent endometritis in the mare. More recent studies have suggested that an accumulation of nitic oxide, a smooth muscle relaxant, in the uterine lumen in susceptible mares (Alghamdi et al., 2005; Fioratti et al., 2010,) and excessive elastosis of uterine vessels, causing poor uterine perfusion in barren, multiparous mares (Esteller-Vico et al., 2010; Gruninger et al., 1998; Nambo et al., 1995) may play major roles in compromised myometrial contractility. Growing interests in uterine blood flow parameters and uterine perfusion over the past few years have generated valuable and important insight into the role of vascular damage and the subfertile mare (Esteller-Vico et al., 2010; Bollwein et al, 2002; Ferreira et al., 2008). It is generally agreed among scientists and practitioners that if a mare is unable to spontaneously eliminate an infection in 4 days, she would be considered as a mare being affected with persistent endometritis. It is our impression that if a mare is unable to spontaneously eliminate an infection after two days, she is either persistently infected or on her way of becoming persistently infected. This impression is supported by observation on uterine clearance of bacteria in normal mares (Katila, 1995).

Treatment strategies for endometritis

In the past, acceptable pregnancy rates in most broodmare operations were within the 50-60% range and is difficult to perceive in today's market. Today, acceptable ranges would be in the 75-85% range with 90-100% ranges not being unusual. This increase in rates can be attributable to increased knowledge of the pathopyhsiology of endometritis and the infertile mare, instrumentation and more efficient and effective treatment strategies. A common goal for any broodmare practitioner is to get the mare pregnant. One single-most factor that has contributed to our increase in pregnancy rates has been the Caslick procedure. This is a fundamental requirement for most, if not, many barren mares, yesterday and it continues to be a major contributing factor to successful pregnancy today. When isolation of microbials from the uterus and sensitivity tests for antimicrobials were in vogue, extensive and repetitive use of antimicrobials were infused into the uterus

of mares with endometritis. The use of antimicrobial infusions of the uterus is beneficial in cases of known bacterial growth causing endometritis and is currently used by many practitioners, including its use empirically as a single post-ovulation treatment in mares. Although the mechanism is not known, clinical impressions suggests that repetitive, prolonged and excessive use of antimicrobials appear to be associated with an increase in the incidence of fungal endometritis in mares and an increase in this condition was apparent in the 80's and early 90's. It is the authors' (IL) belief that prolonged antimicrobial infusion of the uterus has not been used as extensively as it has been over the past 10 years and an apparent decrease in fungal endometritis has been observed. When observed, a number of anti-fungal agents including polyene antibiotics and azole derivatives are available and can be used as treatment strategies. An excellent review of equine fungal endometritis was reported by Dascanio JJ, et. al, including treatment strategies and recommended doses (Dascanio et al., 2001). Lufenuron®, a benzoylphenyl urea derivative has also been tested on a limited number of mares with fungal endometritis. Lufenuron® is believed to have an inhibitor effect on chitin production of fungal elements. While the results appear encouraging, further investigations are required to evaluate its long-term effectiveness in the treatment of fungal endometritis in the mare (Hess et al., 2002). Commonly used antimicrobial and anti-fungal drugs and dosages for treatment of endometritis in the mare is also provided in the Manual of Equine Reproduction, eds: T. Blanchard, D. Varner, J.Schumacher, C. Love, S. Brinsco and S.Rigby (Blanchard et al., 2003). Included is a list of commonly used disinfectants which has been diluted and used as an alternative for antimicrobial treatments. Although commonly used among practitioners, very little is known about the efficacy of using diluted disinfectants when compared with antimicrobials.

A host of agents have been used as chemical curettage for treatment of endometritis in the mare. Included are dimethyl sulfoxide (DMSO), hydrogen peroxide (H202), magnesium sulfate (MgSO4), Streptococcus filtrate, kerosene, and dilute disinfectants (0.2% povodine-iodine solution). Reports available, whether they be anecdotal or in the literature, suggest that there is a beneficial effect in the treatment of chronic endometritis following its use. While these agents all comprise a variety of chemical components, they all have a common denominator of inducing a strong inflammatory response when exposed to the endometrium. Hence, it is the authors' opinion (and an opinion not based on scientifically meritorious investigations) that the limited success of these agents, when used as treatments for persistent endometritis can be, in most part, attributed to the induction of a strong inflammatory response and inciting increased myometrial contractility and uterine clearance. Clearly, many of these agents may also have bactericidal effects and its use is generally reserved for barren mares in which no other treatments have been successful. Regardless of how effective the bactericidal effect, uterine contractility must be optimal for successful treatment to occur. Mechanical curettage is seldom used as a treatment for chronic endometritis in the mare in today's practices. Its use is perceived to be rather invasive of the endometrium, the effectiveness of the procedure has been questioned, and it is more than likely that chemical curettage has replaced its use.

Autologous/heterologous plasma and colostrum have also been used as treatment regimes for endometritis (Dewes, 1980; Asbury, 1984). Colostrum is rarely used as a treatment regime today. The intended use of colostrum as a treatment for endometritis was to enhance the immunoglobulin population in the affected uterus, thereby assisting the immune response in its antimicrobial action. With increased knowledge in the pathophysiology of endometritis in the mare, while immunoglobulins do play a role in uterine defense, its role is presumed to be minor when compared with uterine clearance. The infusion of autologous or heterologous plasma as a treatment strategy for endometritis is still currently being used in some practices. Its intended use and proposed success as treatment for endometritis is to enhance phagocytosis of bacteria by supplementation of opsonins (complement) present in the exogenous serum. Bear in mind that regardless of how effective the antimicrobial effect, uterine clearance and optimal uterine contractility are necessary ingredients for a successful outcome. Therefore, and it may be presumptive to suggest that the successful treatments attributable to the infusion of colostrum and/or plasma may be related to a concomitant increase in uterine contractility and subsequent uterine clearance.

Supplementation of separated PMNs, fresh and cryopreserved have also been reported in the literature and proposed as a successful treatment for persistent endometritis in the mare (Mattos et al., 1999a, b; Zerbe et al., 2003). We are not aware of anyone using these treatment regimes in the field at this writing and presumably, these treatments have not gained popularity as yet in North America.

Treatment strategies have varied considerably among practitioners over the years. With increasing knowledge of the pathophysiology of persistent uterine infections and by far, uterine lavage with isotonic saline and the accompanying use of ecbolics has made the strongest contribution to the reduction of persistent endometritis and increased pregnancy rates in mares than any other current treatment strategy in recent years. Uterine lavage was first used and described by Russian veterinarians as early as 1938 (Zivotkov, 1938). It was reported as an excellent means of eliminating *E. coli* and *Streptococcus zooepidemicus* bacterial infections. Confirmation of uterine lavage as being an effective treatment strategy for chronic endometritis was followed up by Dr. Varadin from Yugoslavia who reported in English, its successful use in mares with endometritis at the first International Symposium on Equine Reproduction in 1975 (Varadin, 1975). Subsequently, its use in North America has exploded over the years based on procedural modifications, experiences and the promising results

obtained from this procedure. An important contribution to the use of uterine lavage is the study by Brinsco and his associates, whose investigation established that lavaging a mare 4 hours after mating would not have any adverse effect on pregnancy in the mare (Brinsko et al., 1991). This study gives the practitioner significant flexibility in the timing of treatment of mares with bacterial and/or sperm induced recurrent endometritis and delayed uterine clearance. The use of ecbolics (oxytocin and prostaglandin) in conjunction with uterine lavage is effective in enhancing uterine contraction and uterine clearance (LeBlanc et al., 1994, Troedsson et al., 1995). Evidences have been provided that failure of pregnancy may result from the use of PGF2α if administered during the periovulatory period (2-4 days) after ovulation (Troedsson et al., 2001 Brendemuehl, 2002). Other similar studies do not share this viewpoint (Nie et al., 2002). However, it is generally agreed among these studies that there is a transient decrease in progesterone concentration, followed by a rebound effect after its administration 1-2 days post-ovulation. Therefore, an alternative ecbolic (oxytocin) is suggested for post-ovulation treatments in mares with fluid retention. While controversy continues to exist as to the effect of prostaglandin on pregnancy when used during the periovulatory period, further investigations will be required to resolve this issue. Regardless, it is clear that fluid remaining in the uterus post ovulation does not provide an optimal uterine environment and its removal is mandatory for embryo survival.

Immune stimulants have been promoted in recent years as a treatment for persistent endometritis in the mare (Rohrbach et al., 2006). There are at least two that are commercially available to the practitioner. One is a cell mediated immunity stimulator and is derived from inactivated *Propionibacterium acnes*. The other, a Mycobacterium cell-wall extract, proclaims to normalize uterine inflammatory response, uterine involution and bacterial reduction in the uterus by a non-specific immunological response during endometritis in the mare. Despite preliminary evidences that the immune enhancers may be a useful treatment strategy for persistent endometritis in the mare, its efficacy requires further documentation in the field as well as in established controlled studies.

Other less commonly used treatment strategies have recently been proposed. The use of corticosteroids in mares with excessive inflammation in response to breeding has been suggested (Dell'Aqua Jr et al., 2004). 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.

Dexamethasone (50 mg), administered once prior to mating, has also been suggested as an adjunct therapy for mares subfertile from persistent endometritis. (Bucca et al., 2008). The authors found beneficial effects in pregnancy rates from a study of 513 mare-cycles using this protocol. Other studies found contrasting results and found no differences in effect on pregnancy rates when using similar protocols (McDonnell and Watson, 1993, Vandaele et al., 2010). Clearly, further investigations are required to unravel this controversy as more recent studies suggest that corticosteroid treatment in mares, although enhancing the reduction of PMNs in the uterus, may enhance uterine bacterial growth (Aurich et al., 2010). Anecdotal reports from several practicing veterinarians indicate that dexamethasone treatment may be beneficial in reducing excessive edema as observed in the occasional mare during the estrus phase of the estrous cycle. Whether the beneficial effect enhances pregnancy rates remains unknown.

Electro-acupuncture has also 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 mares will most likely not improve fertility but may even cause further contamination and interfere with pregnancy.

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